



# Efficacy of topical interventions for temporomandibular disorders compared to placebo or control therapy: a systematic review with meta-analysis

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This systematic review focused on the efficacy of topical products in reducing temporomandibular joint disorder (TMD)-associated pain, in comparison to placebo or control interventions. The EMBASE, Web of Science, Cochrane Library, and MEDLINE via PubMed databases were searched for randomized controlled trials (RCTs) using topical interventions in adults diagnosed with TMD. The pain intensity was the primary outcome, and other clinical findings were the secondary outcomes. The risk of bias was evaluated according to the Cochrane's handbook. The search up to February 7, 2020 identified a total of 496 unduplicated references. Nine RCTs with 355 adult patients diagnosed with TMD were included. The meta-analysis did not show a significant reduction in baseline pain intensity in the nonsteroidal anti-inflammatory drug (NSAIDs) group, when compared to the placebo group ( $P = 0.288$ ). One study demonstrated a statistically significant pain score decrease for Theraflex-TMJ compared to placebo after 10 d of treatment ( $P = 0.003$ ) and follow-up, 5 d after the last application ( $P = 0.027$ ). Ping On reduced pain at 4 weeks of application ( $P < 0.001$ ) but not after 7 d of application ( $P = 0.136$ ). In one study, cannabidiol (CBD) significantly improved the pain intensity compared to placebo ( $P < 0.001$ ). However, no differences were found with capsaicin in the two studies ( $P = 0.465$ ). Evidence was of low quality because the studies were considered as having an unclear or a high risk of bias and a small number of studies were analyzed. The evidence is not sufficient to support the use of topical NSAIDs and capsaicin, and limited evidence was found for Theraflex-TMJ, bee venom, Ping On, and CBD, with only one study reporting for each. Additional studies are recommended to validate these results.

**Keywords:** Meta-analysis; Systematic Review; Temporomandibular Joint Disorders; Topical Administration; Visual Analog Scale.

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## INTRODUCTION

Temporomandibular disorders (TMDs) comprise a

collection of conditions in the masticatory muscles, temporomandibular joint (TMJ), and other related structures [1-4]. TMD-related pain could be classified as acute or chronic, and patients may experience restrictions

Received: August 27, 2020 • Revised: October 23, 2020 • Accepted: November 23, 2020

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of jaw movements [5,6]. The pain may radiate to the head and neck region and produce other symptoms, such as tinnitus and earaches [3]. Furthermore, the progression, treatment outcome, and occurrence of TMD may be affected by behavioral and psychological components [7].

The “Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Classifications” divides TMDs into joint and muscle problems and then sets up five joint-and six muscle-related subcategories [8]. The International Classification of Orofacial Pain is a recent classification system that incorporates DC/TMD and classifications established by the International Association for the Study of Pain [9].

The first-line treatment for most TMD cases consists of conservative therapy to address the etiologic and risk factors [7]. This often includes dietary modifications, occlusal splint fabrication, physical therapy, behavioral modifications to change a patient’s parafunctional habits, patient education, systemic anti-inflammatory drugs, and analgesic medications [4–7,10]. The extended use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with significant adverse effects, such as gastrointestinal, renal, hepatic, and cardiovascular events [11–14]. In patients who cannot tolerate these side effects, topical medications may be a therapeutic alternative [15]. Topical formulations applied to the affected area may deliver effective doses at the local site, minimizing the adverse effects associated with systemic doses [16].

Topical NSAIDs (e.g. diclofenac sodium and methyl salicylate) and nutraceuticals (e.g. capsaicin, bee venom, and cannabidiols [CBDs]) have been documented as options in the management of TMD [2,17–24]. Topical interventions could provide patients with TMD with a better safety profile and a noninvasive option to reduce their pain. A systematic review in 2012 evaluated topical nonsteroidal medications, but it did not include nutraceuticals [15]. Thus, the present systematic review aimed to assess the efficacy of topical interventions in reducing pain and other secondary outcomes associated with TMD.

## METHODS

### 1. Research question

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [25] with the protocol registered in PROSPERO (#CRD42020160723). The PICOS question was as follows: Are topical interventions effective in reducing pain in patients with TMD?

- Population: patients with TMD
- Intervention: topical interventions
- Comparison: placebo or control therapy
- Outcome: reduction in pain (primary) and secondary outcomes, including mouth opening (mm), pain pressure threshold (PPT, pressure applied with a calibrated algometer), TMJ tenderness, and muscle tonus
- Setting: hospital or community-based facility or academic clinical care center

### 2. Inclusion and exclusion criteria

Randomized controlled clinical trials (RCTs) documenting the efficacy of topical interventions in reducing TMD-associated pain and comparing the efficacy with those of placebo or control therapy were included. Clinical guidelines, literature reviews, and systematic reviews were scanned for relevant RCTs. Articles not available in English were not included.

### 3. Search methods for study identification

The search was conducted in four electronic databases (EMBASE, the Web of Science, Cochrane Library, and MEDLINE via PubMed) up to January 24, 2019 using the strategies described in Table 1. The search was repeated on February 7, 2020 in the four previously indicated databases, and no additional relevant references were found.

### 4. Data collection and analysis

All the references found using the previously described strategy were assessed by three authors. Duplicates were

excluded. The titles and abstracts of all records were evaluated based on the inclusion and exclusion criteria. The full articles were then reviewed if a consensus was not met. If a disagreement among the three reviewers still existed after reviewing the entire article, the fourth author decided the final inclusion. Three authors scanned all systematic reviews, clinical guidelines, and reviews from the initial search as well as all eligible RCTs to identify additional relevant references. Any applicable study, which was not included in the initial search, was evaluated using the same criteria and assessed by the same group of authors. If any disagreement arose, they reviewed the full text, and a fourth author made the final decision.

## 5. Data extraction and management

Three authors independently extracted data from the full-text articles of selected and eligible studies with a standardized data entry form. The extracted data included study design, funding source, type of study, country, intervention and sample size, control intervention and sample size, sex, age, co-interventions, adverse events, and outcomes. A fourth author resolved disagreements based on the information and data extracted from the three authors.

## 6. Risk of bias assessment in included studies

The risk of bias per study was assessed by three reviewers and then reviewed by a fourth author, according to the approach described in the Cochrane Handbook [26].

## 7. Statistical analyses

Considering the heterogeneity of the interventions (NSAIDs, nutraceuticals), individual meta-analyses were performed for topical NSAIDs versus placebo/control, Theraflex-TMJ versus placebo, topical NSAIDs versus oral NSAIDs, and each nutraceutical (capsaicin, CBD, Ping On) versus placebo. Treatment effects were recorded as differences in means (DMs) in the change from baseline in pain intensity (0-100 visual analog scale

[VAS]), with confidence intervals (CIs) of 95%. Statistical heterogeneity was evaluated using the Cochran Q test [27] and I<sup>2</sup> statistic [28]. A random-effects model was used to calculate effect estimates if heterogeneity was found (Q test,  $P < 0.10$ ); otherwise, the fixed-effects model was used. Statistical analyses were performed using the Comprehensive Meta-analysis software version 3 (Biostat, Englewood, NJ, USA). Due to the small number of studies analyzed, the sensitivity analyses for studies with a low risk of bias could not be conducted; a funnel plot to assess for publication bias could not be created as well.

## 8. Quality of evidence

Evidence was assessed with GRADE profiler (GRADEpro) software, following the guidelines of the Cochrane Collaboration and GRADE Working Group [26].

