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SYSTEMATIC REVIEW

Is the therapeutic effect of occlusal stabilization appliances more than just placebo effect in the management of painful temporomandibular disorders? A network meta-analysis of randomized clinical trials

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ABSTRACT

Statement of problem. Occlusal devices, particularly the stabilization appliances, have been commonly used as treatment for painful temporomandibular disorders (TMDs). However, the mechanisms of action of these devices are still unclear, including the role of the placebo effect in the pain management.

Purpose. The purpose of this network meta-analysis was to identify to what extent the degree of efficacy of stabilization appliances in the management of painful TMDs arises from the placebo effect only or whether it arises chiefly from an actual effect.

Material and methods. An electronic search was undertaken to identify randomized clinical trials (RCTs) published up to April 2020, comparing the efficacy of the stabilization appliances in patients with painful temporomandibular disorders, with nonoccluding appliances (active placebo), and untreated controls (passive placebo). Outcome variables were pain intensity at follow-ups, the proportion of participants reporting pain improvement, and the number needed to treat. The quality of evidence was rated as per the Cochrane tool for assessing risk of bias. Mean difference was used to analyze via frequentist network meta-analysis by using the STATA software program.

Results. Treatment with stabilization appliances showed a significant reduction in pain intensity when compared with the other groups; but, the lower pain intensity at follow-ups in favor of stabilization appliances when compared with nonoccluding appliances was not statistically significant. However, a significantly higher number of participants reported pain improvement after treatment with stabilization appliances when compared with those treated with nonoccluding appliances or untreated participants.

Conclusions. This network meta-analysis showed no significant difference in reported pain intensity at follow-ups between the treatment of painful TMDs with stabilization appliances or nonoccluding appliances (active placebo). However, a significant difference in participants reporting treatment satisfaction with reduced pain, and a significantly lower number needed to treat in favor of stabilization appliances were found. Patient-reported treatment satisfaction probably included more domains than just pain intensity, such as improvements in physical functioning and psychosocial factors, and deserves further investigation. The authors concluded that stabilization appliances treatment efficacy is beyond the placebo effect. (J Prosthet Dent 2020;■:■-■)

Different treatments are available for patients with painful temporomandibular disorders (TMDs),[1] including counseling,[2] physiotherapy,[3,4] jaw exercises,[2,5] pharmacologic treatment,[6] behavioral medicine,[7,8] physical treatments, including acupuncture,[9,10] transcutaneous electrical nerve stimulation (TENS)[11] heat and cold

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Clinical Implications

Stabilization appliances seem to have a treatment efficacy beyond the placebo effect and can be suggested as one of the initial treatment approaches for patients with painful temporomandibular disorders. However, the evaluation of the effect of the treatment must include more domains than just change the pain intensity. Based on the outcome of this systematic review as well as that of other studies, pain intensity is not an appropriate treatment outcome measure by itself but should be used in combination with other domains such as physical functioning.

application,[12,13] and occlusal appliances.[14,15] However, no panacea has been identified for painful TMD.

For many years, occlusal appliances have been the most common treatment for painful TMDs, with the stabilization appliances (SA) being one of the most used.[2] The most common type of SA, the Michigan splint, has been reported to reduce TMD pain of muscular origin[16-18] and is also effective in the treatment of retrodiscitis of the temporomandibular joint (TMJ),[19] as well as in decreasing parafunctional activity.[20-24] The SA should have a flat, smooth surface in polymethyl methacrylate against the opposing teeth and can be designed with or without palatal coverage.[25]

Although the use of occlusal appliances in the management of painful TMDs is evidence based, the mechanisms of action are still unclear and have been questioned.[14,25-28] Possible mechanisms include a change in the reflective pattern of the masticatory muscles, a decrease of loading of masticatory muscles and of the TMJs, increased awareness of parafunctional activity, and also the placebo effect.[17,28,29] Nonoccluding appliances can be used to assess the placebo effect. However, these have a possible treatment effect because they can affect sensory, as well as cognitive awareness,[30-32] and have been reported to have a pain-reducing effect.[33]

The placebo effect can be described as a mind-body phenomenon where psychological processes affect disease symptoms.[34] While a placebo can amplify the effect of a given treatment, its opposing component, the nocebo, can depress this same effect.[35] Furthermore, there are indications that the placebo effect and the patient-doctor or patient-researcher relationship seem to have the same mechanisms of action regarding biochemical, cellular, and physiological changes.[34] Thus, although supporting evidence seems to exist for different management strategies, one has also to consider how large the extent of the efficacy is from the actual treatment or the placebo and nocebo phenomena, as well as the effect of the patient-doctor or patient-researcher relationship.

