Pharmacologic Interventions in the Treatment of Temporomandibular Disorders, Atypical Facial Pain, and Burning Mouth Syndrome. A Qualitative Systematic Review

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Aims: *To carry out a systematic review of the literature in order to assess the pain-relieving effect and safety of pharmacologic interventions in the treatment of chronic temporomandibular disorders (TMD), including rheumatoid arthritis (RA), as well as atypical facial pain (AFP), and burning mouth syndrome (BMS).* ***Methods:*** *Study selection was based on randomized clinical trials (RCTs). Inclusion criteria included studies on adult patients (≥ 18 years) with TMD, RA of the temporomandibular joint (TMJ), AFP, or BMS and a pain duration of > 3 months. Data sources included Medline, Cochrane Library, Embase, and PsychLitt.* ***Results:*** *Eleven studies with a total of 368 patients met the inclusion criteria. Four trials were on TMD patients, 2 on AFP, 1 on BMS, 1 on RA of the TMJ, and 3 on mixed groups of patients with TMD and AFP. Of the latter, amitriptyline was effective in 1 study and benzodiazepine in 2 studies; the effect in 1 of the benzodiazepine studies was improved when ibuprofen was also given. One study showed that intra-articular injection with glucocorticoid relieved the pain of RA of the TMJ. In 1 study, a combination of paracetamol, codeine, and doxylamine was effective in reducing TMD pain. No effective pharmacologic treatment was found for BMS. Only minor adverse effects were reported in the studies.* ***Conclusion:*** *The common use of analgesics in TMD, AFP, and BMS is not supported by scientific evidence. More large RCTs are needed to determine which pharmacologic interventions are effective in TMD, AFP, and BMS.* J OROFAC PAIN 2003;17:301–310.

Key words: orofacial pain, pharmacologic treatment, randomized clinical trials, systematic review, temporomandibular disorders

One national epidemiologic survey in the United States found that orofacial pain (other than tooth pain) has a prevalence of 10% in the adult population.[1] Orofacial pain includes pain conditions that are associated with the hard and soft tissues of the head, face, and intraoral structures.[2,3] Population-based studies have often not distinguished between different types of orofacial pain conditions. However, the most common subgroups of orofacial pain conditions are temporomandibular disorders (TMD), mucosal pain such as burning mouth syndrome (BMS), and atypical facial pain (AFP), including atypical odontalgia.[4,5]

Temporomandibular disorder is defined as pain related to the masticatory muscles, the temporomandibular joints (TMJs), or both.[6] Atypical facial pain and atypical odontalgia have been suggested to be of neuropathic origin.[7] Burning mouth syndrome is

associated with pain and burning sensations on the lips and in the oral cavity.[8]

These conditions are sometimes difficult to differentiate since they often coexist in the same patient. Many features of TMD pain—pain intensity, frequency of pain, and impact on daily activities—have been found to be similar to those of other pain conditions such as backache.[9] And as in other chronic pain conditions, elevated depression scores have been found for TMD, BMS, and AFP.[8,10,11]

Traditionally, clinical decisions have been based on knowledge gained through training, past experience, practice traditions, and the opinions of recognized authorities. This treatment approach has been questioned, and a more scientific, evidence-based approach has been recommended for managing TMD.[12] Evidence-based practice supports the translation of scientific evidence into clinical practice. In a systematic review of the TMD literature, it was found that less than 5% of the articles were classified as randomized clinical trials (RCTs).[13] Only a few systematic reviews in the epidemiology or management of orofacial pain and TMD have been published.[4,5,13–18]

In the management of chronic orofacial pain, the use of pharmacologic interventions has been suggested both as the main mode and as a complement to other treatment modes.[19] Population-based studies have shown that consumption of analgesics as well as other drugs because of pain is common.[20] Several textbooks and review articles have recommended the use of pharmacologic agents in the treatment of chronic orofacial pain.[2,21,22] Today, there is no "gold standard" in the pharmacologic treatment of chronic orofacial pain. The positive effects of the drugs must be evaluated in relation to possible adverse and toxic effects and possible dependency. An increasing number of harmful effects have been reported from, for example, nonsteroidal anti-inflammatory drugs (NSAIDs).[23,24] Since pharmacologic interventions are common—but efficacy and adverse events are unclear—a systematic review seemed important.