# RESULTS

## 1. Results of the search

Four electronic databases were initially searched up to January 24, 2019 using the strategies described in Table 1. The initial search provided 554 references, and two additional papers were identified after scanning the reference section of the included studies. After removing duplicate papers, 496 references were scanned independently by three authors. Based on the titles and abstracts, only 16 relevant articles were included and their full-text was examined and independently analyzed by the same 3 review authors for inclusion. Seven manuscripts were relevant and included in the analysis. The following articles were excluded: not an RCT ( $n = 1$ ), proceeding or abstract ( $n = 1$ ), not in English language ( $n = 1$ ), different conditions (no TMD,  $n = 5$ ), or editorial ( $n = 1$ ). The search was repeated in all four databases on February 7, 2020 and two [17,24] new relevant references were found; thus, a total of 9 studies were included in the analysis (Fig. 1).

Table 1. Electronic database search strategies

Electronic database	Search strategy
<b>MEDLINE via PubMed</b> search strategy: (searched up to 1/24/2019; re-run on 2/7/2020)	("Temporomandibular Joint Disorders"[Mesh] OR "Temporomandibular Joint Dysfunction Syndrome"[Mesh] OR "TMD" OR "TMJ pain" OR "TMJ arthritis" OR "TMJ" OR "TMJ capsulitis" OR "TMJ arthralgia" OR "Myofascial pain" OR "Orofacial Pain" OR "Facial Pain"[Mesh]) AND ("Administration, Topical/therapy"[Mesh] OR "topical" OR cream OR patch) AND ("Capsaicin"[Mesh] OR "Bee Venom"[Mesh] OR "Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR "Bee venom" OR "Ping " OR "NSAIDS" OR "Non-Steroidal anti-inflammatory" OR "nonsteroidal anti-inflammatory" OR diclofenac OR "Theralex" OR " muscle relaxant") Language: English Species: humans Article types: randomized controlled trials, clinical trials, systematic reviews, review, meta-analysis, guideline, practice guideline
<b>The Web of Science and The Cochrane Library</b> (searched up to 1/24/2019; re-run on 2/7/2020)	((capsaicin OR "Bee venom" OR "Ping " OR "Non-Steroidal anti-inflammatory" OR "nonsteroidal anti-inflammatory" OR diclofenac OR "Theralex" OR (muscle relaxant)) AND ("TMD" OR (TMJ pain) OR (TMJ arthritis) OR "TMJ" OR (TMJ capsulitis) OR (TMJ arthralgia) OR (Myofascial pain) OR (Orofacial Pain) OR (facial pain))) AND ("topical" OR cream OR patch)
<b>EMBASE</b> (searched up to 1/24/2019; re-run on 2/7/2020)	#1 'capsaicin/exp OR capsaicin OR 'bee venom'/exp OR 'bee venom' OR OR 'non-steroidal anti-inflammatory' OR 'nonsteroidal anti-inflammatory' OR 'diclofenac'/exp OR diclofenac OR 'theralex' OR (('muscle'/exp OR muscle) AND relaxant) #2 'topical' OR cream OR patch #3 'tmd' OR (tmj AND pain) OR (tmj AND arthritis) OR 'tmj' OR (tmj AND capsulitis) OR (tmj AND arthralgia) OR (myofascial AND pain) #4. #1 and #2 and #3

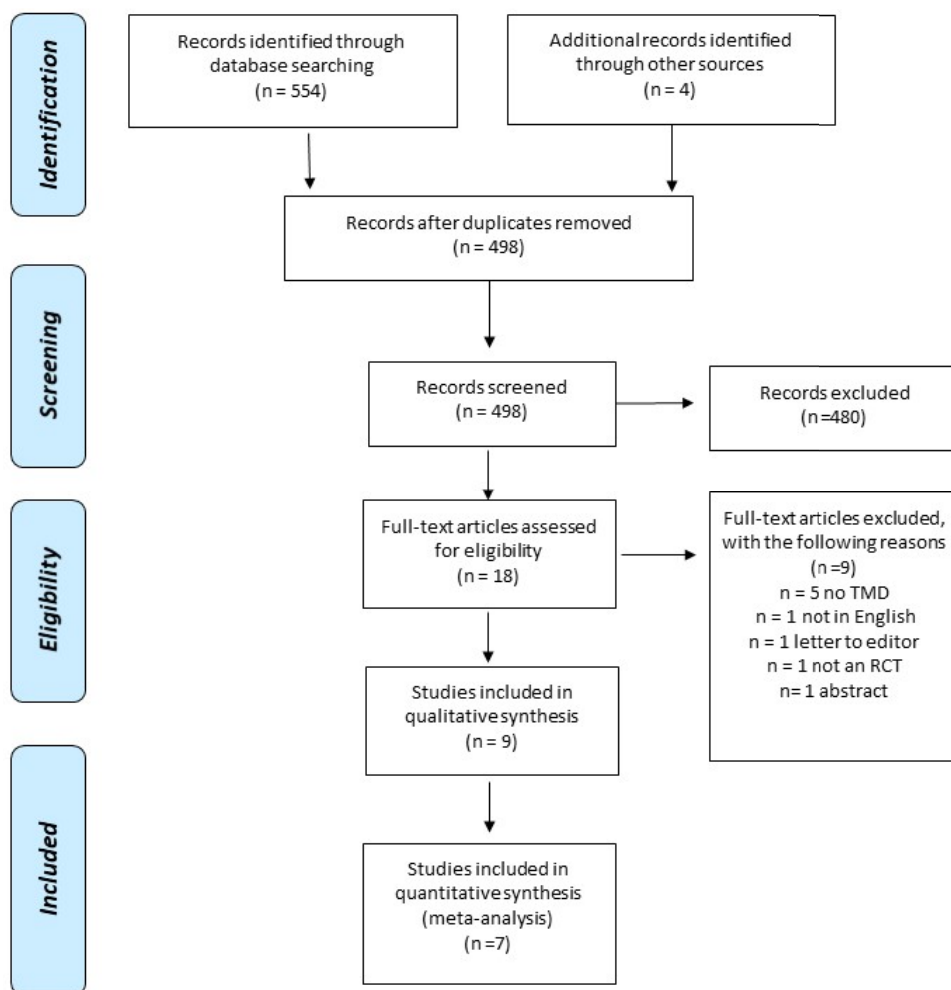


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram [25].

