Research Article ISSN 2639-9490

Oral Health & Dental Science

Clinical Effectiveness of Anxiolytics and Antidepressants in the Management of Temporomandibular Disorders (TMD)

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Received: 01 May 2024; **Accepted:** 04 Jun 2024; **Published:** 15 Jun 2024

Citation: Boujoual, Wahid OH, AL Jalil Z, et al. Clinical Effectiveness of Anxiolytics and Antidepressants in the Management of Temporomandibular Disorders (TMD). Oral Health Dental Sci. 2024; 8(2); 1-12.

ABSTRACT

***Introduction**: Temporomandibular joint disorder is a benign pathology, with polymorphic expression and subject to multiple factors that contribute to its etiology, which makes a diagnosis of certainty difficult. Wide ranges of therapeutic options are available, including orthoses, physiotherapy, pharmacotherapy (analgesics, muscle relaxants, anxiolytics, antidepressants, etc.)*

***Objective**: The aim of our work is to conduct a systematic review evaluating the clinical efficacy of anxiolytics and antidepressants in the treatment of temporomandibular disorders in the light of Evidence Based Dentistry.*

***Methods**: The collection of data from the scientific literature was carried out among the production that appeared during the period from 2000 to 2023. The literature search was carried out by exploiting databases accessible via the Internet, namely: Medline through its search engine Pubmed, Elsevier, Google scholar, Research for life and Web of science. A bottom-up manual search covering the same study period was carried out in order to expand our bibliography. The writing of this systematic review followed the guidelines of PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).*

***Results:** 11 relevant articles were retained after critical reading guided by CASP-type reading grids. Then, the articles were classified in 3 categories; Administration of anxiolytics and antidepressants alone or in association with cognitive-behavioral therapy or in association with the wearing of occlusal trays, and classified in tables according to the PICO criteria (Participants/Interventions/ Comparison/ Results "Outcomes").The results of our study show a significant decrease in the intensity of pain and depression as well as an improvement in the quality of life and sleep in patients treated with anxiolytics and antidepressants.*

***Discussion:** The results of our studies concerning the efficacy of anxiolytics and antidepressants in temporomandibular disorders are corroborated by other systematic reviews and meta-analyses. However, the conduct of new research with a longer observation period, a large sample size and following a correct methodology remains necessary.*

***Conclusion:** The lack of valid evidence evaluating the efficacy of anxiolytics and antidepressants in the treatment of AMD is disproportionate to the importance of the psychological dimension in the management of these disorders.*

Keywords
Temporomandibular disorders, Anxiolytics, Benzodiazepines, Antidepressants.

Introduction

Approximately 75% of the general population have at least one sign of temporomandibular disorders [1]. Indeed, any dental surgeon may encounter in their daily practice one of the three cardinal signs of temporomandibular disorders (TMD), namely pain, joint noise, and dyskinesia. According to Gola et al., in 2005, the manducatory system is defined as a set of passive joint elements (temporomandibular and occlusal) as well as an active muscular element whose dynamics are coordinated by the neurosensory system [2,3]. The multifactorial etiopathogenesis of these dysfunctions, on a structural, psychosocial, and systemic level, makes their diagnosis difficult and at first glance complicated [4].

The study of temporomandibular disorders requires paying attention to the psycho- social environment of the patient, in addition to the physical damage to the device. A state of depression and significant events occurring in the patient's life can generate and accentuate the perception of disorders of the masticatory system. Early, conservative, and comprehensive therapeutic care including the psychological dimension would reduce daily disability in everyday life and its impact on professional activity as well as the evolution towards chronic forms. Several therapeutic options are available for the treatment of these disorders namely: occlusal splints, maxillofacial physiotherapy, cognitive-behavioral therapies, therapeutic education, hypnosis, relaxation, and pharmacological therapies (Analgesics, anti- inflammatories, anxiolytics, antidepressants, muscle relaxants, etc.)
Many theories have put forward the existence of cause-and-effect relationships between temporomandibular disorders and the psychological state of patients, hence the interest in the indication of anxiolytics and antidepressants in the treatment of the latter. However, the lack of consensus concerning the place of anxiolytics and antidepressants in the management of disorders of the temporomandibular joint (TMJ) means that practitioners find themselves confused about the use of these molecules. This led us to conduct this systematic review, applying the evidence-based dentistry approach.

