Review Article

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Reduction of headache intensity and frequency with maxillary stabilization splint therapy in patients with temporomandibular disorders–headache comorbidity: a systematic review and meta-analysis

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This systematic review and meta-analysis aimed to analyze the effectiveness of maxillary stabilization splint (SS) therapy to reduce headache (HA) intensity and HA frequency in patients with temporomandibular disorders (TMD)-HA comorbidity. Randomized controlled trials (RCTs) using full-arch coverage, hard resin, and maxillary SS therapy were included. Electronic databases, including Cochrane Library, MEDLINE through PubMed, Web of Science, and EMBASE, were searched. The risk of bias was analyzed based on Cochrane's handbook. The search yielded 247 references up to January 28, 2020. Nine RCTs were included at a high risk of bias. The comparison groups included other splints, counseling, jaw exercises, medications, neurologic treatment, and occlusal equilibration. Four studies reported a statistically significant reduction in HA intensity, and five studies reported significant improvement in HA frequency from baseline at 2-12 months in patients with TMD-HA comorbidity treated with a full-arch hard maxillary SS. HA frequency in tension-type HA (TTH) comorbid with TMD diagnoses of myofascial pain (MFP) or capsulitis/synovitis improved significantly with SS than that with full-arch maxillary non-occluding splint (NOS) in two studies. Comparison groups receiving hard partial-arch maxillary splint nociceptive trigeminal inhibition (NTI) showed statistically significant improvements in HA intensity in patients with mixed TMD phenotypes of MFP and disc displacement comorbid with "general HA." Comparison groups receiving partial-arch maxillary resilient/soft splint (Relax) showed significant improvements in both HA intensity and frequency in patients with HA concomitant with MFP. The meta-analysis showed no statistically significant difference in the improvement of pain intensity at 2-3 months with comparison of the splints (partial-arch soft [Relax], hard [NTI], and full-arch NOS) or splint use compliance at 6-12 months with comparison of the splints (partial-arch Relax and full-arch NOS) versus the SS groups in patients with various TMD-HA comorbidities. In conclusion, although SS therapy showed a statistically significant decrease in HA intensity and HA frequency when reported, the evidence quality was low due to the high bias risk and small sample size. Therefore, further studies are required.

Keywords: Meta-Analysis; Migraine; Stabilization Splint; Systematic Review; Temporomandibular Joint Disorders; Tension-Type Headache.

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INTRODUCTION

The relationship between headache (HA) and temporomandibular disorders (TMD) has been explored for decades [1–8]. TMD-HA comorbidities can become chronic, incapacitating neurological and musculoskeletal conditions [3]. TMD-HA comorbidity increases the diagnostic difficulty of both TMD and HA [7,9,10], contributes to misdiagnoses [8], and increases management difficulty of both TMD [11] and HA [7]. One study found that certain comorbidities, such as migraine and chronic fatigue syndrome, increased TMD pain intensity and duration [12]. Comorbid conditions may share risk factors that increase the likelihood of developing both comorbid conditions [10]. Consistent with this, TMD-HA comorbidity is greater than random chance, according to one research group [7]. Taken together, there is a synergistic bidirectionality in TMD-HA comorbidity, with HA increasing the burden of TMD, and TMD increasing the burden of HA [11,13].

Beyond the shared pathophysiology of these conditions [14–16], several other factors account for this complexity, including the changing definitions of both TMD [17–19] and HA, including HA attributed to TMD [20,21]. Additionally, patients with comorbid conditions are more challenging to treat [10]. Third, not all patients respond to the same treatment, such as TMD or HA. Fourth, TMD and HA have traditionally been treated by different disciplines; for example, TMD by dentists and HAs by physicians. Fifth, TMD-HA comorbidity spans the life cycle of pediatric, adult, and geriatric patients [22–24]. Last, the phenotype of both HA [23,25] and TMD changes over the life cycle [22,24,26].

TMD is the second most frequent musculoskeletal pain condition [27]. In 2015, Horst et al. reported that patients seeking care from general dentists had chief complaints of temporomandibular joint (TMJ) pain and masticatory muscle pain as frequently as tooth pain/periodontal pain within a 12-month period [28]. They reported that the chief complaint in 1 out of 6 patients was orofacial pain [28]. Another study reported a TMJ and muscle disorders (TMJMD)-type pain prevalence of 6.1% in women and 2.9% in men [24]. The prevalence of TMJMD-type pain by race/ethnicity is as follows: non-Hispanic Caucasian, 4.9%; Hispanic/Latino, 3.7%; Non-Hispanic Black, 3.5%; Others, 3.5% [24].

TMD does not only increase the frequency and intensity of migraine [7] and Tension-Type HA (TTH) (both primary HA disorders) [29], but also their chronicity [8,30]. TMD can also be the cause of HA, known as HA attributed to TMD (secondary HA) [21]. TMD occurs with greater frequency (statistically significant) in chronic HA and episodic HA patients than in patients without HA [31]. Painful TMD significantly increases the risk of chronic migraine (odds ratio [OR], 30.1); for episodic migraine, the OR was 3.7 [29]. Similarly, the OR for TMD in chronic migraine is 95.9, 7.0 for episodic migraine, and 3.7 for episodic TTH [29], showing how tightly woven the comorbidity is between TMD and chronic migraine. However, TMD is an under-recognized cause of chronic HA, causing 14%–26% of chronic HAs [32]. One research group found that almost all TMD patients had HA (85.5%), with 55.3% and 30.2% having chronic migraine and episodic migraine, respectively [5]. Nilsson et al. [33] estimated that the prevalence of HA in patients with TMD is 40%–70%.

TTH is the most prevalent primary HA disorder, with a lifetime prevalence of 30% to 88% [34]. Migraine is the leading cause of years lived with disability among individuals aged 15-49 years old [35] and the second leading cause of years lived with disability globally [36]. The prevalence of adult migraine is 20.7% in women and 9.7% in men; racial/ethnic prevalence is 19.2% in Native Americans, 15.5% in Whites, 15.0% in Blacks, 14.9% in Latinos, and 10.2% in Asian Americans [37]; these percentages are comparable to those in an earlier study [38]. Barriers exist for appropriate migraine diagnosis and treatment: 28.3% of adult patients with episodic migraine [39], and 5% of adult patients with chronic migraine receive appropriate migraine treatment [40]. Additionally, approximately one-third of migraineurs taking newly

prescribed triptans, the most frequently prescribed medication for migraines, had inadequate pain relief [41].

One research group proposed that TMD causes central sensitization through the trigeminal system as a means of migraine progression from episodic migraine to chronic migraine [7]. Several research groups have reported that treating TMD can reduce HAs [6,33,42–46]. However, many dentists are uncomfortable diagnosing or treating TMD [47–49]; one study of recent dental graduates attributed their lack of confidence in TMD diagnosis and treatment to insufficient TMD training in the dental school curricula [48]. TMD management generally focuses on conservative reversible therapy, including counseling, physical therapy, pharmacotherapy, behavior modification following self-care instructions, and intraoral occlusal appliances [19]. The evidence for intraoral appliance efficacy in TMD is greatest for stabilization splints (SS) [50–52], which have fewer adverse risks than those in partial-arch intraoral appliance designs, including intraoral appliance aspiration [53], increased TMJ sounds [54], or permanent occlusal changes [53,55]. Similarly, a systematic review and meta-analysis found that SS was more effective in reducing masticatory muscle and TMJ pain than that by non-occluding splints (NOS) or no treatment [51].

The objective of this systematic review and meta-analysis was to determine the effect of maxillary SS therapy on HA intensity and HA frequency in patients with TMD-HA comorbidity.

METHODS

This systematic review adhered to the Preferred

Table 1. Details of the methods for this systematic review

Methods	Details of the methods
Inclusion and exclusion criteria	Studies were limited to publications in English of Randomized Controlled Trials (RCT) on the efficacy of hard maxillary SSs with full coverage in patients with temporomandibular disorders and comorbid headache or migraine compared to any active or passive intervention.
Data collection and analysis	All the articles selected by the search strategies listed above, after the removal of duplicates, were screened by three authors. The title and abstract of all papers were reviewed according to the inclusion and exclusion criteria. If a consensus among the three reviewers was not met, the full article was then reviewed by them. If a disagreement among the three reviewers still existed after reviewing the full article, final inclusion was decided by agreement with a fourth author. The bibliography sections of all reviews, systematic reviews, and clinical guidelines from the original search, as well as all eligible RCTs, were scanned by three authors for any additional relevant references. Any new applicable study not in the initial search results was submitted to the same inclusion/exclusion criteria and then reviewed by the same three authors. If there was a disagreement, the full text was reviewed, with a fourth and fifth author making the final decision.
Data Extraction and Management	Three authors independently extracted data from the full-text articles of eligible RCTs. The data extracted included demographics of the participants, control group, intervention group, method of intervention, and the outcome of the results. Any disagreement with the data and information extracted between the three authors was resolved by consensus with the fourth and fifth review authors.
Assessment of risk of bias in included studies	The assessment of the risk of bias for each included RCT was undertaken by the three reviewers independently and reviewed by a fourth author, as part of the data extraction process, and in accordance with the approach described in the Cochrane Handbook [56].
Statistical analyses	Only RCTs on SSs with TMDs patients suffering from comorbid headaches were included. Treatment effects were calculated to compare the results across them. When authors reported medians (m) and Interquartile range (q1, q3), the results were converted to means and standard deviations (SD) with the following formulas: mean = (q1+m+q3)/3; SD = (q3 − q1)/1.35. When authors reported the standard error of the mean (SEM), results were converted to standard deviations SD = SEM * sqrt (N), with N as the sample size in that intervention group. For pain intensity (0-10 scale), treatment effects were expressed as the difference in means (DM) of the change in pain intensity from baseline with 95% confidence intervals (CI). For compliance prevalence in each group (percent of patients compliant with the intervention), treatment effects were expressed as Risk Ratios (RR) with 95% CI. Statistical heterogeneity was tested with Cochran's Q test [75] and the I2statistic[76]. Estimates of the effect were combined with a random-effects model if there was heterogeneity (Q-test p-value < .10), or with the fixed-effect model otherwise. All statistical analyses were performed using Comprehensive Meta-Analysis version 3 software (Biostat, Englewood, NJ, USA). Due to the small number of studies, sensitivity analyses for low risk of bias studies could not be conducted, nor a funnel plot to assess for publication bias.