Table 2. Summary of eligible RCT studies

Reference	Country, study type	Interventions and sample size per group	Temporomandibular disorder diagnosis	Sex	Age (mean $\pm$ standard deviation) [range], yr
Campbell et al. [17]	USA DBRCT N = 16	I: 8% Capsaicin, n = 8 C: vehicle cream, n = 8	1. RDC/TMD group IIIa criteria for arthralgia of the TMJ (Dworkin and LeResche [61]); 2. TMJ pain of greater than 6 month duration; 3. VAS pain score $\geq 3$ out of 10 for the previous week or the day of testing; 4. Subjects had to have a joint component with or without muscle pain but were excluded if they only had myalgia.	0M/16F	27.4 $\pm$ 11.9
Di Rienzo Businco et al. [18]	Italy Not blinded RCT N = 36	I: Topical diclofenac, n = 18 C: Oral diclofenac, n = 18	Dysfunction of the temporomandibular joint – details on of diagnosis diagnostic criteria not specified.	19F/17M	M = 43 yr [34-61 years]
Li et al. [2]	Hong Kong DBRCT N = 45	I: Ping On Ointment, n = 28 C: Petroleum jelly, n = 27	1. RDC/TMD Group I criteria [61]; 2. For joint and muscle pain complaints, subjects were required to self-report of pain occurring daily or nearly for at least 1 month of daily or nearly daily pain; 3. Subjects with myogenic pain were included if they met the inclusion and exclusion criteria	13M/32F	I: 44.0 $\pm$ 13.1 C: 47.1 $\pm$ 9.3
Lobo et al. [19]	USA DBRCT N = 52	I: Therflex-TMJ cream, n = 26 C: Placebo cream, n = 26	1. Pain report in the masseter muscle either at rest or during when performing daily activities; 2. Pain on palpation of the masseter muscle; 3. Pain in the temporomandibular joint either at rest or when performing daily activities during function	5M/47F	Age not specified
Nitecka-Buchta et al. [20]	Poland DBRCT N = 68	I: Bee venom ointment, n = 37 C: Vaseline, n = 42	Polish version of RDC/TMD Group Ia and Ib [62]	10M/58F	Mean = 23 yr [22–34 yr]
Nitecka-Buchta et al. [24]	Poland DBRCT N = 60	I: CBD formulation, n = 30 C: control formulation, n = 30	Polish version of RDC/TMD Group Ia and Ib [62]	27M/33F	I: 23.2 $\pm$ 1.6 yr C: 22.6 $\pm$ 1.9 yr
Shin & Choi [22]	Korea DBRCT N = 20	I: 1% indomethacin cream, n = 10 C: Ultrasound gel, n = 10	Chief complaint of Temporomandibular joint pain and tenderness on upon palpation of temporomandibular joint.	5M/15F	I: 26.2 $\pm$ 13.5 yr C: 18.7 $\pm$ 4.6 yr
Wilson F. [23]	Canada DBRCT N = 28	I: Pennsaid, n = 14 C: 45.5% dimethyl sulfoxide [DMSO] solution, n = 14	1. Primary degenerative joint disease as diagnosed through by radiographs radiography utilizing Cone-Beam CT; 2. A baseline score $\geq 30$ mm on a 100- mm VAS scale (moderate pain) [63].	0M/28F	I: M = 30.4 yr [19-44 yr] C : M = 28.4 yr [18-44 yr]
Winocur et al. [21]	Israel DBRCT N = 30	I: active capsaicin cream, n = 17 C: Placebo cream, n = 13	1. History of TMJ pain for at least 3 months in a defined area; 2. Pain in the joint area associated with function; 3. Presence of TMJ tenderness to upon palpation on the reported affected side.	6M/24F	I: 35.6 $\pm$ 14.2 C: 37.5 $\pm$ 16.7

Legend: DBRCT, double-blinded randomized controlled trial; RDC/TMD, Research Diagnostic Criteria for Temporomandibular Disorders; I, intervention; C, control; n, subject number; M, male; F, female; VAS, visual analog scale; TMJ, temporomandibular joint; TMD, temporomandibular disorders; DMSO, dimethyl sulfoxide; CBD, Cannabidiol; m, mean; M, median.

## 2. Included studies

Nine studies were qualified for the qualitative analysis of the efficacy of topical medications in the treatment of TMD [2,17-24] (Table 2). The studies included in this review were eight randomized, double-blinded placebo-controlled clinical trials and one not blinded placebo-controlled RCT [18].

### 1) Population

The total patient sample size included in this review was 355 patients (272 females, 83 males). Patients' age ranged from 18 to 61 years, although not all studies reported the patients' age range. These studies were conducted in Europe [18,20,24], North America [17,19, 23], Asia [2,22], and Middle East [21] (Table 2).

The inclusion criteria were as follows: a) TMD

**Table 3.** Details of the interventions

Reference	Topical intervention		Control therapy		Tx duration	
	Intervention's main component(s), manufacturer	Other ingredients	Administration route, dosage, and instructions	Main ingredients		Route, dose, and instructions
Campbell et al. [17]	Capsaicin 8% cream (Westlab Pharmacy, Gainesville, FL, USA)	Andydrous ointment, butylated hydroxytolene NF, polysorbate 80, water	Topical, 0.1 mL	Vehicle cream (andydrous ointment, butylated hydroxytolene NF, polysorbate 80, water)	Same as the intervention	1/xdaysd 7 daysd
Di Rienzo Businco et al. [18]	Diclofenac sodium solution	In a patented carrier with dimethyl sulfoxide [DMSO]	Oral, 16 mg/ml, 10 drops	Oral diclofenac sodium	Oral, 50 mg twice a day	4/xdaysd 14 daysd
Li et al. [2]	<i>Ping On</i> Ointment ointment (18% peppermint oil, 20% menthol, (Ping On Ointment Company Limited, Hong Kong)	8% bee wax, 6% birch oil, 6% natural camphor, 4% eucalyptus oil, 3% aromatic oil and 1% sandalwood oil)	Topical, rub ointment	0.5% ping <i>Ping On</i> ointment and petroleum jelly	Same as the intervention	5 min. 2x/dayd 4 weeks
Lobo Lobo et al. [19]	Theraflex-TMJ cream (active ingredient: Methyl methyl salicylate) (NaBob/Rx, San Mateo, CA)	Copper, Zinc zinc, and Managanese manganese Amino amino acid complex, Lysinelysine-aspartate (dipeptide), MSM, Aloe aloe vera, highly purified licorice extract, sweet almond oil, proprietary herbal blend, capric/ caprylic triglycerides, emulsifying agents, and water	Topical, apply ¼ - ½ tsp of cream on painful muscle or over painful joint	Placebo cream	Same as the intervention	2x/dayd 2 weeks
Nitecka-Buc hta et al. [20]	0.0005% bee venom ointment		Topical, massage over masseter muscles	Vaseline	Same as the intervention	3x/dayd 14 daysd
Nitecka-Buc hta et al. [24]	Cannabidiol 2.0 g ointment (20% CBD oil)	Purified water, 3.0 g Ointment Cholesterol cholesterol, 5.0 g	Topical, massage over masseter muscles	Purified water, 3.0 g Ointment Cholesterol, 5.0 g	Same as the intervention	2x/dayd 14 daysd
Shin & Choi [22]	1% indomethacin (Vigel <sup>®</sup> , Chodang Pharmaceutical Industry Inc., Korea)	in In a base consisting primarily of water and lanolin	Topical, 1% indomethacin with an US massage to the TMJ	Ultrasound coupling medium (Aquasonic <sup>®</sup> , Parker Laboratories, USA).	Same as the intervention	15 min 1x/dayd 2 daysd
Wilson F. [23]	Pennsaid <sup>®</sup> (1.5% diclofenac)	In 45.5% dimethyl sulfoxide [DMSO] solution).	Topical, apply drops	45.5% DMSO	Same as the intervention	4x/daydsd 90 daysd
Winocur et al. [21]	0.025% capsaicin cream (Zostrix, RAFA Laboratories Ltd)		Topical - rub into the skin	Ingredients not specified (also prepared by RAFA)	Same as intervention	20-30 sec. 4x/dayd 4 weeks

Legend: TMJ, Temporomandibular Joint; DMSO, dimethyl sulfoxide; CBD, Cannabidiol; US, ultrasound

diagnosis classified using axis I of the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) criteria [2,20,24]; b) clinical findings of pain in the masseter and/or joint and tenderness in the TMJ [19,21,22]; c) primary degenerative joint disease based on the RDC/TMD criteria Group IIIa [17], or diagnosed by radiography [23] or moderate pain and cone-beam computerized tomography [23]; and d) dysfunction of the TMJ [18].

## 2) Interventions

The interventions are described in Table 3. The reviewers grouped them into three categories based on the active ingredient (NSAID or not) and the control group (placebo, dimethyl sulfoxide [DMSO], or oral NSAID).