The main objective of our work is to describe, through an analysis of the literature, the clinical effectiveness of anxiolytics and antidepressants in the management of dysfunctions of the manducatory system.

Material and Method

This is a systematic review of the literature on the effectiveness of anxiolytics and antidepressants in the treatment of disorders of the masticatory system. The documentary research was based on computer databases accessible via the internet and without language restrictions during the period from 2000 to 2023. The databases used were: Medline, Elsevier, Google Scholar, Research for Life, and Web of Science. The IT search strategy was carried out using the Mesh terms; "Temporomandibular joint disorders", "Anti-anxiety agents", "Benzodiazepines", and "Antidepressive agents" via these Boolean equations:
"Temporomandibular joint disorders" [Mesh]" And Antianxiety agents (pharmacological action)" [Mesh], "Temporomandibular joint disorders" [Mesh] And "Benzodiazepines" [Mesh], "Temporomandibular joint disorders" [Mesh] and "Antidepressive agents" [Mesh].

The articles included were human studies, articles accessible in Full Text, comparative studies, controlled clinical trials, and randomized clinical trials. The excluded ones were: studies published before 2000, studies carried out on animals, case series, studies inaccessible in Full Text, retrospective studies, studies financed by manufacturers, and studies whose sample presents systemic diseases.

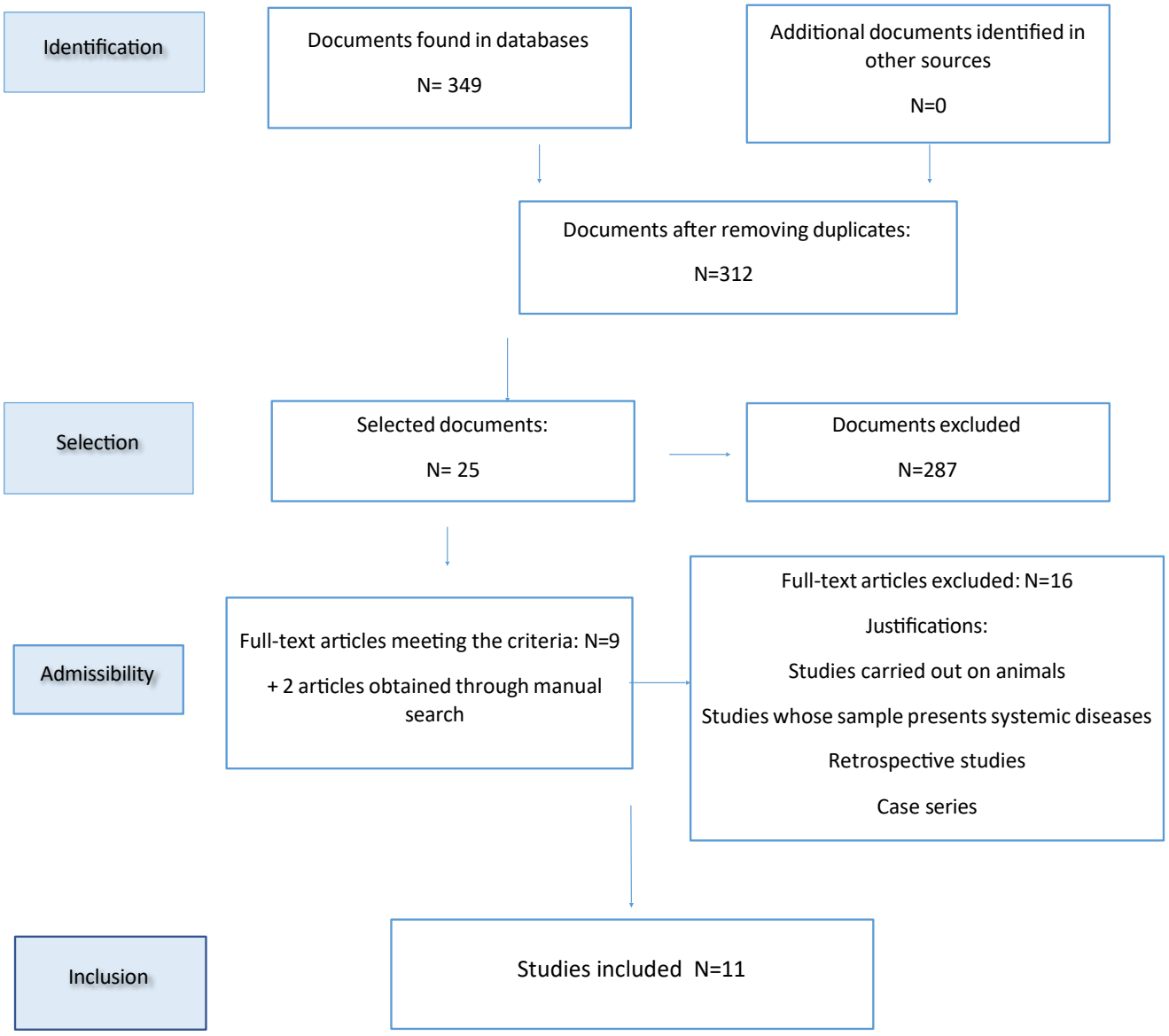
Data extraction and quality assessment were completed by three readers independently, with formal processes of discussion and consensus building in case of disagreement, to minimize subjectivity during the multiple stages of production. The initial search on Pubmed, Elsevier, Google Scholar, Research for Life, and Web of Science search engines identified 349 articles.