Abbreviations: DM, difference in means; N, sample size; RCT, randomized controlled trial; SD, standard deviation; SEM, standard error of the mean; SS, stabilization splint TMD, temporomandibular disorders; TMJ, temporomandibular joint; TTH, tension-type HA; VAS, visual analog scale.

Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [56], and the protocol was registered with PROSPERO # (removed for blind copy). The PICOS question was:

- Study design: Randomized Controlled Trials (RCTs).
- Population: Patients with TMD and comorbid HA or migraine.
- Intervention: Full-arch coverage, hard resin, or maxillary SS therapy.
- Comparison: No treatment or other treatment.
- Outcomes: Primary outcomes were the Frequency of HAs and Intensity of HAs. Secondary outcomes were the number of responders, mandibular range of motion (mm), migraine disability assessment score (MIDAS), pain pressure threshold, tenderness to palpation, rescue medications, compliance with splint, and adverse events.
- Setting: Orofacial pain clinic or university clinical care center.

Details of the methods (inclusion/exclusion criteria, data collection and analysis, data extraction and management, assessment of risk of bias, and statistical analyses) are described in Table 1.

Four electronic databases (MEDLINE, Cochrane, Web of Science, and EMBASE) were searched up to January 28, 2020, using the strategies described in Table 2. The risk of bias assessment followed the Cochrane handbook [56]. Quality of evidence assessment and summary of the findings were conducted using the GRADE profiler (GRADEpro) software, following the GRADE Working Group guidelines [56].

Table 2. Electronic database search strategies

Electronic database	Search strategy
MEDLINE via PubMed (searched up to January 28, 2020); re-run on January 28, 2020. Search strategy:	Language: limited to English Species: limited to Humans Article types: limited to Clinical Trials, Randomized Controlled Trials, Reviews, Systematic Reviews, Guidelines, Meta-analysis, and Practice Guideline (("Temporomandibular Joint Disorders"[Mesh] OR "Temporomandibular Joint Dysfunction Syndrome"[Mesh] OR (Arthralgia) OR (Capsulitis) OR (TMJ Syndrome) OR (TMJ pain) OR (Disc Displacement of TMJ) OR (Disk displacement of TMJ) OR (Disc Derangement of TMJ) OR (Disk displacement of TMJ) OR (TMJ adhesions) OR (tmj ankylos*) OR (Masticatory muscle myalgia) OR (myalgia) OR (masticatory muscle myofascial pain) OR (myofascial pain) OR (Sensitization) OR (peripheral sensitization) OR (central sensitization) OR (Arthritis) OR (osteoarthritis) OR (rheumatoid arthritis) OR (psoriatic arthritis) OR (tmj arthritis) OR (Tendonitis) OR (fibromyalgia)) AND ((Headache) OR (Headache attributed to TMD) OR (migraine) OR (episodic migraine) OR (chronic migraine) OR (migraine without aura) OR (migraine with aura) OR (tension-type headache) OR (episodic tension-type headache) OR (chronic tension-type headache) OR (TAC) OR (TACs) OR (Trigeminal autonomic cephalalgia*) OR (cluster headache) OR (paroxysmal hemicrania continua) OR (SUNCT) OR (SUNA))) AND ((Orthotic) OR (stabilization splint) OR splint OR (nightguard) OR (night guard) OR (occlusal guard) OR (bruxism appliance) OR (occlusal appliance))
The Web of Science and The Cochrane Library (searched up to January 9, 2019); re-run on January 28, 2020. Search strategy:	(((Arthralgia) OR (Capsulitis) OR (TMJ Syndrome) OR (TMJ pain) OR (Disc Displacement of TMJ) OR (Disk displacement of TMJ) OR (Disc Derangement of TMJ) OR (Disk displacement of TMJ) OR (TMJ adhesions) OR (tmj ankylos*) OR (Masticatory muscle myalgia) OR (myalgia) OR (masticatory muscle myofascial pain) OR (myofascial pain) OR (Sensitization) OR (peripheral sensitization) OR (central sensitization) OR (Arthritis) OR (osteoarthritis) OR (rheumatoid arthritis) OR (psoriatic arthritis) OR (tmj arthritis) OR (Tendonitis) OR (fibromyalgia)) AND ((Headache) OR (Headache attributed to TMD) OR (migraine) OR (episodic migraine) OR (chronic migraine) OR (migraine without aura) OR (migraine with aura) OR (tension-type headache) OR (episodic tension-type headache) OR (chronic tension-type headache) OR (TAC) OR (TACs) OR (Trigeminal autonomic cephalalgia*) OR (cluster headache) OR (paroxysmal hemicrania continua) OR (SUNCT) OR (SUNA))) AND ((Orthotic) OR (stabilization splint) OR splint OR (nightguard) OR (night guard) OR (occlusal guard) OR (bruxism appliance) OR (occlusal appliance))
EMBASE (searched up to January 2019); re-run on January 28, 2020. Search strategy:	#1 'temporomandibular joint' OR 'jaw disease' OR 'myalgia' OR 'capsulitis' OR 'myofascial pain' OR 'tendinitis' OR 'osteoarthritis' #2 headache OR (headache AND attributed AND to AND tmd) OR migraine OR (episodic AND migraine) OR (chronic AND migraine) OR (migraine AND without AND aura) OR (migraine AND with AND aura) OR ('tension type' AND headache) OR (episodic AND 'tension type' AND headache) OR (chronic AND 'tension type' AND headache) OR tac OR tacs OR (trigeminal AND autonomic AND cephalalgia*) OR (cluster AND headache) OR (paroxysmal AND hemicrania AND continua) OR sunct OR suna #3 orthotic OR (stabilization AND splint) OR splint OR nightguard OR (night AND guard) OR (occlusal AND guard) OR (bruxism AND appliance) OR (occlusal AND appliance) #1 and #2 and #3

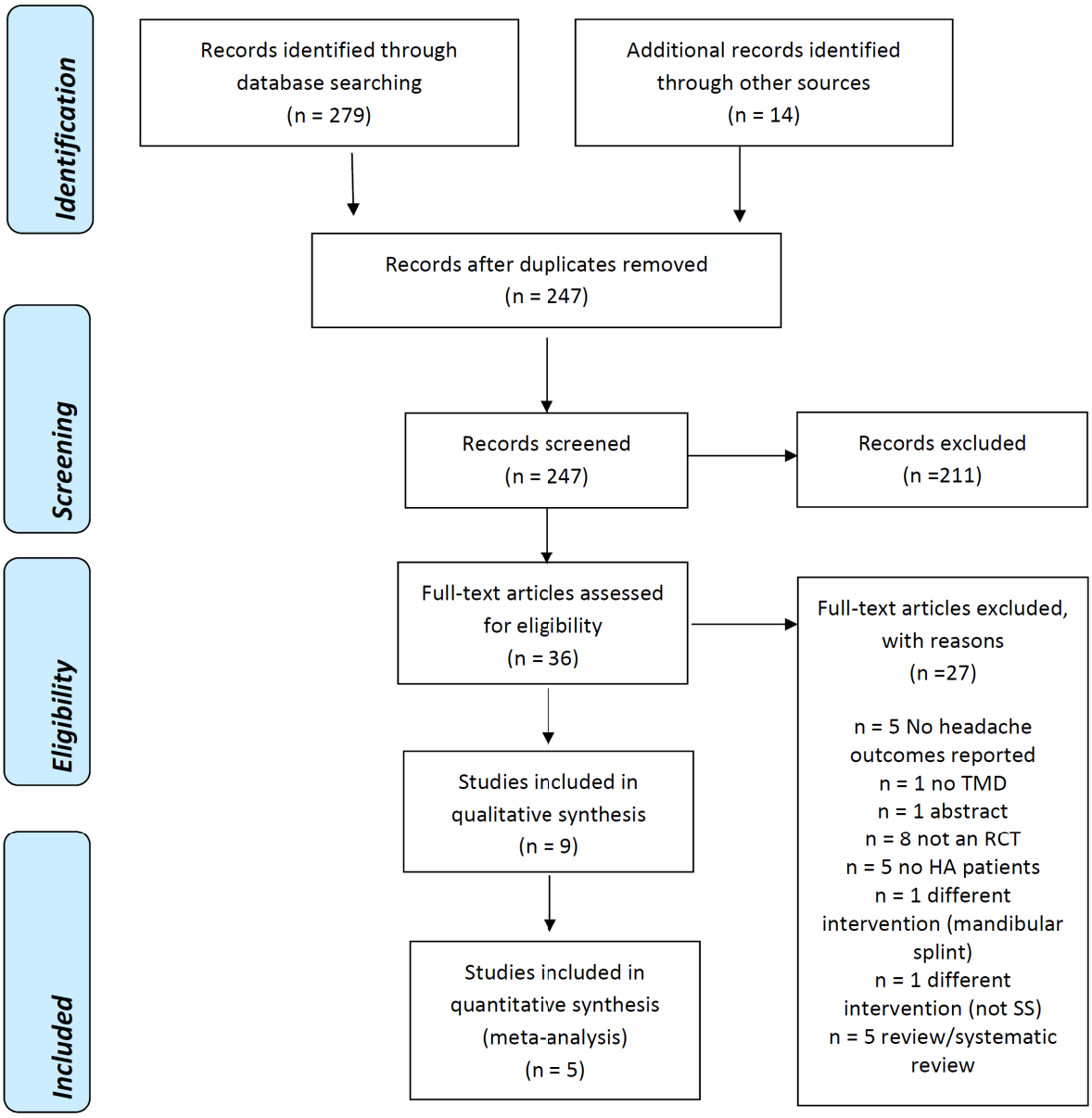


Fig. 1. PRISMA flow diagram [56]. Abbreviations: HA, headache; RCT, randomized controlled trial; SS, stabilization splint; TMD, temporomandibular disorders.