- Topical NSAIDs (1% indomethacin cream [22], 1.5% diclofenac with 45.5% DMSO [23]) versus topical

Table 4. Co-interventions and adverse events in included RCTs

Reference	Interventions and sample size	Co-interventions	Reported adverse events	No. of events in the intervention group	No. of events in controls
Campbell et al. [17]	I: 8% Capsaicin, n = 8 ; C: control, n = 8	Not Stated	No data	No data	No data
Di Rienzo Businco et al. [18]	I: Topical diclofenac, n = 18 C: Oral diclofenac, n = 18	Not stated	Epigastric burning Oppression Modest irritation and heat sensation on the cutaneous region Epigastralgia	0 5 3 1	12 7 0 16
Li et al. [2]	I: <i>Ping On</i> Ointment, n = 28 C: Petroleum jelly, n = 27	Patients were allowed to continue using their analgesics	Eye irritation Burning sensation Itchiness	6 3 1	0 0 1
Lobo Lobo et al. [19]	I: Theraflex-TMJ cream, n = 26; C: Placebo, n = 26	Not stated	No data	No data	No data
Nitecka-Buchta et al. [20]	I: Bee venom ointment, n = 37 C: Vaseline, n = 42	Massage to the masseter muscles 3 x/ day d for 2 weeks	Allergic reaction to bee venom	1	3
Nitecka-Buchta et al. [24]	I: CBD formulation, n = 30 C: control, n = 30	Not Stated	No data	No data	No data
Shin & Choi [22]	I: 1% indomethacin cream, n = 10 C: gel, n = 10	TMJ ultrasound massage for 15 min.	No data	No data	No data
Wilson F. [23]	I: Pennsaid, n = 14 C: 45.5% DMSO solution, n = 14	Patients were allowed to use extra strength acetaminophen for break-through pain	<b>Gastrointestinal reaction</b> (Nausea) <b>Application site on the skin Rx*</b> Dry skin Paresthesia Peeling Burning Itchy <b>Other reactions*</b> Halitosis Altered Taste Dizziness Xerostomia	1 (7.1 %) 5 (35.7%) 2 (14.3%) 2 (14.3%) 3 (21.4%) 1 (7.1%) 4 (28.6%) 1 (7.1 %) 1 (7.1 %) 0 0 1 (7.1 %)	0 0 0 1 (7.1%) 0 3 (21.4%) 0 1 (7.1 %)
Winocur et al. [21]	I: active capsaicin cream, n = 1; C: Placebo cream, n = 13	Not stated	Warm sensation, stinging, burning, or redness.	13/15 mild to moderate intensity	2 patients with mild symptoms

Legend: I, intervention; C, control; n, subject number; TMJ, temporomandibular joint; DMSO, dimethyl sulfoxide; CBD, cannabidiol.

placebo [22] or DMSO [23].

- Topical Theraflex-TMJ cream versus placebo cream [19].
- One study [18] evaluated the difference between topical NSAID (16-mg/ml diclofenac sodium solution versus oral NSAID (50-mg tablet of oral diclofenac sodium administered twice a day after a meal for 14 d.)
- Nutraceuticals (capsaicin [17,21], CBD [24], bee

venom [20], Ping On [2]) versus placebo.

All interventions of topical treatments were applied directly by the patient, except for the indomethacin cream that was applied only once through ultrasound treatment (phonophoresis) [22]. Patients were instructed to apply the topical treatment once [17], two [2,19,24], three [20], or four times a day [18,21,23]. Treatments lasted between 2 and 90 d (Table 3).

**Table 5.** Summary of risk of bias for eligible RCT studies

Study	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other potential bias	Overall bias
Campbell et al. [17]	-	-	?	-	-	?	?
Di Rienzo Businco et al. [18]	?	?	?	-	-	?	?
Li et al. [2]	-	-	?	-	-	?	?
Lobo Lobo et al. [19]	-	-	?	-	-	?	?
Nitecka-Buchta et al. [20]	-	-	?	-	-	?	?
Nitecka-Buchta et al. [24]	-	?	?	-	-	?	?
Shin & Choi [22]	?	?	?	?	-	?	?
Wilson F. [23]	-	-	?	+	-	?	+
Winocur et al. [21]	?	?	?	-	-	?	?

KEY: “-” is low; “+” is high and “?” is unclear risk of bias.

### 3) Comparison groups

Patients in the comparison groups received a non-active vehicle (petroleum jelly [2], Vaseline [20], placebo cream [17,19,21,24], or inert ultrasound gel [22]) or control therapy, including oral diclofenac [18] or 45.5% DMSO [23] (Table 3).

### 4) Co-interventions

Two studies mentioned that rescue medications were allowed during the study [2,23]. One study allowed the patients to continue their analgesic treatment [2], and the other study used extra strength acetaminophen for patients with breakthrough pain [23] (Table 4).

### 5) Outcomes

The primary reported outcome was change in joint pain, measured using the 0-10 VAS [17,18,20,21,24], 0-100 VAS [2,22,23], or 0-10 Numerical Graphic Rating Scale (NGRS) [19]. For VAS 0-10, 0 indicates no pain, whereas 10 indicates worst pain. For 0-100 VAS, 0 indicated no pain and 100 indicates worst pain. In the VAS, the patient draws a line on a 0-10-cm or a 0-100-mm scale. The NGRS is a verbal scale. Secondary outcomes included mouth opening, defined as maximum vertical mouth opening (in millimeters) without evoking pain [2], voluntary and assisted vertical mouth opening [23], and active and passive mouth opening [21]. Other secondary outcomes included joint tenderness (VAS)

[2,18], muscle pain (VAS) [20], functional limitation of mouth opening (0, difficulty in opening mouth; 5, maximum mouth opening) [18], PPT measured with an algometer [22], muscle tenderness (score 0-3) [21], pain disability index scores [23], median values of muscular tonus [20], adverse events, changes in thermal sensitivity (Campbell), and masseter muscle activity as measured by surface electromyography (24).

### 3. Risk of bias in included studies

The risk of bias assessment in nine included studies [2,17–24] is presented in Table 5 and Fig. 2 (graph of risk of bias).

*Random Sequence Generation:* Six studies [2,17,19, 20,23] were defined as having a low risk for random sequence generation (considering randomized envelope selection, block randomization, and a random digit table). Three studies [18,21,22] were assessed to have an unclear risk, since the authors stated that the studies were randomized, but there was no mention on how the randomization was performed.

*Allocation concealment:* Five of the studies [2,17,19, 20,23] were considered as having a low risk, since they used sealed envelopes to conceal the random sequence. Four of the studies [18,21,22,24] did not indicate the allocation concealment method; thus, they were considered as having an unclear risk.

*Blinding:* Blinding of the researchers, participants, and data analysts or assessors were determined. None of the



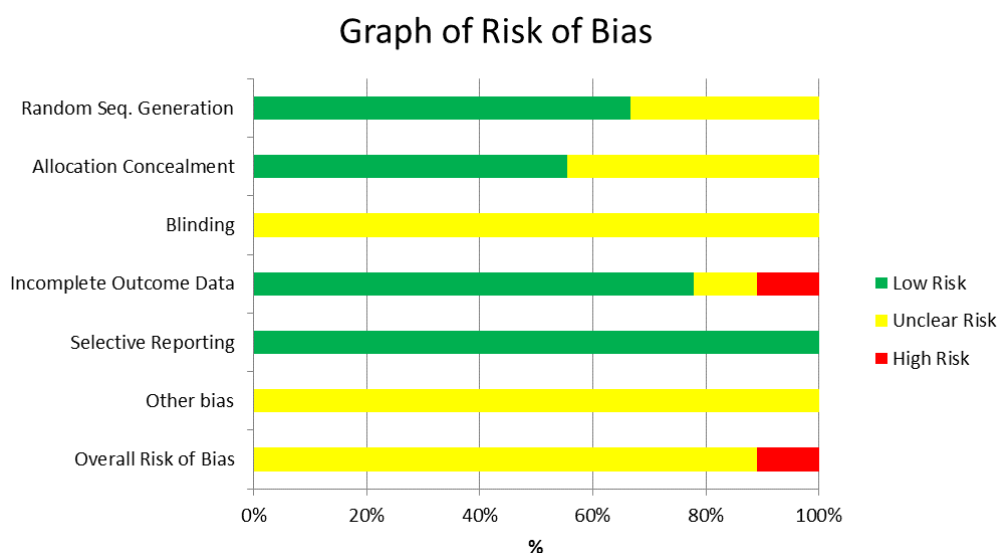


Fig. 2. Summary of risk of bias of eligible randomized controlled trials (RCTs).

studies effectively indicated the blinding process for all participants, investigators, outcome assessors or data analysts in the research; thus, no studies were considered to have a low risk of bias. All nine studies [2,17-24] were considered to have an unclear risk of bias because the authors indicated that their studies were double-blinded; however, there is no indication of the blinding method for all four groups (investigator, data assessors, analyst, participants).