Therefore, the purpose of this network meta-analysis (NMA) was to identify to what extent the degree of efficacy of SA in the management of painful TMDs arises from the placebo effect only or whether it arises chiefly from an actual effect. The hypothesis was that the actual beneficial effects of SA in the management of patients with painful TMDs would be beyond the placebo effect.

MATERIAL AND METHODS

This NMA followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols PRISMA-P, (Supplementary Table 1)[36], in combination with the NMA of healthcare interventions.[37] Furthermore, this NMA was registered in PROSPERO with No. CRD42020178231.[38]

The 3 focused questions were as follows: Is the therapeutic effect of occlusal stabilization appliances more than just a placebo effect? Is there any difference in therapeutic effect regarding pain intensity using SA, nonoccluding appliance (active placebo), or control/no treatment (passive placebo)? and Does the existing scientific evidence support the treatment of painful TMDs with SA?

Relevant randomized controlled trials (RCTs), regardless of language and publication date, were retrieved by a systematic search of Medline, Embase, CINAHL, the Cochrane Central Registry of Controlled Trials (CENTRAL), and Scopus. The time frame for the search strategy was from the inception of each database to April 22, 2020 (Supplementary Table 2).

Based on the PICOTS (population, intervention, comparator, outcomes, time, and setting/study design) concepts,[39] the following inclusion criteria were adopted. Patients (P): the studies eligible for inclusion in this NMA were those comprising only adult participant with myogenous, arthrogenous, or mixed TMD pain (both myogenous and arthrogenous). The TMD classification had to be based on either the Research Diagnostic Criteria for TMD (RDC/TMD)[40] or the Diagnostic Criteria for TMD (DC/TMD).[41] Intervention (I): RCTs investigating complete-coverage flat hard or resilient SA in the mandible or in the maxilla. Comparator (C): the placebo groups included either an active placebo group using a nonoccluding appliance (including passive nonoccluding appliances) or a passive placebo group using no treatment (including participants who did not receive any treatment or those on a waiting list for treatment). Outcomes (O): the primary outcome was pain intensity scores using a visual analog scale (VAS). Time (T): all reported follow-up times. The follow-up times varied

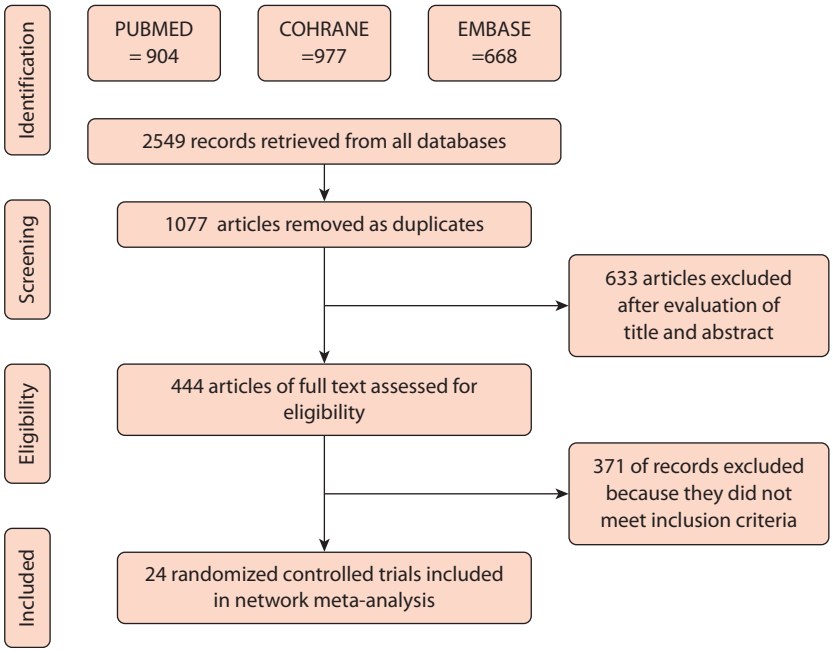

Figure 1. Illustration of PRISMA flow diagram regarding database search strategy. PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis.

from 1 month up to 12 months. Study design (S): RCTs that reported changes in pain intensity scores.