RESULTS

1. Results of the search

The initial search strategy of the databases on January 9, 2019, yielded 279 references and 14 additional records identified through other sources (scanning of the reference section of the included papers). After duplicates were removed, 247 references were scanned, and based on the abstracts and titles, these were reduced to 36 relevant manuscripts. All 36 manuscripts identified were searched for full-text and analyzed for inclusion. Nine manuscripts were relevant for inclusion [9,46,53,57–62]. The main reasons for exclusion were as follows: not an RCT (n = 8), proceedings abstract (n = 1), different conditions (no HA patients [n = 5]), different conditions (no TMD [n = 1]), review or systematic review (n = 5), different interventions (mandibular splint or no SS [n = 2]), and no HA outcomes reported (n = 5).

All four databases were searched again on January 28,

Table 3. Summary of interventions, demographics, and adverse events

Reference	Country	Gender	Age (range or average)	N total Rando-mized	SS Group	N Intervention group	Comparison group (C)	N Comparison group	Adverse events
Costa, et al. [9]	Brazil	6M/54F	18-50 yr	60	SS + counseling	30 24 (analyzed)	Counseling	30 17 (final)	None reported
Doepel, et al. [57]	Finland	7M/58F	18-76 yr	66	SS	33 22 (analyzed)	Resilient/soft PA maxillary splint (Relax)	33 27 (final)	None reported
Ekberg and Nilner [58]	Sweden	8M/52F	20-40 yr	60	SS	30 (analyzed)	FA maxillary NOS	30 10 (final)	AE mentioned but not specified
Ekberg, et al. [46]	Sweden	5M/55F	13-76 yr	60	SS	30 27 (analyzed)	FA maxillary NOS	After 12 months 30 (SS) 20 (mixed) 8 (control)	Some report splint discomfort
Gonçalves, et al. [59]	Brazil	0M/111F	Mean age ± SD: 34.3 ± 8.8	111	SS + Propranolol Placebo	26 23 (analyzed)	-Propranolol -Placebo + NOS -Propranolol + NOS -Propranolol + SS	29 21 (final)	None reported for SS
Jokstad, et al. [53]	Norway	5M/35F	31-62 yr	40	SS	20 20 (analyzed)	Hard PA maxillary splint (NTI)	20 18 (final)	SS: very big or tight. NTI: risk of inhalation, tooth displacement
Magnusson and Syren [60]	Sweden	N/A	16-67 yr	26	SS	14 3 mo: 9 (analyzed)	Therapeutic-jaw exercises;	12 3 months: 9 (final)	AE mentioned but not specified
Schokker, et al. [62]	Nether-lands	10M/38F	SS: 45 ± 13 C: 44 ± 14	55	SS	27 23 (analyzed)	Unspecified Neurologic treatment	28 25 (analyzed)	None reported
Wenneberg, et al. [61]	Sweden	4M/26F	20-40 yr	30	SS	15 15 (analyzed)	Occlusal equilibration	15 15 (analyzed)	OE: Tooth Sensitivity

Abbreviations: AE, adverse events; C, comparison group; F, female; FA, full-arch; M, male; N, sample size; NOS, non-occluding splint; NTI, nociceptive trigeminal inhibition; OE, occlusal equilibration; PA, partial arch; SS, stabilization splint.

2020, and no relevant references were found. The PRISMA flowchart shows a summary of the results (Fig. 1).

2. Included studies

Nine publications were eligible for qualitative analysis [9,46,53,57–62]. The included studies in this systematic review were RCTs where SS (maxillary full-coverage hard resin splints) were compared to various treatments for patients with various TMD-HA comorbidities. Based on the PICOS question, trials with primary and no HAs were excluded by design. One study [58] was a long-term continuation of a previous study [46]. A summary of the interventions and demographics of the included studies is presented in Table 3. Details of the studies, for example, when the SS was worn, active intervention in the comparison group, co-interventions, rescue medications, patients changing the intervention group during the study, other confounding factors, and dropout percentages, are shown in Table 4.

3. TMD diagnostic criteria

TMD was diagnosed using the criteria listed in Table 5. Four studies had TMD diagnosis of myofascial pain (MFP) [9,57–59], one had a mix of MFP and disc displacement (DD) [53], one had capsulitis/synovitis patients [46], and three had a mix of myogenous and arthrogenous TMD or craniomandibular disorders (CMD) patients [60–62] (Table 5).

Table 4. Details of the studies with possible biases and confounding factors

Reference	Tx Duration	When was the SS worn?	Active intervention in the comparison gp	Were there any other co-interventions?	Rescue medications	Was there a 3rd gp?	Were pts allowed to change gp?	Any other confounding factors?	% drop outs
Costa, et al. [9]	5 mos	Nighttime use only	Counseling	Pharmacologic Tx, orthodontic Tx, occlusal appliance (SS)	Yes, HA meds allowed, not specified	No	n = 6 protocol deviations	Tx gp baseline were younger, less HA intensity	31%
Doepel, et al. [57]	12 mos	< 10 wks, nighttime use only; > 10 wks, PRN	Resilient/soft PA maxillary splint (Relax)	Counseling gp 10-week follow up: unsatisfied pts offered SS + additional Tx	Not stated	No	Yes. See "co-intervention" column	Baseline not balanced: gender distribution, HA intensity	24%
Ekberg and Nilner [58]	12 mos	< 10 wks, nighttime use only; > 10 wks, PRN	FA maxillary NOS splint	Yes. See "3rd gp" column	Not stated	At 10 wks, 18 NOS pts and at 6 mos, 2 more NOS pts fitted with SS	Yes. See "3rd gp" column	NOS gp dropouts n = 20	33%
Ekberg, et al. [46]	12 mos	< 10 wks, nighttime use only; > 10 wks, PRN	FA maxillary NOS splint	> 10 wks, 21 NOS pts received SS; 2 mix Tx pts and 1 NOS pt: PT + migraine school + TMJ corticosteroid inj.	Not stated	Yes. See "co-interventions" column	Yes. See "co-interventions" column	NOS gp dropouts n = 21	8%
Gonçalves, et al. [59]	3 mos + Open Label 3 mos	Nighttime use only	Propranolol placebo + NOS splint	1 mo prior: Ibuprofen+ metoclopramide; Open Label: propranolol +SS for all	Ibuprofen 600 mg + metoclopramide 10 mg	1) 30 mg Propranolol tid + SS 2) 30 mg Propranolol tid + NOS	No	Small sample size; Open Label after 3 mos	7.9%
Jokstad, et al. [53]	3 mos	Nighttime use only	Hard PA maxillary splint (NTI)	Counseling, jaw exercises, meds	Yes, existing meds including HA meds	No	Yes. Pts could change splint gp	Small sample size (N = 40); No funding by companies.	5%
Magnusson and Syren [60]	6 mos	Nighttime use only	Jaw exercises (JE)	Analgesic use	Not stated	Yes. See "change gp intervention" column	Yes. Combined Tx gp: 3 from SS gp, 2 from JE gp	Small sample size (N=26); Analgesic use	14%
Schokker, et al. [62])	6 wks	24 hrs/day at least 6 wks, except for eating	Unspecified "Neurologic treatment"	SS: 4/23 PT; SS: 2/23 infrared laser Tx	HA meds allowed	No	No	Small sample size (N = 48); Analgesic use	12%
Wenneberg, et al. [61]	2 mos	Not reported	Occlusal equilibration (OE)	SS: 6/15 exercise 4/15 occlusal adj; OE: 5/15+SS	Analgesic use	Yes. See "co-interventions" column	Yes, 5 pts in OE gp received SS	Analgesic use; Small sample size (N = 30).	Not reported

Abbreviations: adj, adjustment; FA, full-arch; gp, group; h, hours; HA, headache; inj, injection; JE, jaw exercise; meds, medications; mo(s), month(s); n, number of patients; N, total sample size of patients; NOS, non-occluding splint; NTI, nociceptive trigeminal inhibition; OE, occlusal equilibration; PA, partial arch; PRN, as needed; pt (s), patient (s); PT, physical therapy; SS, stabilization splint; tid, three times per day; TMJ, temporomandibular joint; Tx, treatment; wks, weeks.

4. HA diagnostic criteria

The HA diagnostic criteria used in the included studies and the diagnoses of HA are reported in Table 5. In three studies, the patients were diagnosed with HA by a neurologist [9,59,62] (Table 5).

5. Risk of bias in the included studies

The RCTs included in this review were analyzed for risk of bias (Table 6). Details of the assessment of the risk of bias are presented in Table 7. The overall risk of bias was high in all the studies (Fig. 2).