*Incomplete Outcome Data:* Seven studies [2,17-21,24] did not have missing data; thus, they were considered to have a low risk of bias. One trial [22] was deemed to have an unclear risk because it did not mention any dropouts and confirm if all subjects were reported. One study [23] was at a high risk considering the high number of dropouts (> 20%).

*Selective Reporting:* Nine studies [2,17-24] documented the outcomes and were assigned a rating of low risk of bias for selective reporting.

*Other Bias:* Other forms of bias analyzed were co-interventions, funding sources, and imbalance of baseline groups. Nine studies [2,17-24] were considered at an unclear risk because they did not state any co-interventions or funding, and one study [17] had an imbalance of baseline groups.

*Overall Risk of Bias:* None of the studies were

considered to have a low overall risk for bias. Eight studies [2,17-22,24] were assessed as having an unclear risk, and one study [23] was considered at a high risk for bias due to the large number of dropouts (Table 5; Fig. 2).

#### 4. Meta-analyses

Individual studies reporting outcomes are presented in Table 6. Considering the interventions' heterogeneity and comparison groups, the reviewers conducted meta-analyses for change from baseline in VAS pain intensity for two classes of interventions: NSAID versus control groups ( $n = 2$ ; Fig. 3a) and capsaicin versus placebo ( $n = 2$ ; Fig. 3b).

Interventions with only one study reporting relevant outcomes (baseline and post-treatment VAS averages and standard deviation [SD]) for Theraflex-TMJ [19] (Fig. 3c), Ping On [2] (Fig. 3d), and CBD [24] (Fig. 3e) are shown for informational purposes only. Two studies did not provide VAS standard deviations of pain intensity for bee venom [20] and topical treatment versus oral diclofenac [18] and could not be analyzed in this meta-analysis.

##### 1) Topical NSAIDs versus control therapy

In one meta-analysis, this review found a non-

**Table 6.** Results reported by included RCTs

Reference	Intervention vs. control therapy	Outcomes in the intervention group	Outcomes in the control group	Differences between the Intervention intervention and Control control groups(NS: P > 0.05)	Summary
Campbell et al. [17]	I: 8% capsaicin C: vehicle cream	1. Two hours after application increase Increase in VAS pain ratings at 2 h after application. 2. After 1 week decrease Decrease in the VAS pain ratings at 1 week after application	1. Short- term effect: less VAS pain ratings score 2. Long- term effect: higher VAS pain ratings score than the Capsaicin group	VAS measures during at 1 to -7 days d were significantly greater in the control group (P = 0.001). However, the control group initially had started ata higher VAS pain score at baseline	Pain reduction was similar in both groups
Di Rienzo Businco et al. [18]	I: Topical diclofenac C: Oral diclofenac	1. Relief from pain after treatment (p-value not stated)	1. relief Relief from pain after treatment (p-value not stated)	No difference in relief from pain or mouth opening	No difference
Li et al. [2]	I: <i>Ping On</i> Ointment C: Petroleum jelly	VAS pain score decreased significantly (P < 0.001) Maximum Comfortable Mandibular Opening did increase significantly (P = 0.01)	VAS pain score did not decrease significantly Maximum Comfortable comfortable Mandibular mandibular Opening opening increased but not significantly (P > 0.05)	Significant difference between groups in VAS pain score (P < 0.05) and maximum comfortable mandibular opening (P < 0.01) between the two groups	<i>Ping On</i> better than placebo
Lobo Lobo et al. [19]	I: Theraflex-TMJ cream C: placebo cream	Significant decrease in reported pain levels from baseline after 10 days d (P < 0.01), 15 days d (P < 0.001), and follow-up (P < 0.01).	For the control group, no significant differences were found between among the different time periods (P > 0.05).	Significant differences in outcomes between the Theraflex and control groups at 15 days d after tx start of treatment (P < 0.05).	Theraflex was better than placebo
Nitecka-Buchta et al. [20]	I: Bee venom ointment C: Vaseline	1. Changes in VAS scale score before and after 2 weeks were statistically significant (P = 0.00002).	1. Changes in VAS scale score before and after 2 weeks were statistically relevant significant (P = 0.000024).	P value of the difference not reported	Differences not reported
Nitecka-Buchta et al. [24]	I: CBD formulation C: Placebo formulation	Pain intensity in, measured by VAS, scale significantly decreased (70.2%)	No effect on the average pain level VAS pain score of on the masseter muscle	Statistically significant reduction in pain score in CBD group; , but not significant in the control group	CBD is better than Placebo placebo
Shin & Choi [22]	I: 1% indomethacin cream C: Placebo cream	1. Significant improvement in TMJ pain VAS pain score (P = 0.011) 2. The pressure pain threshold was increased (P = 0.005)	No significant improvement in TMJ-associated Pain pain (P > 0.05) nor or pressure pain threshold (P > 0.05)	Differences between groups not reported	Differences not reported
Wilson F. [23]	I: Pennsaid (1.5% diclofenac) C: 45.5% DMSO	1. Functional Pain pain Intensity intensity (100 mm VAS scale); P < 0.001 2. No significant difference in voluntary vertical mouth opening (P > 0.05)	1. Functional Pain pain Intensity (100 mm VAS scale); P < 0.001; 2. No difference in vertical mouth opening (P > 0.05)	No difference in VAS pain intensity (P = 0.304) nor or in voluntary vertical mouth opening (P > 0.05)	No difference
Winocur et al. [21]	I: active Active capsaicin cream C: Placebo cream	1. Present Painpain, Maximal maximum Pain pain intensity, and pain relief scale score decreased significantly with capsaicin (P = 0.0001); 2. Active active and Passive passive Mouth mouth Opening opening increased significantly (P < 0.05)	1. Present Painpain, Maximal maximum Pain pain intensity, and pain relief scale score decreased with placebo (P = 0.0001); 2. Active active and Passive passive Mouth mouth Opening opening increased significantly (P < 0.05)	No differences in the pain level on between either the painful or and non-painful sides regarding of the affected muscle and joint tenderness to palpation.	No difference

Legend: I, intervention; C, control; n, subject number; VAS, visual analog scale; TMJ, temporomandibular joint; TMD, temporomandibular disorders; DMSO, dimethyl sulfoxide; CBD, cannabidiol.

significant favorable difference in the improvement of pain intensity (scale 0-100) from baseline in the topical NSAID group when compared to placebo. NSAIDs improved the pain intensity compared to control therapy in two studies (P = 0.288). Pain intensity improved by an average of -6.54 units more from baseline in the NSAID group than in the control group (95% CI = -18.605 to -5.525; P = 0.288; Fig. 3a).