The first reading for pre-selection purposes was completed independently by three readers. Based on the titles and abstracts, this first screening allowed the elimination of 324 articles, which are not related to the subject. Then the second level of sorting was applied. Indeed, the same readers first applied the eligibility criteria then a full- text reading guided by the scales CASP was carried out to keep only the potentially eligible studies. Ultimately, 11 articles were included as relevant documents relating to our research.

The data extracted from each selected study are author and year of publication, objective, population (sample size), age, gender, treatment, observation duration and follow-up, the variables measured, the measurement tools, and the results obtained by each author. The critical reading of the articles was based on 2 tools for evaluating methodological quality. The first tool is the CASP (Critical Appraisal Skills Program) and the second is the assessment of the risk of bias tool from the "Cochrane Handbook for Systematic Reviews of Interventions" adapted and updated by Higgins and his employees in 2011 [5-8].

The writing of this work followed the guidelines of The PRISMA Statement "Preferred Reporting Items for Systematic Reviews and Meta-Analyse [9].

Results



Flowchart Illustrating the Different Steps of Publication Selection in the Systematic Literature Review.

Table 1: Impact of the administration of anxiolytics and antidepressants according to PICO criteria:

Author	Title	Population	Intervention	Comparaison	Outcomes
Cory R Herman et al. USA 2002 [10]	The Effectiveness of Adding Pharmacologic Treatment with Clonazepam or Cyclobenzaprine to Patient Education and Self-Care for the Treatment of Jaw Pain upon Awakening: A Randomized Clinical Trial.	Sample size: 41 patients Age: Between 18 and 65 years old Gender: 33 females 8 men	Duration of the intervention: 3 weeks The evaluation: Pre-treatment Post treatment Intervention: A daily dose of 0.5 mg of clonazepam A daily dose of 10 mg of cyclobenzaprine	Between 3 groups divided randomly: Group 1: Clonazepam: 13 Patients (2 men and 11 women) Group 2: Placebo: 15 patients (14 women and 1 man) Group 3: Cyclobenzaprine 13 patients (8 women and 5 men)	Subjects in all 3 groups reported side effects related to the medications they were assigned. The intensity of the pain: For group 1: a reduction in pain of 40.1%, going from a score of 0.48 to 0.28. For group 2: a reduction in pain of 40.2%, going from a score of 0.50 to 0.30. For group 3: a statistically significant reduction in pain of 72.7%, from a mean starting score of 0.62 to 0.17. The improvement from baseline for the cyclobenzaprine group was significantly greater than for the placebo group and the clonazepam group. No significant difference between the 3 groups.
					Sleep quality:
					For group 1: a decrease of 0.62 compared to baseline, statistically insignificant (P>0.3). For group 2: a decrease of 1.20 from baseline, statistically insignificant (P>0.06). For group 3: a decrease of 2.15 from baseline, statistically significant (P < 0.02).
Pablo Kimos et al. Canada 2007 [11]	Analgesic action of gabapentin on chronic pain in the masticatory muscles: A randomized controlled trial.	Sample size: 50 patients including 14 patients who dropped out: -7 patients: did not respect the medication dosage and follow-up appointments. -4 patients: stopped taking the drug because of side effects. - One patient had adverse effects whose origin remains unknown. - A patient discovered she was pregnant so she was advised to stop treatment immediately. -A patient was withdrawn from the study because she started taking painkillers. 8 patients were on specific serotinin reuptake inhibitors (SSRI) in the gabapentin group and 5 in the placebo group. 2 patients in the placebo group were on anti- depressants.	Duration of treatment: 12 weeks The evaluation: *Pre-treatment * A: 4 weeks. - 8 weeks - 12 weeks *Weekly follow-up: phone call by an assistant. Treatment : -Stopping analgesics before the start of the trial. -An initial dose: 300mg per day. -An increase of 300mg every 3 days. -Maximum dose 4200mg. -Once the trial is completed: A gradual reduction in dosage of 300 mg every 3 days is recorded. -If the study drug had to be discontinued for any reason, the dosage was gradually decreased by 300 mg every 3 days. -Acetaminophen 500 mg (every 6 hours not to exceed 8 tablets (4000 mg) per day) has been used for pain relief if: -subjects needed pain control between doses. - the drug studied had no analgesic effect.	Between two groups: The experimental group: Gabapentin: 25 patients, 6 of whom abandoned the treatment The control group: Placebo: 25 patients, 8 of whom abandoned treatment	Pain intensity: It results in a significant reduction in the Gabapentin group of 51.04% compared to 24.30% in the placebo group. Presence of statistically significant difference between the two groups. Muscle sensitivity: At baseline: the number of sensitive palpation sites in the masticatory muscles was 9.50 in both study groups. At week 12: For the gabapentin group, the number of sensitive sites drops from 9.50 to 3.04 For the placebo group, there was a reduction to 7.60 sensitive points. The average reduction in the number of tender points was 6.46 in the gabapentin group compared to 1.9 in the placebo group. A significant difference between the two groups appears at week 8 and is maintained until week 12 Impact on life activities: -The reduction in the impact of Temporo-mandibular dysfunction on daily activities was 52.61% in the gabapentin group, compared to a reduction of 18.63% in the placebo group -The effect of gabapentin appears at the 8th week. The effectiveness of gabapentin treatment has not been demonstrated beyond 11 weeks.
		Gender: Women.			
		Age: Between 18 and 45 years old.			