The following exclusion criteria were used: studies in which cointerventions did not include any group of the aforementioned interventions or controls, studies that did not adequately report the required data from the follow-ups to perform a meta-analysis such as the treatment-outcome means and standard deviations, nonrandomized clinical studies, case series, cohort studies and review articles, and publications using duplicated data.

Two of the authors (E.A., A.A.) investigated the risk of bias of RCTs independently by using the modified version of the Cochrane tool for assessing the risk of bias.[42,43] To identify the certainty of effect estimates from the meta-analysis for the outcomes of interest, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach of meta-analysis[43] was used. In the GRADE system, RCTs begin as high-quality evidence but may be down rated because of limitations in the study design (risk of bias). The limitations could be inconsistency, imprecision, indirectness, or publication bias.[44] Summary of confidence for the present evidence was estimated using the GRADEpro Guideline Development Tool (GDT) online software (https://gdt.gradepro.org/app/).[45]

Data were extracted separately by 2 researchers (E.A., A.A.) by using a specific form to summarize the following details: authors, study design, subgroup diagnosis, criteria used for TMD diagnosis, age of participants, male-to-female ratio, number of treatment groups, duration and/or frequency of treatment, outcomes investigated, and follow-up time. Any disagreements were resolved by discussion.

The network geometry was presented with a network plot, used to assess whether the different treatments were connected.[46] For continuous data, the treatment outcome value (VAS; pain intensity scores) was used to compute the mean difference (MD). For dichotomous data, the risk ratio (RR) was analyzed by using the number of participants reporting the treatment outcome of interest (that is VAS; pain intensity scores) at a follow-up time.

NMAs were conducted by using a frequentist framework via a random-effects model in a statistical software program (Stata Release 13, 2013; StataCorp LLC)[47] and the mvmeta command.[48] In addition, pairwise meta-analyses of all possible direct comparisons were performed using the Comprehensive Meta-Analysis Software program, version 2.[49]

The loop-specific approach using the ifplot command in the Stata program and "design-by-treatment" model using the mvmeta command was performed to evaluate the assumption of consistency at local and global levels.[48,50] In addition, the authors assumed a common heterogeneity estimate within each loop.[48] The ranking probabilities for all treatments at each possible rank for each group were analyzed by using the surface under the cumulative ranking (SUCRA) curve.[51] SUCRA can also be presented as a percentage of treatment that can be

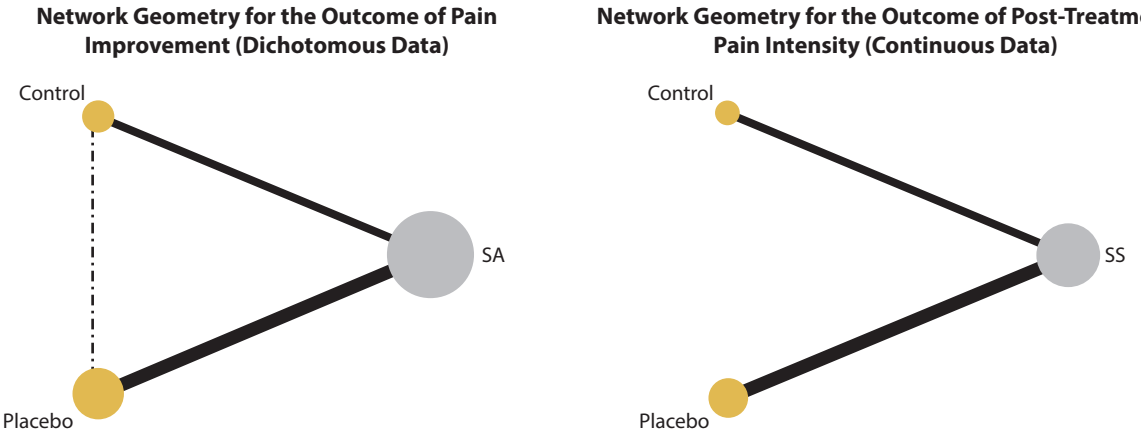

Figure 2. Network geometry. A, Outcome of post-treatment pain intensity. B, Outcome of pain improvement. ss, stabilization appliance.

ranked first without uncertainty. A rank-heat plot to visualize and present the treatment hierarchy across the outcomes of interest was produced.[51,52]

RESULTS

Based on the literature search, 1529 articles were identified. The search in all databases revealed a total of 2549 articles. Of these, 24 RCTs met the inclusion criteria and were included in this NMA.[17,49-72] Figure 1 is a flow chart of the process of article evaluation for inclusion in the present meta-analysis.