A systematic review is an overview of primary studies that contain a statement of objectives and a description of the materials and methods, and have been conducted according to explicit and reproducible methodology. One of the advantages of a systematic review is that the conclusions are more reliable and accurate than in a narrative review.[25]

The objective of this study was to carry out a systematic review of the literature in order to assess the pain-relieving effect and safety of pharmacologic interventions in the treatment of chronic TMD, including rheumatoid arthritis (RA) of the TMJ, as well as AFP and BMS.

Materials and Methods

Inclusion Criteria

Randomized clinical trials on pharmacologic treatment in adult patients (≥ 18 years) with chronic pain because of TMD, RA of the TMJ, AFP, and BMS and with a pain duration of 3 months or more were included in the review. Reports were included if they were randomized comparisons of pharmacologic drugs with other medications, placebo, or no treatment. The diagnostic criteria used were as follows: BMS was defined as oral mucosal pain with no known dental or medical cause for the symptoms; AFP was described as a deeply located throbbing or aching pain involving bony areas of the face (since there is no clear consensus on the definition of AFP, articles were accepted where the diagnosis AFP was reported); TMD was defined as a pain condition located in the TMJ and/or the masticatory muscles.

Exclusion Criteria

Nonrandomized and experimental studies were excluded from the review.

Literature Search

Published articles on RCTs of pharmacologic treatment of adult chronic pain patients with TMD, RA of the TMJ, AFP, or BMS were sought systematically. Searches were conducted in Medline, the Cochrane Library, Embase (January 1966 to October 2000), and PsychLitt (1974 to October 2000). The terms used were facial pain, temporomandibular joint disorders, burning mouth syndrome, randomized controlled trials, meta-analysis, controlled clinical trials, random allocation, double-blind method, single-blind method, placebos, toothache, and chronic disease. No restrictions were made on language or sample size. Reference lists of retrieved reports and review articles were hand searched. Unpublished reports, letters, and abstracts were not considered. Authors were not contacted for original data.

Procedure

Every report that could be described as an RCT was read independently by the 3 authors. Interobserver reliability was not analyzed. All studies were judged independently and consensus was achieved by discussion. The following data were extracted from each article: number of patients and

condition, design, pain duration, drug(s) tested, outcome measures, dose regimen, analgesic outcome, withdrawals, adverse effects and dropouts, quality score, and authors' conclusion. No attempt was made to analyze pre- and postcrossover data. However, washout periods are clearly stated in Table 1. The reviewer's opinion was based on the clinical relevance of the results. To assess the quality of the study, the reviewers assessed each article by a 5-point quality scale.[26] Reports that were described as randomized (words such as randomly, random, and randomization were used) were given 1 point. If the method of randomization was appropriate (table of random numbers, computer-generated), the report earned an additional point. Reports that were described as double-blind were given 1 point. If the double-blinding was appropriate (identical placebo, active placebo, or dummy), an additional point was given. Publications that reported withdrawals and dropouts were given an additional point. An RCT could earn a maximum of 5 points and a minimum of 1 point.

The pain-relieving effect, the main measurement outcome, was estimated by comparing pain intensity measurements reported as visual analog scale (VAS) scores or verbal rating scale scores following pharmacologic intervention compared with controls. Data showing any statistically significant difference ($P < .05$) between drugs or compared with placebo, as reported in the original publication, were extracted. Quality scoring and reviewer's opinion were achieved by consensus (vote-counting procedure).

Results

Four databases were systematically searched for articles. A total of 89 articles were identified with the search strategy. Of these, 42 were reviewed in full text. Besides one Spanish and one Italian article, all were in the English language. In all, 26 randomized studies were found, of which 11 were included in the study (Table 1). All 26 articles were found in Medline or the Cochrane Library. Fifteen randomized studies were excluded because of a lack of data on pain duration or age, dual publication, or unclear diagnosis (Table 2).

The median publication year was 1996 (1983 to 1999). The 11 studies that met the inclusion criteria had a total of 368 patients. Six of the studies had a crossover design (median size 25 patients, range 9 to 32) and in 5 comparisons with parallel groups were conducted (median size 39 patients, range 9 to 150). The follow-up period ranged from 1 hour to 1 year with a median of 4 weeks. Seven studies reported adverse effects, all of which were minor. In only 2 of 11 studies was the randomization adequately described according to the protocol.[26] The median quality score was 4. Four trials were conducted with TMD patients, 2 with AFP patients, 1 with BMS patients, 1 with patients with RA of the TMJ, and 3 with mixed groups of patients with TMD and AFP (Table 1).