GV Pramod et al. Inde 2011 [12]	Analgesic efficacy of diazepam and placebo in patients with temporomandibular disorders: A double blind randomized clinical trial.	Sample size: 35 patients. Gender: 14 males and 21 females. Age: Between 15 and 60 years old.	Duration of treatment: 3 weeks with follow-up visits every week. Post-treatment follow-up: Five weeks after the end of treatment. The treatment: - One placebo tablet in the morning after breakfast - One diazepam tablet (5 mg) per day, in the evening after a small meal - Avoid driving and working on or near machinery after taking the tablet.	The control group: 10 patients (3 men and 7 women) The experimental group: 25 patients (11 men and 14 women)	the intensity of the pain: - intra-group comparison: At the third week: there was a reduction in the placebo group of 65% and a statistically very significant reduction in the diazepam group of 72%. At the eighth week of visit, the reduction in pain was greater in the experimental group (72%) than the control group (67%). - inter-group comparison: No significant difference. muscle sensitivity: The intra-group comparison: At the 3rd week and the 5th week after stopping treatment: there was a reduction in muscle sensitivity in both groups. After five weeks of stopping treatment: the masseter muscle in the diazepam group was the only exception where a slight increase in sensitivity was noted. Intergroup comparison: No significant difference. mouth opening: The intra-group comparison: Group 1: At the 3rd week: Mouth opening increased by 13%. Five weeks after stopping treatment: mouth opening increased by 16.5%. Group 2: At the 3rd week: Mouth opening increased by 30%. Five weeks after stopping treatment: no changes observed. Inter-group comparison: Presence of statistically significant difference.
Célia M. Rizzatti et al. Brésil 2016 [13]	Clinical Evaluation of Amitriptyline for the Control of Chronic Pain Caused by Temporomandibula r Joint Disorders.	Sample size: 12 including: - 2 were absent during the control sessions. - 3 did not take the medication. - 3 were taking other medications which were not prescribed and which could therefore modify the results of the study.	Duration of treatment: 14 days The evaluation: - a form is completed at home every morning: for the seven days preceding the study, the 14 days of treatment and the seven days after stopping treatment. -Weekly check-up appointment. Intervention: a daily dose of amitriptyline 25mg. a daily dose of placebo (same dosage form as amitriptyline).	The experimental group: 6 patients The control group: 6 patients	During the 1st and 2nd week: Presence of significant difference between the variables measured: pain intensity and discomfort in group 1. Group 1 showed a greater reduction in pain, i.e. 76.95% compared to group 2 which noted a reduction of 31.68%. The average discomfort value also showed a greater reduction in group 1, which was 72.95% compared to group 2, which showed an increase of 8%.
		Gender: Only women			
O. PLESH et al. USA 2000 [14]	Amitriptyline treatment of chronic pain in patients with temporomandibular disorders.	Sample size: 25 of which 3 dropped out: Two in the first week due to side effects of treatment. One during the third week. Age: Between 23 and 57 years old.	Duration of intervention: 6 weeks Follow-up: Pre-treatment After 6 weeks and 1 year Intervention: For 1 week : -Stopping any treatment for temporomandibular disorders, including wearing splints and taking painkillers. -During the second visit: Prescription of amitriptyline: one tablet (10 mg) in the evening, for one week. Each week the dose was increased by one tablet until pain relief was satisfactory or the dose reached 30mg (max). -In case the patient experienced side effects, the dose was reduced. -Attempts were made to achieve a stable dose during the last 2-3 weeks of the evaluation.	Between two groups: Group 1 presenting myofascial pain without any joint problems: 9 patients, including 7 women and 2 men. Group 2 presenting myofacial pain as well as temporomandibul ar disorders: 13 patients, all women.	The intensity of the pain: MPQ scores: At baseline, 6 weeks and 1 year: no statistically significant difference between the two groups. The results showed a significant reduction in PRI-T score after 6 weeks and 1 year. According to the visual analog scale: The score of group 1 was 6-2 cm, and of group 2 was 5-6 cm. No statistically significant difference between the two groups. Depression : No subject with a non-depressed score at baseline became depressed. Depression scores at baseline, 6 weeks, and 1 year for the two groups were not statistically different. No significant difference between the two groups (P=0-6). The overall effectiveness of the treatment: Presence of statistically significant difference between the two groups at 6 weeks and 1 year.