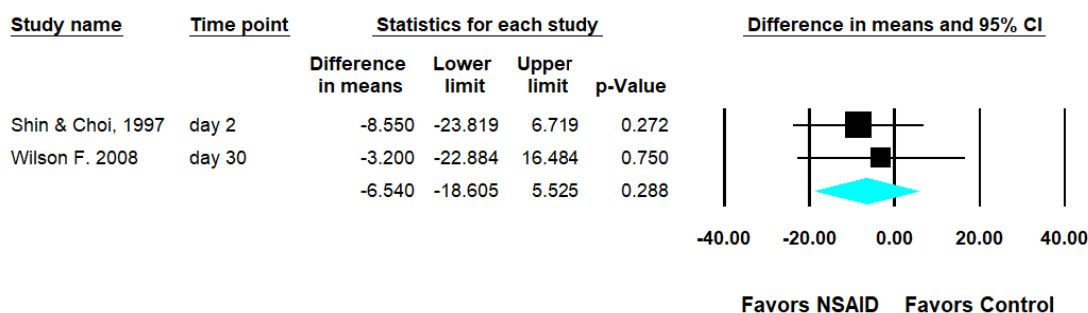
## 2) Capsaicin

In one meta-analysis, capsaicin showed an average improvement in VAS pain score of -4.2 units (0-100 scale) compared to the placebo group in two studies [17, 21] at 7-30 d (95% CI = -15.502 to 7.087; P = 0.465; Fig. 3c). This improvement was not statistically significant.

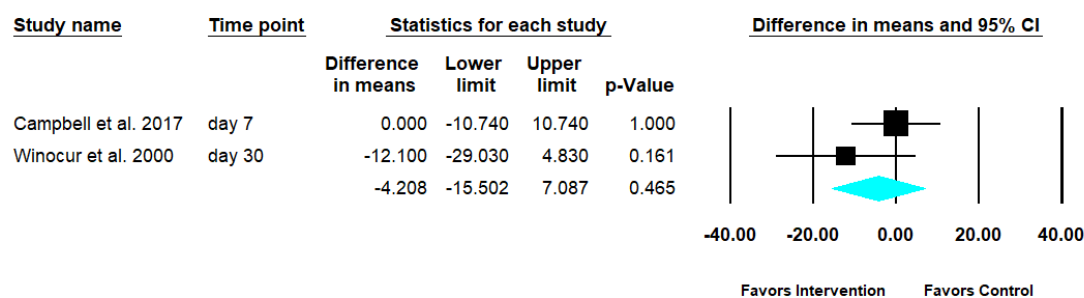
## 3) Theraflex-TMJ versus placebo

Lobo Lobo et al. [19] showed a significant improvement in pain intensity with Theraflex-TMJ cream of -19.5

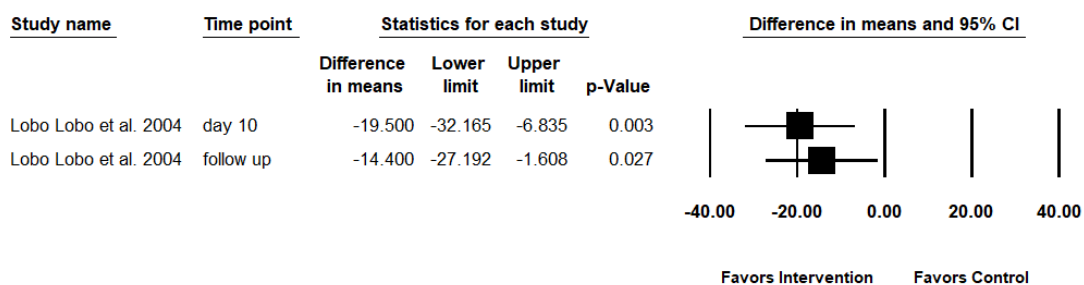
units (on a 0-100 scale) compared to placebo at day 10 (95% CI = -19.500 to -32.165;  $P = 0.003$ ; Fig. 3c) and at follow-up (95% CI = -14.400 to -27.192;  $P = 0.027$ ; Fig. 3c).

**A** Change in VAS pain from baseline

Fixed-effect analysis

**B** Change in VAS pain from baseline

Random-effects analysis

**C** Change in VAS pain from baseline

Fixed-effect analysis

(continued)

(continued)

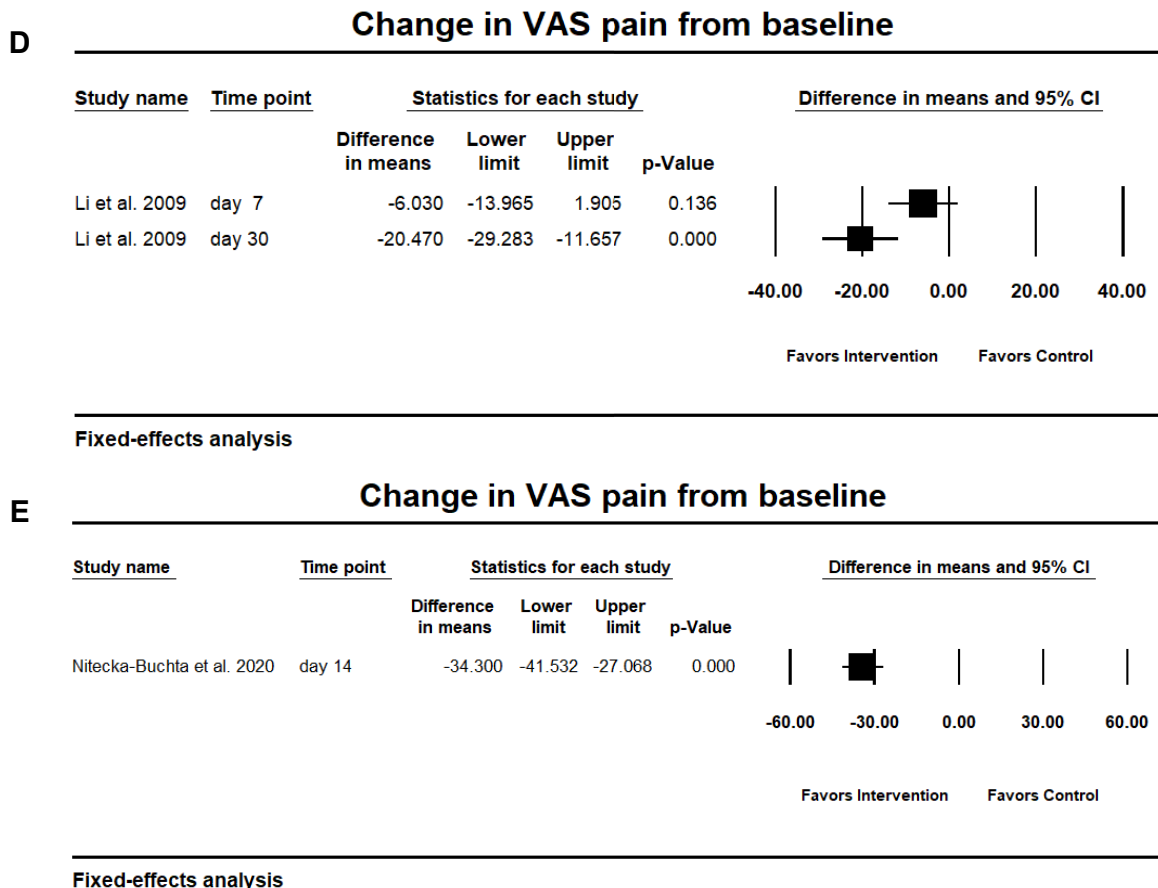


Fig. 3. Meta-analyses: nonsteroidal anti-inflammatory drugs (NSAIDs) versus control (a); capsaicin versus control (b); Theraflex-TMJ versus control (c); Ping On versus control (d); and CBD versus control (e).

4) Nutraceuticals versus controls

No meta-analyses could be undertaken for bee venom versus placebo [20], as the authors did not report standard deviations. Thus, we summarize the results for Ping On and CBD with one study for informational purposes. Li et al. [2] showed a significant improvement in pain intensity with Ping On ointment of -20 units (on a 0-100 scale) compared to placebo at day 30 (95% CI = -29.283 to -29.283;  $P < 0.001$ ; Fig. 3d) but not at day 7 (95% CI = -13.965 to 1.905;  $P = 0.136$ ; Fig. 3d). Nitecka-Buchta et al. [24] showed a significant improvement in the CBD group in VAS pain score of 34 units compared to placebo in one study at day 14 (95% CI = -41.532 to -27.068;  $P < 0.001$ ; Fig. 3e). Further studies are needed to confirm these findings.