The patients were referred to private clinics (n = 1) or orofacial pain clinics (n = 7), or patient referral was unclear (n = 3).

The pharmacologic interventions included amitriptyline, clonazepam, cocaine, diazepam, dothiepin, glycocorticoid, ibuprofen, a combination of paracetamol and codeine plus doxylamine, salmon calcitonin, sodium hyaluronate, sumatriptan, trazadone, and triazolam.

Analgesics and NSAIDs

In TMD patients, 1 study found that mersyndol, an analgesic (450 mg paracetamol, 9.75 codeine, 5 mg doxylamine × 2) was significantly more effective than a placebo.[27] It was difficult to determine which pharmacologic ingredient of mersyndol was most effective. Another study of TMD found that ibuprofen (600 mg × 4) was no better than diazepam or placebo. However, the combination of ibuprofen and diazepam was significantly more effective than placebo.[28]

Antidepressants

Amitriptyline was significantly better than placebo in a study on TMD and AFP. Interestingly, no difference was seen between low (10 to 30 mg) and higher (50 to 150 mg) doses of amitriptyline.[29] Another study found dothiepin to be significantly more effective than placebo in a mixed group of TMD and AFP patients.[30] The results of the study are difficult to interpret since large numbers of patients were excluded and 50% of the patients were allocated to occlusal appliance therapy, with an unclear influence on the results. For BMS, trazadone was found to be no more effective than the placebo.[31]

Benzodiazepines

In a study of TMD patients, clonazepam was found to be significantly more effective than placebo.[32] In another TMD study, triazolam was compared to placebo.[33] No pain reduction was found but sleep improved significantly. Both studies were on small patient groups, which makes it difficult to interpret the results.

Table 1 Pharmacologic Interventions in Chronic Temporomanibular Disorders, Atypical Facial Pain, and Burning Mouth Syndrome