Regarding the continuous data, 11 RCTs evaluated pain intensity at follow-ups in a total of 508 participants. All these 11 RCTs included participants who received complete SA, in total 261 participants. Five of these 11 RCTs included 126 participants who received nonoccluding appliances, and 6 of these 11 RCTs included a total of 121 participants who were untreated controls. Of these 11 RCTs, 8 were on myogenous TMD pain, 1 on arthrogenous TMD pain, and 2 on mixed TMD pain, as shown in Figure 2A.

Concerning the dichotomous data, 16 RCTs investigated the improvement in pain in a total of 679 participants. These participants received either complete-coverage SA (16 RCTs, in total 361 participants), nonoccluding appliances (9 RCTs, in total 156 participants), were untreated controls (7 RCTs, in total 162 participants). Of these 16 RCTs, 9 were on myogenous TMD pain, 5 on arthrogenous TMD pain, and 2 on mixed TMD pain, as shown in Figure 2B.

Seven of the included RCTs had a low risk of bias, 12 an unclear risk of bias, and 5 a high risk of bias, as presented in Supplementary Table 3. The quality of evidence of the studies included in this NMA varied from moderate to very low quality. Factors downgrading the confidence of evidence were within the study limitations, imprecision, or incoherence. More details about the

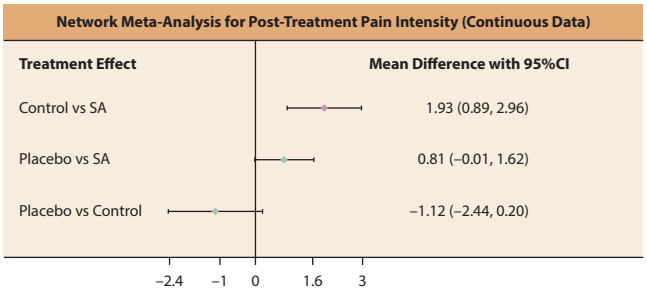

Figure 3. Forest plot of network meta-analysis regarding posttreatment pain intensity of nonoccluding appliances versus stabilization appliances (SA), untreated participants versus SA, and placebo versus control.

quality of evidence for all outcomes of the GRADE system are summarized in Supplementary Table 4.

A full description of the included studies, including the age and sex distribution of the participating individuals, treatment groups (SA/nonoccluding appliance/untreated controls) can be found in Supplementary Table 5. The results from each included individual RCT are reported in Supplementary Table 6. As for continuous data, the means, standard deviations, and sample sizes for the outcome regarding pain intensity are reported. As for dichotomous data, the number of participants reporting improvement in pain intensity is reported.

The results of the outcome variable pain intensity at follow-ups after treatment (continuous data) were as follows. Eleven RCTs evaluated the pain intensity at follow-ups in 508 participants with TMD who received SA, nonoccluding appliances, or were untreated controls. The follow-up time ranged from 1 to 12 months. The analysis was based on 8 RCTs on myogenous TMD pain, 1 on arthrogenous TMD pain, and 1 on mixed TMD pain.

In the direct metaB.-analysis, 6 RCTs assessed pain intensity in participants with painful TMDs and

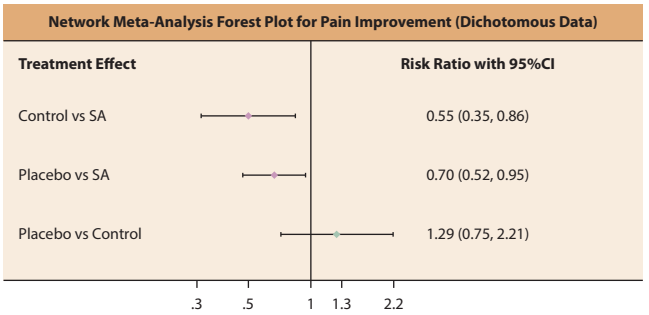

Figure 4. Forest plot of network meta-analysis regarding pain improvement of nonoccluding appliances (control) versus stabilization appliances (SA), untreated participants (placebo) versus SA, and placebo versus control.