5. Co-interventions

Four studies reported to provide co-interventions on the patients [2,20,22,23]. In one trial [2], the patients were allowed to continue their analgesic treatment, and, in one RCT [23], patients were allowed to use extra strength acetaminophen for breakthrough pain. In one study [20], patients performed a simple physiotherapy by massaging the masseter muscle area 3 times per day for 2 weeks prior to the follow-up appointment. In another study [22], the treatment method included the use of ultrasound (1.0 MHz, 0.8-1.5 W/cm<sup>2</sup> continuous output) over the painful TMJ for 15 minutes (Table 4).

6. Adverse events

Adverse events of topical treatments were mainly skin or eye allergy, irritation, redness, or burning sensation

**Table 7.** Summary of evidence and quality of the findings (GRADE)

Topical NSAIDs compared to placebo for treatment of TMD			
Outcomes	No. of participants (studies) Followup	Quality of evidence (GRADE)	Anticipated absolute effects Risk difference with topical NSAIDs (95% CI)
Change in pain intensity from baseline follow-up VAS scale 0-100	40 (2 studies) 2-30 d	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	The mean TMJ pain intensity at first follow-up in the intervention groups was -6.540 lower (-18.605 to + 5.525 higher)
Topical capsaicin compared to placebo for treatment of TMD			
Outcomes	No. of participants (studies) Follow-up	Quality of evidence (GRADE)	Anticipated absolute effects Risk difference with (95% CI)
Change in pain intensity from baseline up VASscale0-100	83 (2 studies) 7-30 d	⊕⊕⊖⊖ LOW <sup>1,2</sup> due to risk of bias, imprecision	The mean change in pain intensity from baseline follow-up in the intervention groups was -4.208 lower (-15.502 lower to + 7.087 higher)

GRADE Working Group grades of evidence

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

<sup>1</sup>All studies assessed unclear or high risk of bias<sup>2</sup>Only two or three studies included in this meta-analysis: small sample size (total number of participants: < 400).

Legend: VAS, visual analog scale; TMJ, temporomandibular joint; TMD, temporomandibular disorders; CI, confidence intervals.

[2,18,20,21,23], with systemic effects, such as nausea, dizziness, and xerostomia, being rarely reported [21]. Adverse effects of oral diclofenac treatment were mainly epigastric burning or retrosternal oppression sensation [18]. No adverse events were reported by three studies [17,19,22] (Table 4).

## 7. Summary of evidence and quality of the findings (GRADE)

Only the trials with similar outcomes were included in the meta-analyses. The evidence was considered of low quality due to the risk of bias and imprecision (small sample sizes in each meta-analysis < 400, and a small number of studies per meta-analysis) present for all meta-analyses in this systematic review (Table 7).

## DISCUSSION

### 1. Main findings

#### 1) Topical NSAIDs versus control therapy

By blocking the cyclooxygenase (COX) pathway and

reducing the production of prostaglandins, NSAIDs are commonly used as the first treatment option for TMD [2,15,19,29]. Nonetheless, non-selective COX inhibitors are well known to be associated with adverse events, such as increased risk of bleeding and gastrointestinal disturbances [30].

In this review, the topical NSAID (1% indomethacin cream [22] and Pennsaid [23]) versus control vehicle groups showed a non-significant reduction in the reported pain levels from baseline of -6.54 units on a 0-100 scale ( $P = 0.288$ ). Kelly [31] stated that the “minimum clinically significant difference” on a VAS is 12 units (95% CI = 9-15 units). The difference in VAS pain score of -6.54 units when comparing topical NSAIDs to placebo groups in this systematic review was not clinically significant.

Different co-interventions might have helped reach the treatment efficacy. Shin and Choi [22] used an ultrasound device to apply the NSAID gel (continuous output of 1.0 MHz, 0.8-1.5 W/cm<sup>2</sup>). Delivering indomethacin at higher ultrasound frequencies ( $\geq 0.7$  MHz) might help in delivering the drug to deeper tissues, since it induces chemical, thermal, or mechanical changes in the cutaneous

tissue [32,33]. Ramakrishnan et al. [34] investigated the efficacy of phonophoresis in treating TMDs using NSAID gel as a coupling agent versus plain therapeutic continuous ultrasound. The authors found that ultrasound treatment without NSAID gel was effective in reducing pain (VAS) and C-reactive protein (CRP) level, an inflammatory marker, and no statistically significant difference in outcomes were found between patients undergoing treatment with ultrasound and NSAID gel and those undergoing plain therapeutic ultrasound.

In one study [23], the authors used Pennsaid (1.5% diclofenac in 45.5% DMSO solution) as the intervention and 45.5% DMSO as the control; however, the results showed that the control group experienced improvements similar to those experienced by the intervention group. This improvement could be due to the DMSO properties, which include anti-inflammatory, analgesia, nerve blockage, bacteriostatic, and vasodilation [35].

## 2) Theraflex-TMJ versus placebo

Theraflex-TMJ (Nabob/Rx, San Mateo, CA), composed of methyl salicylate (derivative of aspirin), which is winter green oil, copper pyrocarboxylate, and zinc pyrocarboxylate, has been investigated as a treatment for masseteric and TMJ-related pain [19]. Copper may provide a therapeutic value in treating arthritis and tissue damage by reducing the production of free radicals and inactivating free radicals produced during inflammation [19]. Prior studies reported that rheumatoid arthritis (RA) patients had higher serum levels of copper and ceruloplasmin than those without arthritis, but not in those with degenerative joint diseases [36,37]. Copper may play a role in taming free radicals, thus reducing inflammation [38]. The mechanism of action of zinc is unclear; however, zinc deficiency is associated with immunosuppression [19,39,40]. Additionally, zinc activates natural killer cells, inhibits inflammatory mediator production, and plays a role in neutrophil function maintenance [41].

The co-interventions might have helped in achieving treatment efficacy. For Theraflex-TMJ, [19] the cream

preparation contains not only an NSAID but also copper and zinc. The anti-inflammatory properties of copper [42] and zinc might have improved the results of this study.

## 3) Topical diclofenac versus oral diclofenac

With only one study reporting the average pain score changes from baseline, when comparing topical versus oral NSAIDs, and given that no standard deviations were reported, a meta-analysis could not be conducted. Authors of the individual study reported that when comparing post-treatment pain between the topical diclofenac and oral diclofenac groups, the improvement in pain intensity assessment on a 0-10 VAS after treatment was not statistically significant ( $P > 0.05$ ). Moreover, no significant differences were found in the improvement in the mouth opening between the two groups ( $P > 0.05$ ). However, the main difference was that patients receiving topical diclofenac had reduced systemic adverse effects, whereas those receiving oral diclofenac showed adverse effects in the gastrointestinal system. The plasma concentration of the topical NSAIDs is small compared to the systemically administered NSAIDs, which in turn reduces the likelihood and risk of renal impairment, cardiovascular events, gastrointestinal adverse reactions, or drug interactions [16,43,44].

It should not be ignored that some cutaneous adverse reactions occur due to topical NSAID applications, such as pruritis, irritation, burning or heat sensation, and contact dermatitis, but they are most likely easy to control and self-limiting [45]. Hsieh et al. [45] found that the control group (menthol patches) had skin irritation and erythema more frequently than the treatment group (diclofenac sodium patch), suggesting that the carrier, not diclofenac, could be the cause.