Study/no. of patients/conditions	Design/study duration	Drug(s) tested	Outcome measures	Dose regimen	Analgesic outcome results	Withdrawals/ adverse effects	Conclusions
Al Balawi et al[36] 19/AFP	Crossover 2 × single treatment/ Washout 3–6 wk	Sumatriptan, placebo	MPQ: sensory, affective, total pain scores	Single dose sumatriptan 0.5 mL (6 mg), saline 0.5 mL sc	1 h: sensory and total pain scores (ns), affective pain score score ($P < .05$); 2 h: sensory, affective, total pain scores ($P < .05$)	1 dropout with sumatriptan since pain symptoms were resolved; higher frequency of adverse events with sumatriptan than placebo	Author: positive effect Quality score: 4 points Reviewer opinion: positive result at 2 h, not for clinical use
DeNucci et al[33] 20/TMD	Crossover 2 × 4-d trial/ Washout 3 d	Triazolam, placebo	Pain intensity and discomfort	Bedtime single dose 0.125 mg increased to a maximum of 0.5 mg/night (mean fourth night 0.42 mg) and placebo	No significant difference	1 patient excluded because no pain reported at baseline No withdrawals	Author: no effect Quality score: 4 points Reviewer opinion: negative results, not conclusive, small study
Feinmann[30] 150 50/ TMD 43/AFP 57/unclassified	4 parallel groups 9-wk trial	Dothiepin + biteguard, placebo + biteguard, dothiepin, placebo	Verbal pain scale (0–4), Montgomery-Asberg Depression Rating Scale, Eysenck personality questionnaire	Bedtime single dose dothiepin titration in the range 25–150 mg/day; mean daily dose 130 mg and placebo	Pain relief: dothiepin ($P < .05$) compared with placebo; no significant difference in depression rating	57 patients excluded: 24 were unwilling to cooperate, 12 did not tolerate dothiepin, 15 spontaneously recovered, 6 had dental causes for the pain; excluded patients were not included in the statistical analysis; drowziness, dry mouth, dizziness, drug-related withdrawals not stated	Author: positive effect Quality score: 4 points Reviewer opinion: not conclusive, high dropout rate, effect of biteguard unclear
Gerschman et al[27] 30/TMD	Crossover 2 × 1-wk trial No washout	Mersyndol, placebo	VAS pain intensity, global estimate	Mersyndol (paracetamol 450 mg, codeine 9.75 mg, doxylamine 5 mg) and 2 placebo tablets every 4 h	VAS pain: mersyndol ($P < .001$) compared with placebo, global estimate mersyndol ($P < .01$) placebo	1 withdrawal due to no intention to participate, 1 dropout since pain was resolved; relaxed feeling; mersyndol (8/30), placebo (4/30)	Author: positive effect Quality score: 4 points Reviewer opinion: positive results, low dose of codeine, the analgesic effect probably related to paracetamol
Harkins et al[32] 20/TMD	2 parallel groups 30-d trial	Clonazepam, placebo	VAS (observer): pain intensity of TMJ, masseter, temporalis during palpation VAS (patient): global pain levels in TMJ, head, neck	Bedtime single dose 0.25 mg, doses were increased weekly by 0.25 mg to a maximum of 1 mg daily and placebo	VAS (observer): left lateral TMJ ($P < .05$), left posterior TMJ ($P < .01$), right TMJ and temporalis and masseter (ns); VAS (patient): left TMJ, head and neck ($P < .05$), right TMJ (ns)	5 dropouts in the clonazepam group since pain was resolved, 7 in the placebo dropped out due to no improvement, 1 dropped out due to migraine, 1 patient had migraine, mild sedation	Author: positive effect Quality score: 3 points Reviewer opinion: not conclusive, small trial, high dropout rate
Kopp et al[34] 41/RA of TMJ	3 parallel groups 4-wk trial	Sodium hyaluronate, glycocorticoid, placebo	VAS pain intensity, global assessment	2 intra-articular injections (0.7 mL) 2 weeks apart, sodium hyaluronate 10 mg/mL, glycocorticoid 40 mg/mL, saline 9 mg/mL	VAS pain intensity glycocorticoid ($P < .01$) compared with saline; global estimate: no difference between groups	No withdrawals, no report of adverse effects	Author: positive effect Quality score: 2 points Reviewer opinion: positive effect for glycocorticoid intra-articulary; small sample size
Marbach and Wallenstein[37] 28 20/TMD 8/AFP	Crossover 4 × 1 single dose intranasal washout ≥ 1 wk	Lidocaine, cocaine 15%, cocaine 25%, placebo	VAS pain intensity, pain relief, mood	Single dose intranasal cotton pledgets (180 mg solution) lidocaine 4% in, cocaine 15% in, cocaine 25% in, saline in	Cocaine: 15% but not 25% significantly better ($P < .05$) than placebo in reducing pain; no significant effect on mood was observed	7 withdrawals no reason given; significant increase in blood pressure after 25% cocaine, 1 patient reported nausea after lidocaine	Author: positive effect Quality score: 3 points Reviewer opinion: not conclusive for chronic pain, not for clinical use

AFP = atypical facial pain; TMJ = temporomandibular joint; TMD = temporomandibular disorder; RA = rheumatoid arthritis; BMS = burning mouth syndrome.
MPQ = McGill Pain Questionnaire; VAS = Visual Analog Scale.
ns = no significance; in = intranasal; sc = subcutaneous.

Table 1 (continued)