Table 5. Headache and temporomandibular disorders' diagnoses and diagnostic criteria

Reference	HA Diagnosis	HA Diagnostic Criteria reference	TMD diagnosis	TMD Diagnostic Criteria reference
Costa, et al. [9]	HA attributed to TMD	ICHD, 3rd edition (beta version), 2013 [77]	Masticatory MFP	RDC/TMD Schiffman et al [69], Dworkin & LeResche [70]
Doepel, et al. [57]	"HA concomitant with MFP" *	No HA Dx reference given	MFP	RDC/TMD Dworkin & LeResche [70]
Ekberg and Nilner [58]	TTH -episodic TTH: 77% -chronic TTH: 23% "No neurological evaluation was performed"	ICHD, 1st edition, 1988 [78]	MFP with/without limited opening	RDC/TMD Dworkin & LeResche [70]
Ekberg, et al. [46]	TTH -episodic TTH: 25/60 -chronic TTH: 35/60	No HA Dx reference given	Capsulitis/Synovitis	Okeson 1996 [71]
Gonçalves, et al. [59]	Episodic migraine with or without aura	ICHD, 1st edition, 1988 [78]	Myofascial TMD, Grades 2 or 3	RDC/TMD Dworkin & LeResche [70]
Jokstad, et al. [53]	"General HA" * 34/38 Unspecified: 4/38	No HA Dx reference given	MFP: 19/38 MFP + DD: 18/38 DD: 1/38	RDC/TMD Dworkin & LeResche [70]
Magnusson and Syren [60]	TTH: 19/23 Unspecified: 4/23	No HA Dx reference given	TMD: 19/23 "mainly muscular" †	No TMD criteria reference given
Schokker, et al. [62]	TTH: 22/48 Migraine: 12/48 "Combination HA" *: 13/48 "Other Dx"a: 1/48	Lance 1978 [79] Blau 1988 [80]	"Myogenous CMD" †: 44/48 "Arthrogenous CMD" †: 4/48	Schokker et al [72]
Wenneberg, et al. [61]	No HA Dx given: "signs and symptoms of CMD, and complaints of HA" *	No HA Dx reference given	"CMD" †	No TMD Dx reference given

* Not a recognized HA diagnosis (ICHD, 3rd edition [21])
† Not a recognized TMD-specific diagnosis (RDC/TMD Schiffman et al. [69]).
Abbreviations: CMD, craniomandibular disorders; DD, disc displacement; Dx, diagnosis; HA, headache; ICHD, International Classification of Headache Disorders; MFP, myofascial pain; RDC/TMD, research diagnostic criteria for temporomandibular disorders; TMD, temporomandibular disorders; TMJ, temporomandibular joint; TTH, tension-type headache.

Table 6. Summary of the risk of bias for eligible RCT studies: (-) low risk; (+) high risk; (?) unclear risk

Study	Random Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting	Other potential bias	Overall Bias
Costa, et al. [9]	-	-	+	+	?	+	+
Doepel, et al. [57]	-	-	+	+	-	+	+
Ekberg and Nilner [58]	-	-	?	+	-	+	+
Ekberg, et al. [46]	-	-	?	+	?	+	+
Gonçalves, et al. [59]	-	-	?	-	-	+	+
Jokstad, et al. [53]	-	-	+	-	?	+	+
Magnusson and Syren [60]	?	+	+	-	-	+	+
Schokker, et al. [62]	?	+	+	?	-	+	+
Wenneberg, et al. [61]	?	+	+	?	-	+	+

6. Individual studies reported outcomes

A summary of the demographics, countries where the included studies were conducted, interventions, study duration, provider of the interventions, co-interventions, rescue medications, and outcomes reported are presented in Table 8.

1) HA intensity

Intervention groups: Five RCTs showed an improve

Table 7. Assessment of the risk of bias details

Risk of Bias	Assessment
Random sequence generation and allocation concealment	The gold standard of random sequence and allocation concealmentwas a randomized computer-generated list and sequentially numbered, opaque, sealed envelopes,respectively. Except for three RCTs [60–62], the rest achieved the aforementioned gold standard. Random sequence generation was assessed as unclear risk of bias and high for allocation concealment, as authors did not clearly explain their methods of randomization nor concealment strategies in three studies [60–62].
Blinding	In terms of blinding, six studies were considered high risk, as the patients were able to tell the difference between therapies (i.e. splint versus jaw exercises [60], neurologic treatment [62], counseling [9], occlusal equilibration [61] PA maxillary splint [53,57]. The blinding of the patients was unclear In three studies, as the authors used FA maxillary NOS; however,the NOS did not cover the occlusal surfaces as does the SS [46,58,59] and were assessed as unclear risk of bias.
Incomplete outcome data	Drop-out rates are another component impacting the risk of bias in the included RCTs. The authors determined 20% of dropouts as a threshold for low risk of bias. Any paper above the threshold was considered to have a high risk of bias [9,46,57,58]. One study did not specify whether drop-outs occurred or not [61] and another did not specify why the 12% of patients dropped out [62] and were assessed as unclear risk of bias. The remaining studies had a low percentage of drop-outs and were assessed as low risk.
Selective reporting	Regarding selective reporting, three RCTs [9,46,53] did not clearly report the pre-specified outcomes;therefore, the risk of bias for them was unclear.
Other biases	Other biasessuch as funding by companies, co-interventions, and unbalanced groups at baseline were examined. All RCTs were funded by research grants except two [60,62], which did not state the sources of funding. All trials were closely balanced at baseline with the exception of one RCT [53], where the two groups differed regarding the prevalence of TMJ pain upon palpation (P = 0.03) and proportion of patients with general pain (P = 0.02); therefore, the study was deemed unclear on this category of risk of bias. All studies had co-interventions as explained in the Co-interventions section and were assessed as high risk of bias for Other bias.

Abbreviations: FA, full-arch; NOS, non-occluding splint; PA, partial arch; RCT, randomized controlled trial; SS, stabilization splint; TMJ, temporomandibular joint.

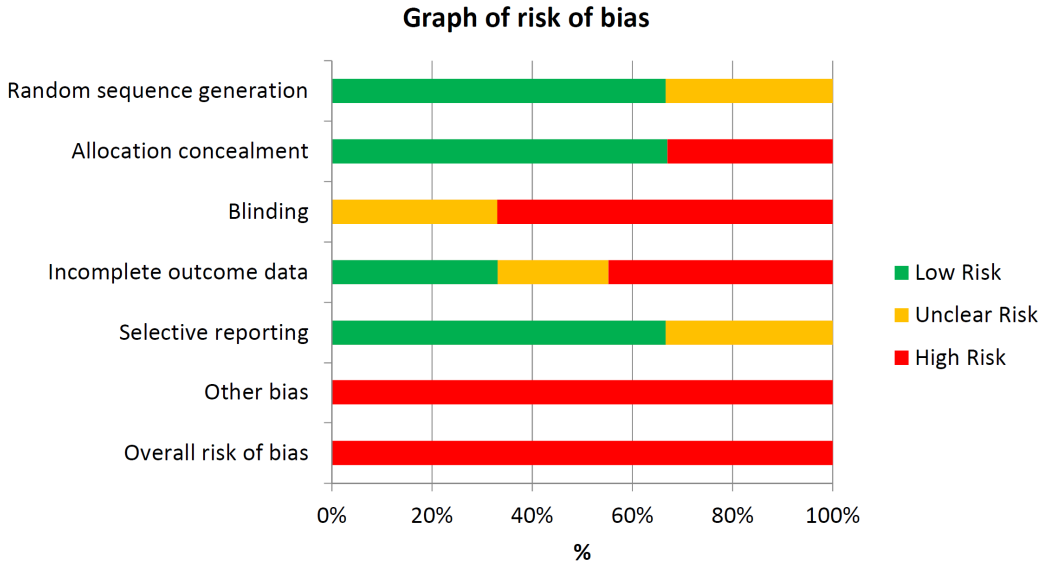


Fig. 2. Summary of the risk of bias of eligible trials.

ment in HA intensity (0-10 scale) with SS at six weeks to three months [9,57,59,61,62] for a mix of HA phenotypes (Fig. 3a; refer to Table 9 for specific TMD and HA diagnoses) in patients with TMD-HA comorbidity.

Comparators: Four RCTs reported an improvement in HA intensity in the comparison groups (Table 9).

Differences between groups: In their comparison to control groups, one trial reported that maxillary SS reduced HA intensity better than unspecified neurologic treatment for a mix of TTH and migraine patients in a six-week trial [62]. Four studies reported no significant differences in HA intensity [9,53,57,59] (Table 9).