N. IVKOV IC et al. Serbie 2008 [15]	TMD chronic pain and masseter silent period in psychiatric patients on antidepressive therapy.	Sample size: 68 patients. Age: Between 20 and 48 years old. Gender: 30 males 38 women	Each subject was seated in an upright position in a comfortable chair with their head well supported. The sites to be tested were chosen by manual palpation to determine the central part of the masseter muscles on the left and right, midway between the upper and lower borders, and 1 cm posterior to the anterior border. Surface electrodes, 4 mm in diameter, were placed at 15 mm intervals along the muscle belly and a ground electrode was placed on the upper left arm. The skin above the recording position was cleaned with alcohol swabs. A conductive gel was placed between the electrode and the skin. The electrodes were fixed using adhesive tapes. After placing and connecting the electrodes, each subject was asked to clench their teeth tightly to check the range of movement. The silent period was induced by light mechanical tapping of the subjects' chin with a hammer (weighing 80 g) in OIM. Seven trials were performed, with an inter-trial interval of 10 s.	Between two groups: The experimental group: 30 adults including 12 men and 18 women. Treated with: antidepressant therapy for 7 months before the start of the trial: - maprotiline (Maprotilin)*: a daily dose of 75 mg. - diazepam (Bensedin): a daily dose of 10 mg. The control group: 38 adults, including 18 men and 20 women.	In the control group: 42% of patients presented signs and symptoms of temporomandibular disorders: -31% of these patients presented muscle disorders. -25% expressed joint disorders (disc displacements). -The rest of the patients (44%) presented a combined form of temporomandibular disorders; muscles and joints. -None of the patients showed signs of other joint conditions (arthralgia, osteoarthritis and osteoarthrosis). In the experimental group: 47% had signs and symptoms of temporomandibular disorders: -7% expressed signs and symptoms of muscular disorders -43% expressed joint disorders (disc displacements) -21% of patients expressed other joint conditions. -The rest of the patients (29%) presented a combined form of TMD (muscular and joint) No significant difference in the prevalence of temporomandibular disorders between the two groups. Presence of significant difference between the two groups for joint conditions, the experimental group presents a higher rate than the control group. Absence of statically significant difference in the rate of muscular disorders between the two groups. For pain intensity: In the control group: 14 patients had grade I, II and III pain. Only 2 patients were characterized by high disability and severe limitation (grade IV of chronic pain) In the experimental group: 64% of patients had grade I chronic pain the rest of the patients had grade II chronic pain The grade of chronic pain in depressed patients was significantly lower compared to the control group. The period of silence of the masseter: In the control group: the duration of silence of the massager increased in parallel with the degree of chronic pain. In the experimental group: the silent period of the masseter did not increase with increasing chronic pain grade. There was no statistically significant correlation. Patients in the control group who did not have Temporo-mandibular dysfunctions showed a masseter silence duration of between 14 and 17 ms, whereas in patients with Temporo-mandibular dysfunctions, the silence duration was between 20 and 32 ms.