Study/no. of patients/conditions	Design/study duration	Drug(s) tested	Outcome measures	Dose regimen	Analgesic outcome results	Withdrawals/ adverse effects	Conclusions
Schwartz et al[35] 9/AFP	Crossover 2 × 3-wk trial washout 1 wk	Salmon calcitonin, placebo	Digital pain scale, global assessment	Salmon calcitonin (1.0 mL) and placebo (1.0 mL) sc; placebo, salmon calcitonin injections were given 3 times a week (100 IU/mL)	No significant difference was seen in outcome measures	3 of 9 patients completed the entire 7-wk trial; reason for dropout was severe adverse effect. Adverse effects were reported by 58% following salmon calcitonin and 14% in placebo; most common adverse effect was nausea after salmon calcitonin	Author: no effect Quality score: 3 points Reviewer opinion: not conclusive, pilot study, few patients, high dropout rate, high frequency of adverse effects
Sharav et al[29] 32 20 TMD 2/TMD + AFP 5/AFP 1/unclassified	Crossover 3 × 4-wk trial washout 2 wk	Low dose: amitriptyline; High dose: amitriptyline, placebo	VAS pain intensity, MPQ, pain relief estimate, Hamilton depression inventory	Bedtime single dose of amitriptyline and placebo. Low dose: 10 mg increasing to max 30 mg/d (mean 23.6 mg), high dose: 50 mg increasing to max 150 mg/d (mean 129.4 mg)	Amytriptyline was superior to placebo in VAS and MPQ ($P < .01$), pain relief ($P < .05$). The analgesic effect did not differ between high- and low-dose amitriptyline; amitriptyline reduced pain in the depressed and nondepressed groups compared with placebo	1 dropout no information given; 3 patients dropped out due to poor adherence with protocol; no data on adverse effects	Author: positive effect Quality score: 4 points Reviewer opinion: positive results
Singer and Dionne[28] 49/TMD	4 parallel groups 4-wk treatment	Diazepam, ibuprofen, diazepam + ibuprofen, placebo	VAS pain intensity, pain relief, categoric pain, pain relief scales Spielberg State-Trait Anxiety Inventory, Zung depression scale, depression adjective checklist	Ibuprofen 600 mg 4 tablets daily (total daily dose 2,400 mg), diazepam 2.5 mg 4 tablets daily (10 mg/d) increasing to max (20 mg/d)	VAS and categoric scale, diazepam + ibuprofen was superior to placebo + ibuprofen ($P < .05$), ibuprofen + diazepam were not significant compared with placebo; no significant difference in mood changes changes between the groups	10 patients dropped out: poor adherence (5), insufficient pain relief or spontaneous remission (2), and medical reasons (3); no data on adverse effects	Author: positive effect mainly related to diazepam Quality score: 4 points Reviewer opinion: positive for combination of ibuprofen and diazepam vs placebo, no long-term treatment because of risk of drug dependency high dropout rate, small sample size
Tammiala-Salonen and Forssell[31] 37/BMS	2 parallel groups 8-wk trial	Trazadone, placebo	VAS pain intensity, MPQ, global assessment, Beck's depression inventory	Bedtime single dose 100 mg/d increasing to 200 mg/d	No significant difference between groups in VAS pain intensity, MPQ, or depression score	7 in trazadone and 2 in placebo groups dropped out due to adverse effects; dizziness ($P < .001$) and drowsiness ($P < .05$) were more common in the trazadone group	Author: no effect Quality score: 4 points Reviewer opinion: negative results, small study

AFP = atypical facial pain; TMJ = temporomandibular joint; TMD = temporomandibular disorder; RA = rheumatoid arthritis; BMS = burning mouth syndrome.
MPQ = McGill Pain Questionnaire; VAS = Visual Analog Scale.
ns = no significance; in = intranasal; sc = subcutaneous.

Table 2 Randomized Clinical Trials Excluded from the Study

Study	Drug(s)	Reason for exclusion
Bogetto et al[55]	Paroxetine, amitriptyline, clordemetildiazepam, amisulpride	Unclear if pain or depression was treated
Feinmann et al[56]	Dothiepin	Dual publication (Feinmann[30])
Feinmann et al[57]	Dothiepin	Dual publication (Feinmann[30])
Franks[58]	Orphenadrine	No data on pain duration
Gallardo et al[59]	Carisoprodol	No data on pain duration, diagnosis unclear
Greene and Laskin[60]	Meprobamate	No data on pain duration or age range
Harrison et al[61]	Sumatriptan	Dual publication (al Balawi et al[36])
Lascelles[62]	Phenelzine, chlordiazeproxide hydrochloride	No data on pain duration, diagnosis unclear
Loldrup et al[63]	Clomipramine, mianserin	Unclear if pain or depression was treated
Rossi et al[64]	Prazepam	No data on pain duration
Sardella et al[65]	Benzydamine hydrochloride	No data on pain duration
Schwartz et al[66]	Carisoprodol	No data on pain duration or age range
Shin and Choi[67]	Indomethacin	Pain duration and age range unclear
Seltzer et al[68]	Dietary tryptophan	Pain duration and age range unclear
Stockstill et al[69]	L-tryptophan and dietary instruction	No data on age range