2) HA frequency

Intervention groups: All six RCTs reporting HA

Table 8. Summary of results of the included studies

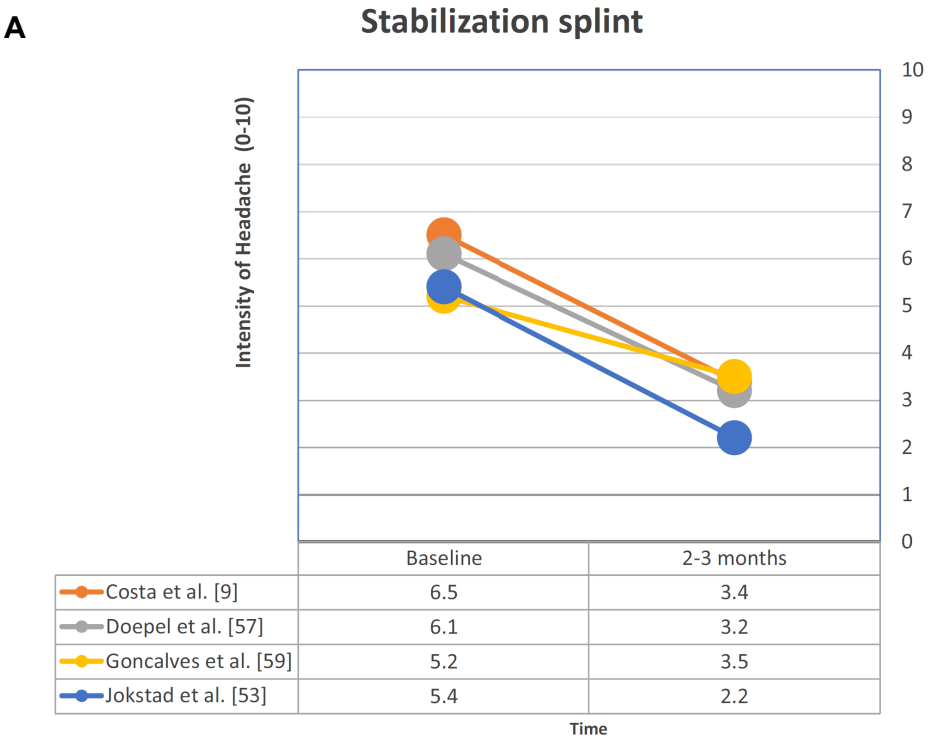
Item	Summary of results
Population	The mean age for the SS groups ranged from 28 to 44 years old, while that for the comparison groups ranged from 29 to 45 years old. Two studies did not report mean ages for the groups, but rather stated overall age of over 18 years old [57] and between 18 to 50 years old [9]. The age of participants ranged from a minimum of 13 to 76 years old [46]. The number of participants ranged from a minimum of 26 [60] to 111 [59], which only included women. RCTs were conducted in Northern European countries (Sweden [46,58,60,61], Norway [53], Finland [57], and Netherlands [62]) and one South American country, Brazil [9, 59]. Centers providing the intervention varied from an orofacial pain center [59], a postgraduate department of prosthodontics in a dental school [9], department of masticatory function [62], and a department of stomatognathic physiology [46,53,57,58,60,61].
Interventions	Maxillary FA hard resin SS was compared to a) two different maxillary PA splint designs (one hard resin [53] and one resilient/soft resin [57]); b) maxillary FA NOS [46, 58]; c) combination therapy of propranolol and maxillary FA NOS, placebo propranolol and NOS, and placebo propranolol and SS [59]. SS and counseling were compared to counseling alone [9]. Three included RCTs compared SS groups to other interventions (jaw exercises [60], unspecified neurologist treatment [62], and occlusal equilibration [61]).
Study Duration	The study duration ranged from six weeks [62] to 12 months [46,57,58]. The participants wore the SS: only at night [9,53,59, 60]; only at night for 10 weeks, then as needed by the patient [46,57,58]; 24 hours/day for at least six weeks, except during meals [62]; one study did not report when the SS was used [61]. Two studies reported different time points with no clear changes between effects at 10 weeks, 6 months, and 12 months [57], or 2 and 5 months [9].
Provider of the interventions	Providers of the splints included experts in stomatognathic physiology [46,53,58,60,61], masticatory function [62], prosthodontics [9, 59], and a general dentist [57]. Counseling was delivered in one RCT to both groups by a therapist [9]. A dental assistant delivered the jaw exercises in one study [60]. One prosthodontist delivered occlusal equilibration [61]. A neurologist evaluated all potential participants, diagnosed HA, and also delivered comparison neurologic treatment [9, 62]. A neurologist with HA subspecialty training examined and diagnosed HA while the other neurologists on the team managed HA treatment and the dentists managed the MFP [59].
Co-interventions	Patients who were not satisfied with the treatment outcome were offered additional treatment, including changing the type of splint and/or other unspecified treatment [46,53,57,58]. Other co-interventions included: Physical therapy and infra-red laser therapy [62]; jaw exercises [9,53,60,61]; TMJ corticosteroid injections [46]; minor occlusal adjustments [61]; medication/analgesic use [9,53,59, 60];oral appliance (SS) in the comparator group [9]; orthodontic treatment [9]; and counseling including lifestyle and disease management [9,53,57]. Counseling included "diet modifications, heating pads, jaw exercises, stretching and self-massage, sleep hygiene, and social and aerobic instructions for the management of HA intensity and frequency" in [9].
Rescue medications	Rescue medications, also a cointervention, were reported as 600 mg ibuprofen and 10 mg metoclopramide for acute migraine treatment [59]. Other studies reported rescue medications to control HA [61,62], or patients were allowed to continue with their HA medications unchanged [53],or patients were allowed to begin an unspecified pharmacologic treatment for HA [9].
Outcomes	The primary outcomes were intensity and frequency of HA. The change in HA intensity was collected pre- and post-treatment on a 0-10 VAS scale [9,53,59], a 0-100 VAS scale [61], a 0-5 NRS scale [62], or a 0-10 NRS scale [57]. Treatment effects reported in our meta-analysis were all reported on a 0-10 scale [53,57,59]. Authors used various questionnaires to collect HA frequency including HA defined as infrequent, frequent or chronic [9]; recurrent/continuous [57]; TTH frequency once a week [58]; HA frequency several times a week or more [46]; HA scale 1 to 5 (1 = almost never to 5 = every day) [61]; or HA scale 0 to 5 (0 = no HA to 5 = HA daily) [62]. HA frequency was not reported in three studies [53,59,60]. Other secondary outcomesreported were change in intensity of MFP [58,61], mandibular range of motion [57,59], MIDAS score [59], joint and muscle tenderness [53], severity of facial pain or TMD pain [58,59,61], PPT [46,53,57,59,61], and compliance with splint use [46,57,58].

Abbreviations: FA, full-arch; HA, headache; MFP, myofascial pain; MIDAS, Migraine Disability Assessment Score; NOS, non-occluding splint; NRS, numerical rating scale; PA, partial arch; PPT, pressure pain threshold; RCT, randomized controlled trial; SS, stabilization splint; TMD, temporomandibular disorders; TMJ, temporomandibular joint; TTH, tension-type HA; VAS, visual analog scale.

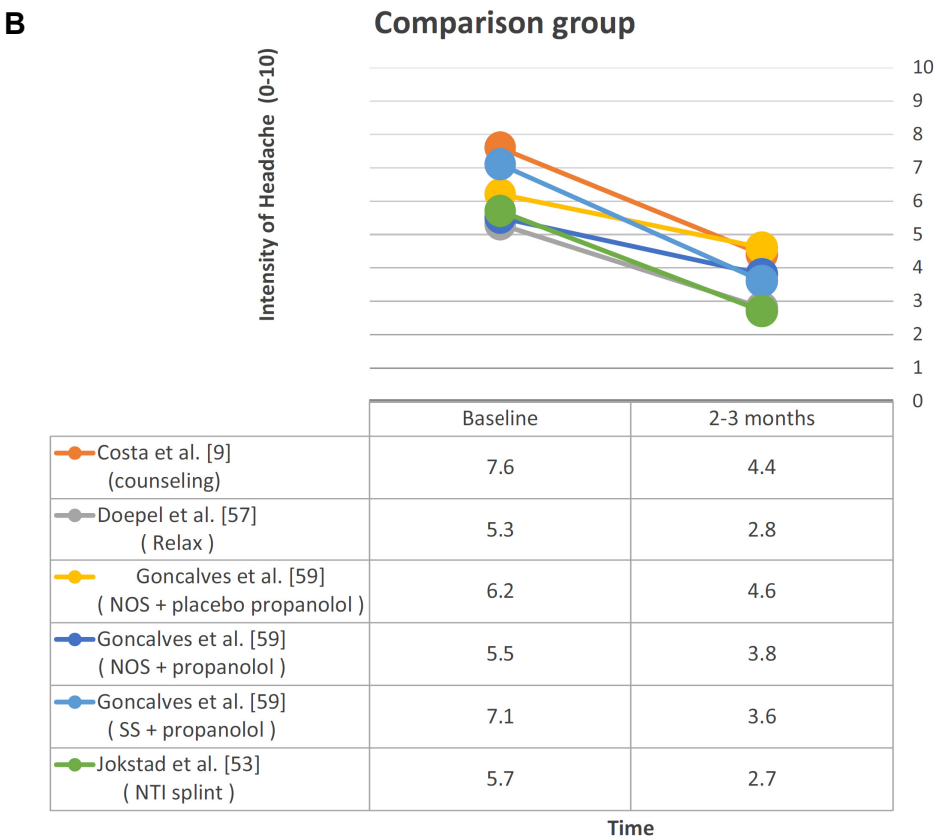
frequency improved significantly compared to baseline in the SS groups [9,46,57,58,61,62] for various TMD-HA comorbidities reported in Table 10.

The comparison groups also had a significant improvement in HA frequency compared to baseline in patients with various TMD-HA comorbidities receiving counseling only [9], resilient/soft partial-arch maxillary splint (Relax) [57], and occlusal equilibration [61]. Patients with TTH receiving full-arch maxillary NOS did not have a significant improvement in HA frequency in two studies [46,58] (Table 10).

Differences between groups: Four RCTs reported that HA frequency improved significantly in the SS group compared to full-arch maxillary NOS for patients with TTH [46,58], unspecified neurologic treatment for patients with a mix of HA phenotypes, mostly TTH and migraine [62], and occlusal equilibration for patients with “complaints of HA” [61] (Table 10).



	Baseline	2-3 months
Costa et al. [9]	6.5	3.4
Doepel et al. [57]	6.1	3.2
Goncalves et al. [59]	5.2	3.5
Jokstad et al. [53]	5.4	2.2



	Baseline	2-3 months
Costa et al. [9] (counseling)	7.6	4.4
Doepel et al. [57] (Relax)	5.3	2.8
Goncalves et al. [59] (NOS + placebo propanolol)	6.2	4.6
Goncalves et al. [59] (NOS + propanolol)	5.5	3.8
Goncalves et al. [59] (SS + propanolol)	7.1	3.6
Jokstad et al. [53] (NTI splint)	5.7	2.7

Fig. 3. Pre- and post-treatment HA intensity (0-10 scale) reported in included studies at 2-3 months in SS groups (A) and comparison groups (B) for TMD comorbid with HA. Abbreviations: NOS, non-occluding splint; NTI, nociceptive trigeminal inhibition; SS, stabilization splint; TMD, temporomandibular disorder.