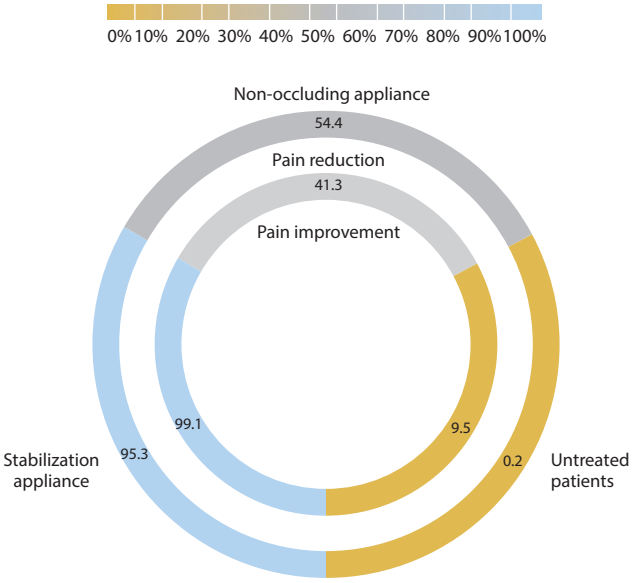

Figure 5. Illustration of rank-heat plot that identifies hierarchy of treatments for pain reduction (post-treatment pain intensity) and pain improvement.

compared SA (n=123 participants) and nonoccluding appliances (n=138 participants). Although there was a lower pain intensity at follow-ups in favor of SA when compared with nonoccluding appliances, this difference was not statistically significant (very-low-quality evidence; MD=-0.502, confidence interval [CI]: -1.322 to 0.318; *P*=.230), as shown in Supplementary Table 7B.

Five RCTs assessed pain intensity in participants with painful TMDs and compared SA A.(n=138 participants) and untreated controls (n=121). Treatment with SA showed a significant reduction in pain intensity when compared with the untreated controls (low-quality evidence; MD=-2.03, CI: - 2.7 to -1.2; *P*<.001), as shown in Supplementary Table 7A.

The NMA included 11 RCTs, 508 participants, and 3 comparisons, namely SA, nonoccluding appliances and untreated controls. The NMA showed that pain at follow-ups was significantly higher in the untreated control group when compared with SA (low-quality evidence; MD=2.04, CI: 1.26 to 2.8). Pain at follow-ups was reduced but not significantly, by treatment with SA when compared with nonoccluding appliances (low-quality evidence; SM=0.50, CI: -0.26 to 1.26), and significantly reduced after treatment with nonoccluding appliances when compared with untreated controls (low-quality evidence; DM=-1.54, CI:-2.6 to -4.6), as shown in Figure 3.

The results of the outcome variable pain improvement (dichotomous data), that is number of participants reporting pain improvement (risk ratio), were as follows. Sixteen RCTs evaluated changes in pain reduction in 679 participants with painful TMDs who received SA, nonoccluding appliances, or were untreated controls. The follow-ups time ranged from 1 to 12 months. The analysis is based on 9 RCTs on myogenous TMD pain, 5 on arthrogenous TMD pain, and 2 on mixed TMD pain.

The direct metaC.-analysis showed a significantly higher number of participants reporting pain improvement after treatment with SA (n=361) when compared with treatment with nonoccluding appliances (n= 156) (moderate-quality evidence; RR=1.37, CI: 1.15 to 1.64; *P*=.001) (Supplementary Table 7D), as well as when compared with untreated controls (n=162) (low-quality evidence; RR=1.51; CI: 1.16 to 1.98; *P*=.002), as shown in Supplementary Table 7C.

The NMA showed a significantly higher number of participants reporting pain improvement after treatment with SA when compared with nonoccluding appliances (moderate-quality evidence; RR=0.70; CI: 0.52 to 0.92) and when compared with untreated controls (low-quality evidence; RR=0.55; CI: 0.35 to 0.86). However, there was no statistical difference in number of participants reporting pain improvement between after treatment with nonoccluding appliances and with untreated controls (very low-quality evidence; RR=1.29; CI: 0.75 to 2.2), as shown in Figure 4.

Regarding treatment ranking from the continuous data, which was pain intensity at follow-ups, the most effective treatment to reduce pain intensity at follow-ups ranging from 1 to 12 months was SA (95.3%; low-quality evidence), followed by nonoccluding appliances (54.4%; low-quality evidence), and finally untreated controls (0.2%; very low-quality evidence), as shown in Figure 5 and Supplementary Figure 1.