Miscellaneous

Corticosteroids (glycocorticoid) injected intra-articularly in patients with RA of the TMJ were found to be significantly more effective than saline.[34] In the same study, sodium hyaluronate did not differ significantly from either placebo or glycocorticoid. Salmon calcitonin administrated subcutaneously was no better than placebo in a small AFP study with a high dropout rate.[35] In one study on AFP patients, sumatriptan was found to be significantly superior to placebo.[36] Finally, in a single-dose study on a mixture of TMD and AFP patients, it was found that intranasal inhalation of cocaine was significantly better than placebo.[37]

In 8 of the studies, the authors concluded that a positive pharmacologic effect of the relevant drug had occurred (Table 1). The reviewers judged the positive effect of the treatment to be clinically relevant in only 4 of the 8 studies. However, no particular treatment could be considered to be effective since only one small study had been published for each treatment.

Discussion

Randomized controlled trials are considered to be the most reliable way to estimate the effect of an intervention.[38] In a randomized trial, each patient has an equal chance of receiving any of the interventions. Randomization also reduces the possibility of bias from placebo responders. Inadequate randomization or inadequate concealment of randomization has been found to increase treatment effects.[39] A wide range of pharmacologic treatments has been used in an attempt to relieve orofacial pain. Unfortunately, most of the trials on these treatments were not randomized and therefore not included in the study. Several RCTs were also excluded from this review since data regarding age, diagnosis, and pain duration were lacking.

In this qualitative systematic review, no evidence-based support was found for any specific pharmacologic treatment for TMD, AFP, or BMS. Four studies were judged to be clinically relevant, but sample sizes were low, and each pharmacologic intervention was only supported by 1 RCT. Strong scientific evidence is based upon at least 2 RCTs.[40] More RCTs are needed to determine which pharmacologic interventions are effective in these pain conditions. All the investigated studies had small patient populations, and multicenter studies are recommended to overcome this problem.

In this review, an adult population was analyzed. Studies including children and adolescents were excluded since the results could be difficult to interpret. Doses would be different, and outcome measures would be affected by differing levels of maturity and cognitive abilities. Experimental studies were also excluded since their aim most often is a mechanism-based explanation and not an evaluation of clinical treatment. Abstracts and letters were not considered since their data are often insufficient for analysis in a systematic review. Strict diagnostic criteria were seldom presented in the studies, and many of the populations seemed to represent a mixture of diagnostic descriptions of TMD, AFP, and BMS. Since the material was not homogeneous for diagnostic

groups and pharmacologic treatments and the results were presented as group means, we decided to conduct a qualitative systematic review instead of a meta-analysis.

The most common designs in pharmacologic intervention studies on pain are the parallel group and the crossover.[41] In this review, 6 studies had a crossover design and 5 had a parallel group design. A relative disadvantage with the parallel group design is that more patients are needed (2.4 times) for the results to be equivalent to those of a crossover design.[42] Since the variability in patient response to treatment is large, the size of the trial is essential to overcome random therapeutic effects.[43] At least 40 patients in each group would be needed to detect differences between groups in postoperative pain.[43] In the review, a median of 30 participants per study was the average. This is a low trial size, especially considering that almost half of the studies had a parallel group design. None of the studies reported that the size of their trial was based on a power calculation. It is possible that the results in some of the studies would have been different if the number of patients had been adequate.

A large variety of subjective and clinical assessment variables were used in the studies. The major reason for TMD, AFP, and BMS patients to seek professional help is chronic pain.[4,5] The main outcome measure in the studies was pain assessment. An acceptable reliability and validity has been reported for categoric and VAS measures in pain.[44]

Even with randomization, selection bias may still be introduced if dropouts occur after allocation.[45] In our review, several of the studies had a high frequency of withdrawals and dropouts. An adequate description of withdrawals and dropouts is important if an analysis of intention to treat is to be calculated. None of the studies were analyzed according to intention to treat.