Table 9. Headache intensity outcomes reported in the included studies

Study	HA Dx / TMD Dx	SS Group	Comparison Group	HA Intensity reported in SS Group	HA Intensity reported in comparison Group	SS versus comparison group
Costa, et al. [9]	HA attributed to TMD / Masticatory MFP	SS + counseling	Counseling	2 mos & 5 mos: HA intensity compared to baseline ($P < 0.001$)	2 mos & 5 mos: HA intensity compared to baseline ($P < 0.001$)	SS + counseling == counseling
Doepel, et al. [57]	"HA concomitant to myofascial pain" * / MFP	SS	Resilient/ soft PA maxillary splint (Relax)	10 wks, 6 mos, 12 mos: HA intensity decreased compared to baseline ($P \leq 0.001$)	10 wks, 6 mos, 12 mos: HA intensity decreased compared to baseline ($P \leq 0.001$)	SS == PA intraoral splint (Relax)
Gonçalves, et al. [59]	Episodic migraine with or without aura / MFP Grades 2 or 3	SS + Propranolol placebo	NOS + placebo propranolol	No p-value per group	No p-value per group	SS == FA maxillary NOS
Jokstad, et al. [53]	"General HA" * / MFP; MFP + DD; DD	SS	Hard PA maxillary splint (NTI)	3 mos: HA intensity compared to baseline ($P = 0.002$)	3 mos: HA intensity compared to baseline: ($P = 0.01$)	SS == PA intraoral splint (NTI)
Schokker, et al. [62]	TTH; Migraine; "Combined HA" *; "other Dx" * / "Myogenous CMD" †; "Arthrogenous CMD" †	SS	Unspecified neurologic treatment	HA intensity decreased in 65% of patients, unchanged in 22%, and increased in 13%.	HA intensity decreased in 32% of patients, unchanged in 64%, and increased in 4%.	SS reduced HA intensity compared to comparison Tx
Wenneberg, et al. [61]	"HA complaints" * / "CMD" †	SS	Occlusal equilibration	Statistically significant reductions in HA VAS intensity ($P < 0.01$)	Statistically significant reductions in HA VAS intensity ($P < 0.05$)	Not reported

* Not a recognized HA diagnosis (ICHD, 3rd edition [21])
† Not a recognized TMD-specific diagnosis (RDC/TMD Schiffman, et al [69]).
Abbreviations: CMD, craniomandibular disorders; DD, disc displacement; Dx, diagnosis; FA, full-arch; HA, headache; MFP, myofascial pain; mos, months; NTI, nociceptive trigeminal inhibition; NOS, non-occluding splint; PA, partial arch; SS, stabilization splint; TMD, temporomandibular disorders; TTH, tension-type headache; Tx, treatment; VAS, visual analog scale; wks, weeks.

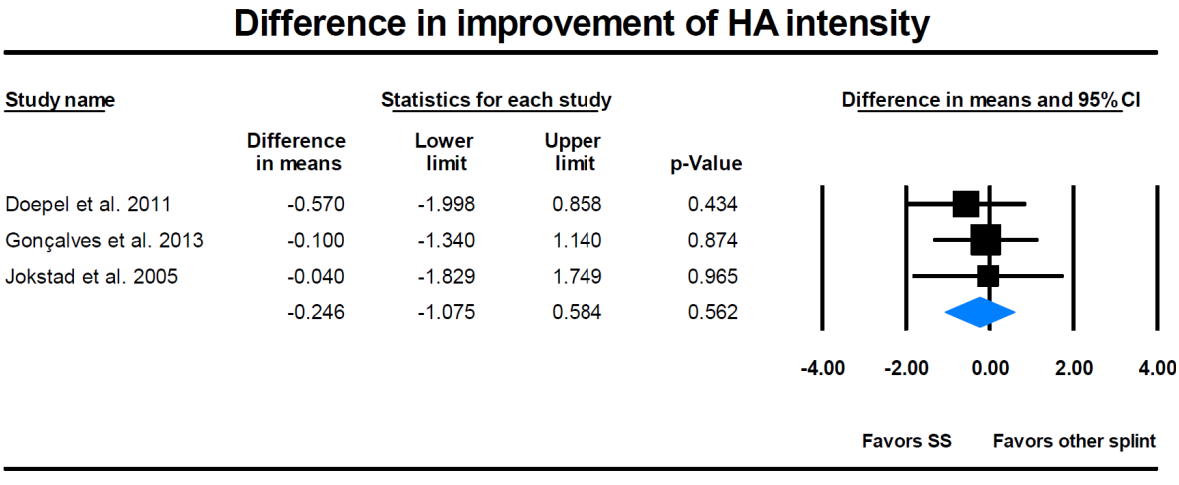


Fig. 4. Meta-analysis. Difference in average improvement from baseline in HA intensity (0-10 scale) between SS groups and comparison splints in patients with TMD comorbid with HA. Abbreviations: CI, confidence interval; HA, headache; SS, stabilization splint; TMD, temporomandibular disorders.

7. Results of the Meta-analyses

1) HA intensity

Three RCTs [53,57,59] out of nine studies in this systematic review reported changes in HA intensity from baseline at 2-3 months (0-10 scale) compared to comparator splints (Table 9 and Fig. 4). Meta-analysis showed no significant difference in improvement in pain intensity at 2-3 months of -0.246 units (0-10 scale) in the SS group compared to the comparator splints, including the Relax splint, NOS, and NTI (95% CI =

Table 10. Headache frequency outcomes reported in the included studies

Study	HA Dx / TMD Dx	SS Group	Comparison Group	HA Frequency reported in SS group	HA Frequency reported in comparison group	SS versus comparison group	SS versus comparison group
Costa, et al. [9]	HA attributed to TMD / Masticatory MFP	Counseling + SS	Counseling	5 mos: HA freq (infrequent, frequent or chronic) improved vs. baseline, P = 0.001	5 mos: HA freq (infrequent, frequent or chronic) compared to baseline, P = 0.01	Baseline, 5 mos: NS	SS + counseling == counseling
Doepel, et al. [57]	"HA concomitant to MFP"* / MFP	SS	Resilient/ soft PA maxillary splint (Relax)	10 wks, 6 mos, 12 mos: HA freq decreased (recurrent/ continuous) compared to baseline, P < 0.001	10 wks, 6 mos, 12 mos: HA freq decreased (recurrent/ continuous) compared to baseline, P < 0.001	Baseline, 10 wks, 6 mos, 12 mos: NS	SS == PA intraoral splint (Relax)
Ekberg and Nilner [58]	TTH / MFP with/without limited opening	SS	FA maxillary NOS	TTH once/wk vs. baseline at: 10 wks, P = 0.039; 6 mos, P = 0.039; 12 mos, P = 0.003 TTH daily at 10 wks, P = 0.031	6 mos: HA once/wk compared to baseline: NS 12 mos: Not reported	Improved in SS vs. NOS at 10 wks, P = 0.003; 6 mos, P = 0.039; 12 mos, P = 0.010	SS improved HA freq significantly compared to FA maxillary NOS
Ekberg, et al. [46]	TTH / Capsulitis/ Synovitis	SS	FA maxillary NOS	10 wks: HA several times/wk or more compared to baseline, P = 0.021	10 wks: HA several times/wk or more compared to baseline: NS	10 wks: SS reduction in HA several times/wk compared to NOS, P = 0.020	SS improved HA freq significantly compared to FA maxillary NOS
Schokker, et al [62]	TTH; Migraine; "Combined HA" *; "other Dx"* / "Myogenous CMD"; "Arthrogenous CMD"†	SS	Unspecified neurologic treatment	HA freq: 60% decreased, 32% unchanged, 5% increased, P < 0.025	HA freq: 32% decreased, 68% unchanged	HA freq (0 = no HA to 5 = HA daily) decreased in SS more than comparison gp (P < 0.025)	SS improved HA freq significantly compared to unspecified neurologic treatment
Wenneberg, et al [61]	"HA complaints"* / "CMD"†	SS	Occlusal equilibration (OE)	HA freq (1 = almost never to 5 = every day) decreased significantly in the SS gp, P < 0.01	HA freq decreased significantly in the OE gp, P < 0.01	HA freq decreased significantly greater in SS gp, P < 0.01	SS improved HA freq significantly compared to the OE gp

* Not a recognized HA diagnosis (ICHD, 3rd edition [21])
†Not a recognized TMD-specific diagnosis (RDC/TMD Schiffman et al [69]).
Abbreviations: CMD, craniomandibular disorders; Dx, diagnosis; FA, full-arch; freq, frequency; gp, group; HA, headache; ICHD, International Classification of Headache Disorders; MFP, myofascial pain; mos, months; NOS, non-occluding splint; NS, not significant (P > 0.05); OE, occlusal equilibration; PA, partial arch; RDC/TMD, Research Diagnostic Criteria/TMD; SS, stabilization splint; TMD, temporomandibular disorders; TTH, tension-type headache; vs, versus; wk (s), week (s).

-1.075 to 0.584; P = 0.562) (Fig. 4).

2) Compliance with splint use

Only three RCTs reported compliance with splint use at 6 and 12 months [46,57,58]. Meta-analysis showed no significant difference in compliance with splint use at 6 months (risk ratio [RR] = 0.999; 95% CI = 0.727 to 1.374; P = 0.997; Fig. 5A) or at 12 months (RR = 1.121; 95% CI = 0.493 to 2.548; P = 0.785; Fig. 5B) between SS and comparator splint groups including relax splint and full-arch NOS.

8. Adverse effects

See Table 3 for adverse events reported by the authors of the included RCTs.

9. Quality of the Evidence (GRADE)

Review authors pooled in the meta-analysis RCTs that reported similar outcomes. The reasons for the low quality of evidence were the high risk of bias, small sample size of participants in each meta-analysis (< 400 total subjects per meta-analysis), and the small number of studies pooled in each meta-analysis (n = 3; Table 11).