Yaron Haviv et al. Israël 2015 [16]	Myofascial Pain: An Open Study on the Pharmacotherapeutic Response to Stepped Treatment with Tricyclic Antidepressants and Gabapentin.	Sample size: 42 patients (initially on amitriptyline). Gender: 31 women (74%) and 11 men (26%). Age: 37± 15 years - 13 patients: on amitriptyline completed the study period. - 14 patients: no improvement was reported despite high doses (25 to 35 mg) of amitryptiline. Following which, a switch to gabapentin is reported. -15 patients reported side effects at the initial dose (10 mg of amitriptyline) and were transferred to nortriptyline: - 10 of these patients completed the study while on nortriptyline. - 5: no improvement was noted and they switched to gabapentin. At the end of the study, 23 patients received TCAs (13 amitriptyline + 10 nortriptyline) and 19 patients received gabapentin.	Follow-up: Logs were used: Regional spread of pain was mapped on a diagram of the head and neck, with seven areas identified anatomically: preauricular, angle of mandible, body of mandible, maxilla, temporal, sub-occipital and submandibular. - Patients were asked a standard question to find out if the pain specifically wakes them from sleep. Intervention: Amitriptyline (10 mg) daily in the evening In case the patient experienced side effects, a dose of nortriptyline 12.5 mg was administered once daily. Patients who did not respond to treatment or experienced side effects to TCAs were switched to gabapentin. Gabapentin treatment was initiated at 300 mg daily in the evening, then the dose was increased every 3 days by 300 mg.	Between two groups: Group 1: Received tricyclic antidepressants (Amitriptyline and nortriptyline) as treatment. Group 2: received gabapentin as treatment.	For pain intensity: No significant difference at baseline between the two groups: TCA (6.5 ± 1.9) and GBP (6.7 ± 1.7 P > 0.05) Only one patient, in the TCA group, reported nocturnal awakenings related to pain. Bilateral pain was reported in 69.6% (n = 16/23) of TCA patients and 58% (n = 11/19) of GBP patients. Mouth opening: At baseline was not significantly different between the TCA and GBP groups (43.9 ± 8.1 mm versus 39.7 ± 9.9 mm,: P > 0.05). Pain spread: was significantly higher in the GBP group (5.1 ± 2.7) compared to the TCA group (3.3 ± 1.9) Muscle tenderness: was not significantly different between the TCA and GBP groups (11.4 ± 8.2 vs. 13.2 ± 9.7, P > 0.05). VPS scores: -In the TCA group: a significant reduction at the end of treatment. -In the gabapentin group: a less marked reduction than the group treated with tricyclic antidepressants.

Table 2: Impact of the administration of anxiolytics and antidepressants in combination with cognitive-behavioral therapy according to PICO criteria:

Author	Title	Population	Intervention	Comparaison	Outcomes
P.CAL DERO N et al. Brésil 2011 [17]	Effectiveness of Cognitive- Behavioral Therapy and Amitriptyline in Patients with Chronic Temporo- mandibular Disorders - A Pilot Study.	Sample size: 47 of which 9 dropped out. Age: between 17 and 52 years old.	Intervention: -One week before the start of the trial period, patients stopped treatment for disorders of the masticatory system. -For those who received pharmacological treatment alone: one tablet in the evening for 7 consecutive weeks. -For those who received CBT and pharmacological treatment, the same protocol was used in combination with weekly 90-minute CBT sessions for 7 weeks, led by psychologists. -CBT sessions included: explanatory lectures, relaxation training and explanation of coping strategies. Duration of treatment: 7 weeks Follow-up: Pre-treatment At three times after the start of treatment: 1 week 7 weeks, Post-treatment: 4 weeks after the end of treatment	Between 4 randomly divided groups: 1 – Amitriptyline 25mg: 11 patients (2: dropped out – 6: completed all sessions – 3: only completed a few sessions). 2- Amitriptyline 25 mg and CBT: 12 patient patients (4: completed all sessions – 4: completed only a few sessions – 3: dropped out – 1: was excluded due to side effects). 3- Placebo and CBT: 11 patients (5 completed all sessions -4: only completed a few sessions -2: dropped out). 4- Control group: placebo: 13 patients (7: completed 4: only completed a few sessions - 2: dropped out).	The intensity of the pain: At baseline: no statistically significant difference between the 4 groups. During the 1st week: The amitriptyline and CBT group and the placebo and CBT group had significantly higher VAS scores than the other groups. During the 7th week: A higher score in the amitriptyline and CBT group than the amitriptyline alone group A significant reduction was observed at week 7, compared to baseline, for all four groups The Depression : At baseline and after 7 weeks: No statistically significant difference. At the 11th week: A reduction in the score of the placebo and CBT group compared to the other groups. Life quality: Presence of statistically significant difference only at the 7th week for the amitriptyline and CBT group. Sleep quality: No significant difference between the 4 groups.

Table 3: Impact of the administration of anxiolytics and antidepressants in combination with occlusal splints according to PICO criteria:

Autor	Title	Population	Intervention	Comparaison	Outcomes
Célia M. Rizzatti et al. Brésil 2016 [13]	Clinical Evaluation of Amitriptyline for the Control of Chronic Pain Caused by Temporomandibular Joint Disorders.	Sample size: 12 including: - 2 were absent during the control sessions. - 3 did not take the medication. - 3 were taking other medications which were not prescribed and which could therefore modify the results of the study. Gender: Only women	Duration of treatment: 14 days The evaluation: - a form is completed at home every morning: for the seven days preceding the study, the 14 days of treatment and the seven days after stopping treatment. -Weekly check-up appointment. Intervention: a daily dose of amitriptyline 25mg. a daily dose of placebo (same dosage form as amitriptyline).	The experimental group: 6 patients The control group: 6 patients	During the 1st and 2nd week: Presence of significant difference between the variables measured: pain intensity and discomfort in group 1. Group 1 showed a greater reduction in pain, i.e. 76.95% compared to group 2 which noted a reduction of 31.68%. The average discomfort value also showed a greater reduction in group 1, which was 72.95% compared to group 2, which showed an increase of 8%.
F. INCHI NGOL O et al. Italie 2011 [18]	Combined occlusal and pharmacological therapy in the treatment of temporo-mandibular disorders.	Sample size : : 35 patients Gender: Female: 21 Male: 14 Age: F: 40 +- 10 years M: 30 +- 5 years	Duration of treatment: 12 months Follow-up: Pain intensity was assessed at T0 and after 6 months, 12 months and 18 months using the visual analog scale. The treatment: Patients were asked to wear their upper arch occlusal splints overnight for 12 months. For pharmacological treatment: Delorazepam drops, 1 mg/ day (12 drops/day) for 12 months, decreasing one drop every month until reaching 1 drop/day during the 12th month. Thiocolchicoside, 1 tablet 4 mg/12 hours for 12 months. After 12 months of treatment, all patients were asked to gradually get rid of their aligners: Do not wear it: Sunday the 1st week, Sunday and Wednesday the second week, Sunday, Tuesday and Friday the third week. Friday the 3rd week, Sunday, Tuesday Thursday and Saturday the 4th week Only on Sundays for the following two weeks. The remaining period of time (6 weeks) was considered necessary for complete withdrawal from pharmacological treatment.	Between two randomly divided groups: Group 1: 19 patients (received as treatment occlusal splints (Michigan splint) and pharmacological treatment (delorazepam (drops) + thiocolchicoside (cp)) Group 2: 16 patients (received occlusal splints and placebo)	At baseline: No significant difference between the two groups. At 6 months: No significant difference. At 12 and 18 months: Presence of significant difference The effectiveness of these two types of therapies was evaluated by analyzing data from the V.A.S. from a statistical perspective: the comparison between the 2 groups showed a significant reduction in pain only at 12 and 18 months after the start of the experience.