## 4) Capsaicin

By eliciting the release of substance P and targeting the vanilloid 1 transient receptor potential, capsaicin has been utilized in the treatment of neuralgias, RA, osteoarthritis, and neuropathy [17,21,46,47]. Topical capsaicin may reduce pain and inhibit cutaneous

hypersensitivity through nociceptor fiber defunctionalization based on an *in vitro* study [48]. Defunctionalization occurs through continued capsaicin applications, which may result in decreased responsiveness to noxious stimuli [49]. Additionally, capsaicin is believed to have anti-inflammatory analgesic effects [47,48].

In one meta-analysis involving two studies [17,21] in this systematic review, capsaicin cream versus placebo showed no main treatment effect in terms of TMJ-associated pain. In one study, joint sensitivity to palpation on the affected side disappeared in 4 of 15 patients in the capsaicin group and in 3 of 13 patients in the placebo group by the end of the experiment [21]. In patients with chronic soft tissue pain, patients receiving 0.05% topical capsaicin had diminished pain scores than those receiving placebo [47]. The efficacy of capsaicin in treating TMD-associated pain remains equivocal [17,21]. Topical application of capsaicin often results in burning or itching sensation [46,48]. Defunctionalization occurs through continued applications, which may result in decreased responsiveness to noxious stimuli [47,48]. Further studies are needed to confirm this.

#### 5) Ping On cream

A topical medication, Ping On cream, consisting of Chinese herbs (natural camphor, menthol, peppermint oil, birch oil, eucalyptus oil, sandalwood oil, bee wax, and aromatic oil) along with petroleum jelly, was reported to reduce both TMJ- and muscle-related pain in one RCT [2]. Birch oil, which also consists of methyl salicylate, has anti-inflammatory properties. The ethanolic extract of propolis (bee wax) has also been proposed to have anti-inflammatory effects in rats [50]. Menthol may produce analgesic effects by activating TRPM8, heat-activated TRPV3, and inhibiting TRPA1 as well as desensitizing TRPM8 [51].

Li et al. [2] showed statistically significant improvements in VAS pain score with Ping On ointment of 20 units compared to placebo at day 30 ( $P < 0.001$ ). However, the improvement of 6 units at day 7 was not statistically significant ( $P > 0.05$ ). Further studies are

needed to confirm these findings. No previous studies have been conducted specifically with Ping On ointment in the treatment of TMD.

#### 6) Bee venom

Bee venom, also known as apipuncture, has been utilized for arthritic pain [52]. Bee venom, or apitoxin, consists of a mixture of proteins, including adolapin, which is a COX inhibitor and thus has anti-inflammatory and analgesic properties [53]. According to the authors, the use of bee venom [2] versus placebo resulted in changes in VAS score after 2 weeks of treatment, which were statistically significant and favorable to bee venom ( $P < 0.001$ ); however, we could not conduct a meta-analysis as the standard deviations of the VAS pain score were not reported. Prior reviews did not discuss the results of bee venom therapy in the context of TMD-associated pain relief. Lee et al. [54] reported that bee venom acupuncture helped in the treatment of arthritis; however, the evidence is limited. According to a systematic review by Lee et al. [55], one study reported a significant reduction in morning stiffness and joint swelling and tenderness, and an improvement in the quality of life of patients with RA. However, the evidence is of low quality, as it is based on the results of only one RCT. Although the bee venom is used to treat RA and other neurological conditions, bee venom therapy may have some adverse effects, including local swelling or itching [56]. More studies are needed to investigate the effect of topical bee venom for TMD treatment in humans.

#### 7) CBD

CBD and tetrahydrocannabinol (THC) are active components of *Cannabis sativa* L. Wong et al. found that the trigeminal ganglion had both CB1 and CB2 receptors that innervate the rat masseter muscles and proposed that these receptors are involved in analgesia [57]. In this review, the improvement in VAS pain score of 34 units from baseline (0-100) at day 14 was significantly more favorable to topical CBD compared to placebo ( $P <$

0.001). Transdermal cannabinoids have shown efficacy in reducing pain and inflammation in mice [58]. Animal models have shown that topical CBD application has a potential for pain relief as well as pain-related behaviors and inflammation, with no evident side effects [59]. A recent study that reviewed the efficacy of CBD in the treatment of joint disease and orthopedic joint replacement found no approved pharmaceutical products that contain only CBD for pain [60]. Further prospective placebo-controlled studies to investigate the effect of topical CBD for treating TMD in humans are needed.

## 2. Overall completeness and applicability of evidence

The electronic databases searched were Cochrane Library, Medline via PubMed, EMBASE, and Web of Science, up to February 7, 2020; the search was limited to English published articles. We manually searched the reference sections and included studies to identify additional studies. The results of this systematic review are applicable to TMD patients aged 18-61 years. Since the reported treatment duration ranged from 2 d to 90 d, this review does not address the long-term efficacy of topical interventions. These results are applicable to both genders and Europeans [18,20,24], North Americans [17,19,23], and Asians [2,21,22].

## 3. Heterogeneity of the review and analysis of biases

In this review, it was evident that there was clinical heterogeneity in multiple areas. Owing to the different interventions applied in the study group, subgroup analyses comparing topical NSAIDs versus placebo, systemic versus topical NSAIDs, and plant- or animal-based nutraceuticals versus placebo were performed separately. The population selected was heterogeneous, except for two studies that included only female patients [17,23], which could lead to a bias in the results if the response to the intervention differed between female and male patients. There is also a heterogeneity in the treatment and follow-up durations; one trial had a follow-up duration of 2 d [22] and another had the longest follow-up after treatment of 90 d [23]. Some of the studies

allowed the patients to use medications, such as extra strength acetaminophen, [23] or continued analgesic treatment [2], during the trial that could bias the results. Additionally, heterogeneity was observed in the topical intervention's application methods; the treatment method in two studies included application of ultrasound massage [22] or a simple massage to the masseter muscles [20], which could bias the results, if the massage affected the patients' response to the topical intervention.

## 4. Implications for research

This systematic review and meta-analyses demonstrated that topical medications had low evidence in reducing pain associated with TMD due to its high or unclear risk of bias. The quality of the evidence was low due to the unclear blinding and small sample size of the subjects in each meta-analysis. The studies did not mention any funding sources. The meta-analyses highlight the need for future well-designed, double-blinded randomized, placebo-controlled studies with larger sample sizes of patients receiving NSAIDs, Ping On, CBD, and bee venom. Future studies should also explore other topical agents that may be useful in reducing pain, such as menthol and other compound medications. In addition, the efficacy of higher doses of NSAIDs and other topical interventions as well as their duration of use, compliance rate, and possible side effects need further investigation.

## 5. Implications for clinical practice

Utilizing topical interventions for patients who are pharmacophobic or who may develop side effects from systemic interventions may be considered as an adjunctive treatment, as this treatment method results in minimal resorption of the drug into the blood stream and mild side effects. Nevertheless, caution should be considered in patients who might develop severe side effects from topical agents, which could be avoided by always testing a small skin area before starting treatment.

## 3. Conclusions

There is not enough evidence to support the use of



topical NSAID and capsaicin cream to palliate pain in patients with TMD, and limited evidence was found for bee venom, Ping On, CBD, and Theraflex-TMJ topical cream. The low quality of the evidence was due to the unclear or high risk of bias and the limited number of studies for each intervention. Additional studies with minimal risk of bias and larger numbers of participants are needed to confirm these results.

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**Reyes Enciso:** Conceptualization, Formal analysis, Investigation, Methodology, Validation, Writing - original draft, Writing - review & editing

**ACKNOWLEDGMENTS:** The protocol was sent to PROSPERO on December 1, 2019 and published on July 21, 2020 with registration # CRD42020160723.

**DECLARATION OF INTERESTS:** The authors have no conflicts of interest to declare.

**FUNDING:** The authors have not received funding for this work.

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