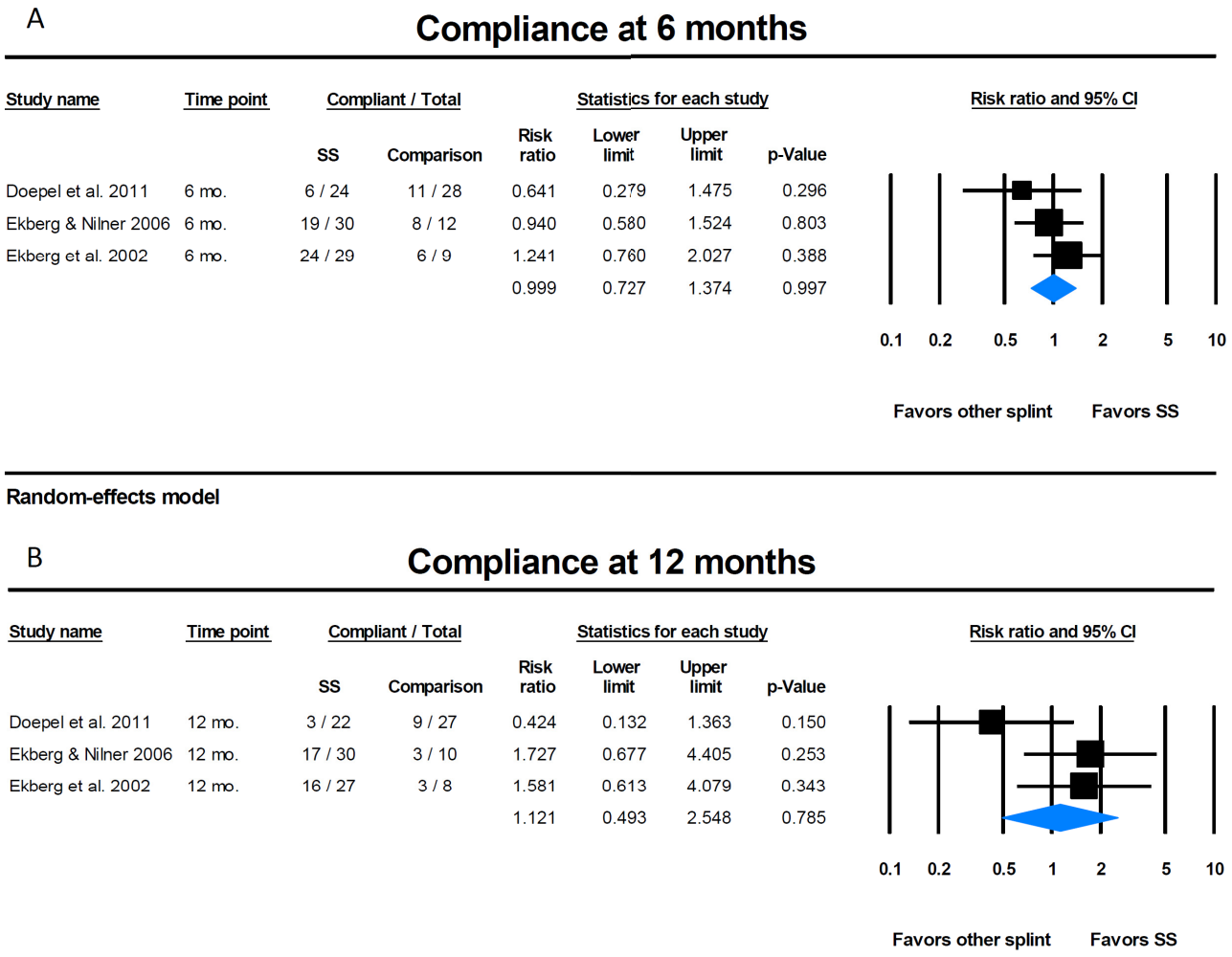


Fig. 5. Meta-analysis. Difference in post-treatment compliance between SS groups and comparison splints at 6 months (A) and 12 months (B) in patients with TMD comorbid with HA. Abbreviations: CI, confidence interval; HA, headache; mo, months; SS, stabilization splint; TMD, temporomandibular disorders.

DISCUSSION

1. Main findings

1) SS versus other splints

The main finding of this systematic review was a statistically significant reduction in HA frequency and HA intensity when reported in patients with TMD-HA comorbidities treated with full-arch coverage, hard resin, and maxillary SS (Tables 9-10; Figs. 3-4). This finding is consistent with that of previous reports. One study reported reduced HA frequency with mandibular SS use [45] at the one-year follow-up [63]. Similarly, an 8-year follow-up survey reported reduced HA frequency with intraoral appliance use in TMD patients with MFP, arthralgia, and TMJ osteoarthritis in 88% of the respondents [64]. Additionally, this finding is consistent with a study reporting that SS was equally effective in reducing HA intensity regardless of their fabrication process, whether conventionally made or computer-aided design/computer-aided manufactured (CAD/CAM) [65].

Comparison groups receiving a resilient/soft partial-arch maxillary splint with coverage extending anteriorly

Table 11. Summary of the evidence and quality of the findings (GRADE)

Stabilization splints compared to comparison splints for the treatment of "TMD comorbid with HA" *					
Outcomes	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Comparator splint	Risk difference with SS (95% CI)
HA Intensity (scale 0-10)	131 (3 studies* [53][57][59]) 2-3 months	⊕⊕⊖⊖ LOW†‡ due to risk of bias, imprecision	N/A	N/A	The mean HA intensity in the SS groups was 0.246 units lowerthan in the comparison splint groups (1.075 lower to 0.584 higher)
Compliance with splint use at 6 months	132 (3 studies* [46][57][58]) 6 months	⊕⊕⊖⊖ LOW†‡ due to risk of bias, imprecision	RR 0.999 (0.727 to 1.374)	510 per 1000	1 fewer patient was compliant in the SS groups per 1000 than in the comparison splint groups (from 139 fewer to 191 more)
Compliance with splint use at 12 months	124 (3 studies* [46][57][58]) 12 months	⊕⊕⊖⊖ LOW†‡ due to risk of bias, imprecision	RR 1.121 (0.493 to 2.548)	333 per 1000	40 more patients were compliant in the SS groups per 1000 than in the comparison splint groups (from 169 fewer to 516 more)

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 the effect and is likely to change the estimate.

* "HA concomitant with MFP" [57]; MFP comorbid with TTH [58]; capsulitis/synovitis comorbid with TTH [46]; MFP comorbid with episodic migraine with or without aura [59]; MFP + Disc displacement mix comorbid with "general HA" [53].
†All studies assessed at high risk of bias.
‡Small sample size (< 400 total participants).

Abbreviations: CI, confidence interval; DD, disc displacement; HA, headache; MFP, myofascial pain; RR, risk ratio; SS, stabilization splint; TMD, temporomandibular disorders; TTH, tension-type HA.

from the cuspids (Relax) [57] or a hard partial-arch maxillary splint with coverage of the maxillary central incisors only (NTI) [59] showed statistically significant improvements in HA intensity, and the resilient/soft partial-arch maxillary splint (Relax) [57] also showed significant improvement in HA frequency. These findings are consistent with previous studies using non-SS intraoral appliances that resulted in reduced HA in patients with TMD-HA comorbidity [33,45,63]. In addition, soft splint therapy reportedly reduced both intensity and frequency for migraine and "tension vascular HA", but not "tension HA" [63]. Another study reported that both a resilient/soft splint and an NOS reduced HA frequency at 6 and 12 months in patients with TMD [33].

No differences were found in HA intensity between SS and other non-SS splints (resilient/soft partial-arch maxillary splint [Relax], hard partial-arch maxillary splint [NTI], and full-arch maxillary NOS) for various time intervals (3 months [53], 6 months [59], and 12 months [57]). This finding is not consistent with two studies that reported that the improvement in HA frequency was greater in the SS group than in the NOS [46,58]. Therefore, further research is required.

2) SS versus other treatments

Combination therapy of SS with propranolol was more effective in reducing HA intensity for migraine with or without aura comorbid with MFP than monotherapy with either SS or propranolol [59]. Combination therapy of counseling with SS did not provide any significant differences for HA attributed to TMD comorbid with MFP when compared to counseling without SS [9]. This finding is inconsistent with a previous study, which reported that occlusal splint therapy resulted in greater HA reduction when occlusal splint therapy with no patient education was compared to TMD patient education without occlusal splint therapy [44].

Improvement in HA intensity ($P < 0.025$) and frequency ($P < 0.025$) were significantly better in the SS group than in patients receiving unspecified neurologists' treatment during a 6-week trial [62]. This study is

contrary to current HA medicine practices, which include triptans, botulinum toxin A, calcitonin gene-related peptide (CGRP) monoclonal antibodies, and receptor blockers such as gepants, vagal nerve stimulation, supraorbital nerve stimulation, cognitive behavioral therapy, and a number of other medications and therapies to address HA, including TTH or migraine [66-68].

2. Heterogeneity of the review

Clinical heterogeneity was found in this systematic review and included a variety of comparison and active interventions (Table 3), TMD and HA diagnostic criteria (Table 5), duration of the treatment (6 weeks to 1 year, Table 4), times the splint was worn (24 hours, only at night, or as needed, Table 4), and the provider of the splint (Table 8). Heterogeneity of outcome measurements and comparison groups prevented us from performing a meta-analysis of HA frequency and other outcomes.

TMD diagnostic criteria: Criteria for TMD changed over the timeline of the publication of the included studies (1988-2015), and the authors used different diagnostic criteria (Table 5) [69-72]. However, it is unclear how this might have affected the results.

HA criteria: HA diagnoses included in the studies were heterogeneous, as were the HA patient sample populations under study (Table 5).

Comparison group: SS was compared to other intraoral appliance designs [46,53,57-59], jaw exercises [60], unspecified neurological treatment [62], occlusal equilibration [61], and counseling [9] (Table 3). Due to the fact that these are all active interventions that may also work in treating HA, not true placebo, the meta-analysis may not show a significant effect of SS compared to the comparison group. Due to the heterogeneity of the comparative interventions, the authors conducted a subgroup analysis with three studies comparing SS to other splints for HA intensity, but could not perform a meta-analysis for HA frequency or other comparison groups.

Gender: Both genders were represented by a majority of females, which corresponds to the gender prevalence of patients with TMD-HA comorbidity [9] (Table 3).

Study duration: Review authors could not comment on the long-term effects over 12 months due to the study's duration by design (Tables 4 and 8).

Daily splint use: Further studies are needed to understand the best prescribed use of the splint for specific TMD-HA comorbidities (Table 4).

Provider of the interventions: In spite of the clinician's training heterogeneity, all the SSs were full-arch coverage, hard resin, and maxillary design; therefore, minimal effect due to training differences is anticipated (Table 8).

Setting: The RCTs analyzed in our systematic review were conducted in educational institutions at the university level, which might only represent advanced cases that required specialist care. However, patients who have not been referred to advanced educational settings should also be selected in RCTs in order to have a better understanding of TMD in the general population.