When it comes to the treatment ranking from the dichotomous data, the RR was based on number of participants reporting pain improvement. The most effective treatment to reduce pain in participants with painful TMDs at follow-ups ranging from 1 to 12 months was SA (99.1%; moderate-quality evidence), followed by nonoccluding appliances (41.3%; low-quality evidence), and finally untreated controls (9.5%; very low-quality

evidence), as shown in Figure 5 and Supplementary Figure 1.

The additional analyses for continuous data revealed that the weighted mean of pain intensity at follow-ups were 2.49 (CI: 1.83 to 3.14) for SA, 2.94 (CI: 1.67 to 4.20) for nonoccluding appliances, and 4.70 (CI: 3.50 to 5.90) for untreated controls (Supplementary Tables 8A-C). For dichotomous data, however, the proportions of pain improvement at follow-ups were 63% (CI: 57% to 68%) for SA, 48% (CI: 40% to 55%) for nonoccluding appliances, and 31% (CI: 18% to 49%) for untreated controls (Supplementary Table 8D-F).

Regarding the number needed to treat (NNT), values of 3.4 for the SA group, 6.7 for the nonoccluding appliance group, and 7.1 for the untreated control group were found. This means that 3.4 patients with painful TMDs need to be treated with SA to get 1 responder, while it takes 6.7 patients treated with a non-occluding appliance to get 1 responder and finally 7.1 of the untreated controls to get 1 responder.

For the all outcomes variables (post-treatment pain intensity and pain improvement), loop specific tests did not detect any triangular or quadratic loops due to inconsistency between direct and indirect evidence (local inconsistency). Similarly, based on the design-by-treatment interaction model to test a global inconsistency in the networks, no significant inconsistency was identified within the evidence networks as a whole ($P>.05$).

DISCUSSION

The main finding of the present study was that the efficacy of the SA is real and beyond the placebo effect, with a significant pain-reducing effect at follow-ups and a smaller NNT (3.4) among the 3 groups studied in this NMA. The SA showed significantly greater pain reduction than untreated controls, a finding consistent with previous studies.[33,53,55,67,69,73] Although there was no significant difference in pain intensity levels at follow-ups between the SA and nonoccluding appliances, which was consistent with previous studies,[26,31,56,63] the proportion of participants reporting pain improvement at follow-ups was significantly higher for SA, both when compared with the nonoccluding appliance and with untreated controls, which also was consistent with previous studies.[30,31,62,74] Furthermore, the NNT was significantly lower for SA than for nonoccluding appliances and untreated controls and at the same level as treatments with topical and systemic analgesics[75-77] (naproxen, ibuprofen, and aspirin) and granisetron[78] and better than treatment with botulinum toxin A.[79] Finally, SA was ranked first as the most effective treatment for both pain intensity at follow-ups and the proportion of participants reporting pain improvement.

In this NMA, the nonoccluding appliance served as an active placebo group, while the untreated controls as a passive placebo group. Significant differences were not found between SA and nonoccluding appliances regarding pain intensity at follow-ups, but an actual placebo effect cannot be excluded because the nonoccluding appliances showed a significant pain-reducing effect when compared with untreated controls, which also was a conclusion of a systematic review from our group.[33] However, the pain-reducing effect of the nonoccluding appliances might not be an actual placebo effect, as they still have a certain actual treatment effect. They affect not only the cognitive awareness of the participant regarding parafunction but also the sensory awareness because of a change in the tongue position.[30-32] Moreover, the new intraoral condition, from the foreign object and the patient-doctor relationship, probably plays a role. It seems that, regardless of the design of the occlusal appliance, the initial response of most patients is positive where pain response is concerned.

A significant difference was found in participants reporting pain improvement and/or treatment satisfaction with SA and nonoccluding appliances but not in reported actual pain intensity at follow-ups. The most probable explanation is that reported treatment satisfaction and objective treatment evaluation is not only based on pain intensity. Pain intensity itself is not a reliable tool for assessing treatment efficacy because other factors seem to play a more important role in a patient's awareness of general improvement. Several studies have shown that treatment success reported by participants with painful TMDs is poorly correlated with changes in pain intensity[80,81] but is correlated with variables including physical functioning such as jaw movements and fatigue, individual patient characteristics such as psychosocial and behavioral aspects, and the presence of comorbidities such as depression, anxiety, and somatization.[80-84] Furthermore, by recognizing pain as a multidimensional experience,[85] future studies should not only include pain intensity as a single outcome variable but also supplement this with both cognitive (that is attentional modulation of pain)[86,87] and affective perspectives (that is emotional modulation of pain).[88-90] The lack of evaluation of physical and psychological treatment outcomes further strengthens the theory that changes in pain intensity might not completely answer for the treatment efficacy of SA. Instead, the number or percentage of responders to treatment is probably a more reliable outcome measure.