To evaluate the quality of studies, different scoring systems have been proposed.[44] In the present systematic review, we used the scoring system by Jadad et al,[26] which has been used in several studies and found to be reliable.[44] The median score for the studies in this systematic review was 4, which is comparable with the mean presented in similar reviews of pharmacologic interventions.[44]

The analgesic drugs and NSAIDs used in this review were ibuprofen and acetaminophen combined with codeine. Here the results were conflicting. The lack of clinical studies supporting the efficacy and effectiveness of analgesics in the management of chronic orofacial pain becomes more critical as increasing information on adverse effects has been reported in the use of NSAIDs and Cox-2 inhibitors.[23,24] However, none of the studies in this review reported serious adverse effects. The only indication for a short-term trial with analgesics is in patients with acute exacerbations and clinical signs of inflammation of the chronic pain condition. Here, too, however, few RCTs have been published and the evidence is weak.[46]

There is evidence that antidepressants are effective in several chronic pain conditions.[47,48] In our review of a mixed population of TMD and AFP patients, one study found that amitriptyline gave significant pain reduction compared with placebo. Another study reported positive findings using dothiepin but was difficult to interpret because of the analysis of the data. In BMS patients, one study found that trazodone did not have any effect. Several studies have reported that depressive symptoms are common in TMD,[11] AFP,[10] and BMS patients.[8] In clinical trials where chronic pain and depression coexist, patients may obtain relief from both disorders.[49] Today it is accepted that tricyclic antidepressives, eg, amitriptyline, exert an analgesic effect independent of the drug's antidepressive effect.[47,48] In this review, only minor adverse effects were reported. The most common adverse effects, such as dry mouth, constipation, blurred vision, and urinary retention, are related to the anticholinergic properties of the drugs.

Chronic pain patients in the United States are 3 to 4 times as likely to be using benzodiazepines as the general population, and they also continue treatment for longer periods than nonpatients.[50] Concerns have been raised regarding the adverse effects of benzodiazepines, such as sedation, cognitive impairment, depression, and most of all, the risk of abusing and becoming dependent on benzodiazepines.[50] Benzodiazepines may, however, be useful in the short-term treatment of anxiety, muscle spasm, and insomnia, which are frequently associated with acute pain and may occur during acute exacerbation of chronic pain conditions.[49] In this review, one study found diazepam in combination with ibuprofen to be significantly better than placebo. The effect was mainly attributed to diazepam.[28] Only minor adverse effects were reported in this study.

Intra-articular corticosteroids are widely used in the management of arthritic conditions.[51] In one study it was found that corticosteroids injected into the TMJ produced significant improvement compared with saline and sodium hyaluronate. No side effects were reported in this study.[34] Case reports of adverse events following intra-articular injections have been published.[52,53] Contradictory

to these findings are the results of a long-term radiographic follow-up of intra-articular injections that found no negative effects on the TMJ.[54] There is little consensus in the literature on the appropriate technique of administration, and no clinical studies have compared various preparations for safety and effectiveness.[51]

Due to considerable side effects, salmon calcitonin, cocaine, and subcutaneous sumatriptan cannot be recommended for the clinical treatment of chronic orofacial pain.

One recent systematic review of the treatment of BMS identified 6 trials.[18] Only 1 of these studies was evaluated in the present systematic review.[31] The other studies did not meet the inclusion criteria or were excluded because of missing data. However, the authors' conclusions in both reviews were that there is little research evidence that provides a clear guidance for treatment of patients with BMS. Instead of focusing on different etiologic factors, a better understanding of the neurophysiologic mechanisms involved in the pain conditions should improve assessment and treatment of patients with orofacial pain.

One of the major shortcomings of the studies in this systematic review was the low sample size. To overcome this problem in the future, large RCTs—preferably multicenter and cross-cultural investigations—are recommended to assess the efficacy of drugs and increase the generalizability of the results.

The authors of this review judged 4 of the 11 small studies to be positive and clinically relevant. No clear indication was found that any drug is superior to any other in the treatment of orofacial pain, even though patients with TMD and AFP tended to benefit more from antidepressant medication than BMS patients. Further research on each drug is needed since a single small study is not enough to provide evidence of effectiveness.

Conclusions

The common use of analgesics in TMD, AFP, and BMS is not supported by scientific evidence. More RCT studies (eg, of anticonvulsants, antidepressants, analgesics, and nonsteroidal anti-inflammatory drugs) are needed to determine which pharmacologic interventions are effective in these pain conditions.

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