3. Biases, co-interventions, and confounders in the studies

Protocol deviations: In order to avoid unnecessary pain to the patients or less effective treatment, in two RCTs, the participants were invited to change splint design if they were unhappy with the treatment outcome or splint assignment at 10 weeks [53,57]. Patients who reported a negative treatment outcome or discomfort had their appliances readjusted or were given a new appliance at 10 weeks [46,58] (Table 4). These studies were assessed as having a high risk of bias.

Co-interventions: Bias in the study can be introduced when patients receive treatment other than the intervention under study. This could change treatment outcomes if the co-intervention had an effect on the outcomes being measured. All included studies had co-interventions (Table 4).

Other biases could have been introduced in the studies via unbalanced groups at baseline in age or HA intensity [57] or large numbers of dropouts during the study [9,46, 57,58] (Table 4).

4. Compliance with splint use and adverse events

Meta-analysis showed no significant difference in compliance with splint use at 6 or 12 months between SS groups and other splint designs ($P > 0.05$; Fig. 5a and 5b). Patients using SS reported higher compliance with splint use than those using full-arch maxillary NOS [46,58], but less compliance with splint use at 6 and 12 months than those using resilient/soft partial-arch maxillary splint (Relax) [57]. Overall, the review authors found no significant difference in compliance with splint use in our meta-analysis of three studies [46,57,58].

Fricton et al. [73] found that compliance with SS use was good for TMD pain if well fitted and not bulky. Although not reported in the included RCTs, the literature reports negative outcomes with the hard partial-arch maxillary splint (NTI), including aspiration of the splint [53], increased temporomandibular sounds [54], and irreversible occlusal changes, such as posterior tooth intrusion/anterior tooth intrusion [53,74]. Malocclusion resulting from intraoral appliance use and unfavorable internal TMJ changes are more likely with hard partial-arch maxillary splints (NTIs) and resilient/soft partial-arch maxillary splints (Relax) than with SS [55]. Therefore, partial-arch maxillary splints may carry a higher risk of adverse outcomes than SS. Further studies are required to confirm these results.

5. Overall completeness and applicability of the evidence

Four electronic databases were searched for RCTs published in English (The Cochrane Library, Medline via PubMed, Web of Science, and EMBASE) up to January 28, 2020. It is important to discuss the applicability of the included studies reported in this systematic review. Both genders were represented by a majority of females, which corresponds to the gender prevalence of patients with TMD-HA comorbidity [9]. Geographically, the included studies were conducted in five countries, with patient participation limited to those in Northern European countries and Brazil, without representation of the rest of the world's population, affecting its external validity. Therefore, any conclusion or recommendations drawn from these results cannot be reliably applied to other geographic areas without further corroboration.

Another key research design issue is that the included RCTs were conducted at teaching institutions and hospitals. These treatment locations may reflect patients with greater TMD-HA comorbidity complexity and may not accurately represent patients with TMD-HA comorbidity outside of these settings. Clinicians cannot truly rely on the findings if patient TMD-HA comorbidity complexity is different or if clinicians cannot mimic the settings in which the studies were conducted. Further studies outside these settings are required.

The mean patient age in the included RCTs fairly represents reported adult patients worldwide with TMD-HA comorbidity; however, the pediatric/adolescent and geriatric populations are not well represented. Comorbidity of TMD and HA disorders can begin in the pediatric/adolescent population with a different presentation/phenotype than that seen in adults. Adult TMD-HA comorbid treatment regimens may not be efficacious in pediatric/adolescent patients. Similarly, geriatric populations may require modification of TMD-HA comorbid treatment regimens for efficacious care of their particular needs. Further studies are needed in pediatric/adolescent and geriatric populations.

6. Implications for research

With regard to the included RCTs, further research should minimize bias by blinding investigators and subjects/patients during the entire study period. In addition, a proper computer randomization scheme with allocation concealment achieved at the beginning of the study using sealed envelopes or other similar means must be part of the study protocol. Furthermore, protocol deviations or co-interventions such as counseling, physical therapy, occlusal adjustments, the use of other dental appliances, and infrared laser should always be recorded in both intervention and control groups and kept to a minimum or eliminated if possible. No rescue

medications such as analgesics, anti-inflammatories, or HA medications should be allowed unless absolutely necessary. Relevant medication information (e.g., medication type and dosage, when taken during the study and the duration of the effect of the medication) must be recorded as well. For RCTs with greater clinical implications, larger samples of more diverse patients and longer follow-up periods are necessary. The current included studies had a maximum of 111 patients and follow-up periods of up to 12 months. Ethical considerations prevent researchers from denying the standard of care treatment and/or rescue medications for treating patients' pain in long-term studies, thereby making it difficult to develop long-term recommendations based on short-term studies. Strategies that can introduce bias in the study, such as additional splint adjustments, changing splint design assignments, or modification of splint design during the course of the RCT, should be documented and used with great discretion.

All included RCTs used cointerventions in their SS and comparison groups, suggesting that further research on combination therapy for patients with TMD-HA comorbidity is needed to understand which treatment strategies result in better patient outcomes.

TMD-HA comorbid-specific surveys and standardized outcome questionnaires should be developed to provide easily accessible patient-centered measures of pain intensity, frequency, chronicity, comorbidities, and other influencing factors. Recognizing TMD-HA comorbidity in all of its complexities is important to develop treatment strategies that result in satisfactory treatment outcomes. For example, having a diagnostic classification code specific for TMD-HA comorbidity may be beneficial in reducing barriers to more effective treatment of both TMD and HAs by facilitating access to dental/orofacial as well as medical care, along with insurance reimbursement for these patients.

Finally, to understand the scope of TMD-HA comorbidity over the lifespan, how their presentations change based on age, gender, race/ethnicity, socioeconomic status, duration of illness, and how other comorbidities impact these patients and our ability to treat them effectively, more epidemiologic data are needed, particularly population studies. Similarly, research funding should be prioritized to better understand TMD-HA comorbid development in children and adolescents to identify when it is the most efficacious time to intervene to prevent the development of TMD-HA comorbidity, and by what methods. Increased collaboration between dentists and physicians in research teams could bring further clarity to dentistry/orofacial pain and HA medicine. Multi-site clinical trials with research teams including dentists, physicians, and statisticians will bring different skills, knowledge, insight, and clarity to bear on common problems and related issues for patients with TMD-HA comorbidity. Guideline development to coordinate TMD-HA comorbidity diagnosis and management for patients with specific demographics having specific TMD diagnoses as well as specific HA diagnoses across dentistry/orofacial pain and medicine should improve patient outcomes and is a worthwhile goal. Identifying barriers and their solutions, effective treatment, and good outcomes for all patients with TMD-HA comorbidity is an important research priority deserving of funding.

7. Implications for clinical practice

Incorporating SS therapy as a non-pharmacological intervention for patients with TMD-HA comorbidity may reduce HA intensity and HA frequency as part of a coordinated combined treatment strategy in collaboration with their physicians. Several included RCTs suggest that SS therapy may decrease HA intensity and HA frequency in patients with TMD-HA comorbidity of migraine. Specifically, SS therapy in patients with MFP-TTH comorbidity may result in reduced HA intensity and frequency. Additionally, using a non-pharmacologic intervention to reduce HA intensity and HA frequency in patients with TMD-HA comorbidity may be beneficial in polypharmacy patients, patients with contraindications to medications normally used to treat TMD and HA, and those patients whose personal preference is to avoid

medications. Having a variety of coordinated treatment strategies, based on the patient's diagnoses, medical history, demographics, preferences, and lifestyle will enable clinicians to help their patients in a patient-centered approach.

Closer collaboration between dentists and physicians in treating patients with TMD-HA comorbidity could improve patient outcomes and may be facilitated by changes in insurance reimbursement patterns. It is important for clinicians to remember that just as there are many types of TMD, there are many types of HA, some of which are deadly [20]. Any suspicious or "red flag" HA should be referred immediately to an HA specialist/neurologist/physician. Similarly, "red flag" orofacial pain conditions should also be investigated expeditiously by an orofacial pain specialist or clinicians with overlapping knowledge and skill sets. Finally, the synergistic bidirectionality of TMD and HA in TMD-HA comorbidity should be considered in all patients, including children, adolescents, and the elderly, in order to minimize the development or impact of TMD-HA comorbidity and ultimately improve patient outcomes. In a clinical setting, if there is TMD, rule out HA; if there is HA, rule out TMD.

In conclusion, this systematic review found a statistically significant reduction in HA frequency in five studies and HA intensity in four studies in patients with TMD-HA comorbidity treated with full-arch hard maxillary SS. HA frequency in TTH comorbid with TMD diagnoses of either MFP or capsulitis/synovitis was improved significantly better with SS than full-arch maxillary NOS in two studies. Meta-analysis showed no statistically significant difference in improvement of HA intensity at 2-3 months with comparison splints (partial-arch resilient/soft maxillary [Relax], full-arch maxillary NOS, and partial-arch hard maxillary [NTI]), or compliance with splint use at 6-12 months with comparison splints (Relax and full-arch maxillary NOS) versus the SS group in patients with various TMD-HA comorbidities. Not every study reported p-values for HA intensity and HA frequency. In addition, the quality of the evidence was low because of the high risk of bias and small sample sizes. No major adverse effects were noted in this review for SS, although partial-arch intraoral appliances have a higher adverse risk profile than SS, including intraoral appliance aspiration [53], increased TMJ sounds [54], or permanent occlusal changes [53,55]. The findings of this review support additional research to clarify the effect of maxillary SS therapy in patients with TMD-HA comorbidities. RCTs with more participants with varying comorbidities, demographics (age, ethnic/racial, geographic location, socio-economic, and gender), study design changes that minimize the risk of bias, and increase active treatment duration with longer follow-up are needed to confirm the results of this review and increase applicability. Furthermore, additional studies regarding common pathophysiologic mechanisms of TMD-HA comorbidity and the bidirectionality of TMD and HA are still needed. The authors could not comment on the possible effects of SS on patients with primary HAs without diagnosed TMD, since review authors excluded the studies regarding this topic.

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