Although a single-dimension scale such as the VAS has been the most used scale for pain measurement, it is not capable of identifying all the changes, a limitation of most studies. Because data on how these different appliances affect physical and psychological factors such as

mouth opening, fatigue, and psychological distress are lacking, the reported treatment satisfaction with SA cannot be excluded from an actual difference in treatment efficacy on these variables. In addition, these factors seem to play a greater role in the evaluation of TMD treatment than just pain intensity.[80,81] Based on this, one can conclude that treatment with SA is better than treatment with nonoccluding appliances and untreated controls. The improvement observed in untreated controls, although not as significant as in the other groups, was also expected. As in many situations, including mild to moderate TMD symptoms, the regression to the mean and the time effect usually have a beneficial outcome on pain outcomes.

The placebo effect may be present in all these groups studied. Evaluation of the efficacy of a treatment outcome should always contain an evaluation of a probable placebo effect. The placebo effect has been shown to occur in at least half of the participants[91] and to be even greater in studies investigating analgesic mechanisms where placebo control groups were used.[92] Furthermore, the placebo effect has also been shown to be stronger in patients than in healthy controls and also in clinical trials compared with experimental studies.[93,94] One plausible explanation could be that the placebo effect mimics, at least partially, the selective serotonin reuptake inhibitor mediation.[91] This would, in turn, result in a positive placebo (treatment) effect on pain catastrophizing, pain disability, depressive symptoms, and trait anxiety, which are all factors associated with the multidimensional perception of pain. Consequently, this would result in decreased pain intensity at follow-ups and can explain why no significant differences were found between SA (active treatment) and nonoccluding appliances (active placebo),even though significantly more participants reported treatment satisfaction in favor of SA.[95] Taken together, this indicates that the treatment effect of SA is beyond the effect of placebo.

Limitations of this NMA include that because the interventions were occlusal stabilization appliances, blinding either only the participants or both participants and researchers was not possible. Therefore, the blinding component of participants and researchers was eliminated from the assessment tool for the risk of bias. Second, the performance bias, the reliability of the participant to follow instructions, could not be ensured, which could affect the outcome of the included RCTs because the primary outcome of the present study was pain, which depends on the participant's perception. Third, the follow-ups times were diverse, and fourth, owing to the small number of RCTs that could be included, it was not possible to differentiate between myogenous or arthrogenous TMD pain. However, these limitations might not have affected the outcome of the present NMA, as it investigated to which extent the treatment effect could be explained by the placebo effect and not which treatment approach is more beneficial. For instance, it was not the treatment effect of SAs on myogenous or arthrogenous TMD pain that was the main focus, but instead to what extent the placebo effect affected the treatment outcome with SAs.

Strengths of the present study included the GRADE system that was used to estimate the certainty of confidence for all outcomes to avoid overestimation and underestimation of evidence. Second, this study included not just active treatment (SA) and placebo treatment (active placebo) but also untreated controls (passive placebo). Third, only RCTs with Research Diagnostic Criteria for TMD and Diagnostic Criteria for TMD diagnoses of TMD were included; thus, there were no confounding factors regarding diagnosis. Fourth, a recent novel approach using NMA of RCTs was conducted.

CONCLUSIONS

Based on the findings of this NMA of randomized clinical trials, the following conclusions were drawn:

1. No significant difference was found in reported pain intensity at follow-ups between treating patients with painful TMDs with SA or nonoccluding appliances (active placebo).
2. A significant difference was found in participants reporting treatment satisfaction with reduced pain and a significantly lower NNT in favor of SA.
3. Patient-reported treatment satisfaction probably included more domains than just pain intensity, such as improvements in physical functioning as well as psychosocial factors, and deserves further investigation.
4. Based on these findings, the authors concluded that SA treatment efficacy is beyond the placebo effect.

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