IVA Z Alajbeg et al. Croatie 2018 [19]	Comparison of Amitriptyline with Stabilization Splint and Placebo in Chronic TMD Patients: a Pilot Study.	Sample size: 21 patients, 8 of whom dropped out.	Duration of treatment: 12 weeks Follow-up: Pre-treatment During treatment: At 1 week, 6 weeks. , 12 weeks Intervention: A dose of 25 mg of amitriptyline, in the evening.	Between 3 groups divided randomly: Group A: Amitriptyline (7 patients including 3 who dropped out) Group B: Placebo (7 patients including 3 who dropped out) Group C: occlusal splints (7 patients including 2 who dropped out)	-Pain decreased continuously in group A and group C. No significant difference for group B. - A significant improvement in quality of life during the treatment period was only noted in groups A and C. No significant difference for group B. -An increase in mouth opening compared to baseline was observed in the 3 groups: Group C showed a significant increase compared to Group A and B.
N. IVKOV IC et al. Serbie 2008 [15]	TMD chronic pain and masseter silent period in psychiatric patients on antidepressive therapy.	Sample size: 68 patients. Age: Between 20 and 48 years old. Gender: 30 males 38 women	Each subject was seated in an upright position in a comfortable chair with their head well supported. The sites to be tested were chosen by manual palpation to determine the central part of the masseter muscles on the left and right, midway between the upper and lower borders, and 1 cm posterior to the anterior border. Surface electrodes, 4 mm in diameter, were placed at 15 mm intervals along the muscle belly and a ground electrode was placed on the upper left arm. The skin above the recording position was cleaned with alcohol swabs. A conductive gel was placed between the electrode and the skin. The electrodes were fixed using adhesive tapes. After placing and connecting the electrodes, each subject was asked to clench their teeth tightly to check the range of movement. The silent period was induced by light mechanical tapping of the subjects' chin with a hammer (weighing 80 g) in OIM. Seven trials were performed, with an inter-trial interval of 10 s.	Between two groups: The experimental group: 30 adults including 12 men and 18 women. Treated with: antidepressant therapy for 7 months before the start of the trial: - maprotiline (Maprotilin)*: a daily dose of 75 mg. - diazepam (Bensedin): a daily dose of 10 mg. The control group: 38 adults, including 18 men and 20 women.	In the control group: 42% of patients presented signs and symptoms of temporomandibular disorders: -31% of these patients presented muscle disorders. -25% expressed joint disorders (disc displacements). -The rest of the patients (44%) presented a combined form of temporomandibular disorders; muscles and joints. -None of the patients showed signs of other joint conditions (arthralgia, osteoarthritis and osteoarthrosis). In the experimental group: 47% had signs and symptoms of temporomandibular disorders: -7% expressed signs and symptoms of muscular disorders -43% expressed joint disorders (disc displacements) -21% of patients expressed other joint conditions. -The rest of the patients (29%) presented a combined form of TMD (muscular and joint) No significant difference in the prevalence of temporomandibular disorders between the two groups. Presence of significant difference between the two groups for joint conditions, the experimental group presents a higher rate than the control group. Absence of statically significant difference in the rate of muscular disorders between the two groups. For pain intensity: In the control group: 14 patients had grade I, II and III pain. Only 2 patients were characterized by high disability and severe limitation (grade IV of chronic pain) In the experimental group: 64% of patients had grade I chronic pain the rest of the patients had grade II chronic pain The grade of chronic pain in depressed patients was significantly lower compared to the control group. The period of silence of the masseter: In the control group: the duration of silence of the massager increased in parallel with the degree of chronic pain. In the experimental group: the silent period of the masseter did not increase with increasing chronic pain grade. There was no statistically significant correlation. Patients in the control group who did not have Temporo-mandibular dysfunctions showed a masseter silence duration of between 14 and 17 ms, whereas in patients with Temporo- mandibular dysfunctions, the silence duration was between 20 and 32 ms.

Table 4: Risk of bias in studies.

Studies	Randomisation	Secrete Assignation	Blind procedure	Complete tracking	Risk of bias
Pramod GV[12]	Adequate	Adequate	Yes	Yes	Weak
Kimos P[11]	Adequate	Adequate	Yes	8 appropriate exclusions	Weak
Cory R[10]	Adequate	Adequate	No	Yes	Weak
Calderon P[17]	Adequate	Not clear	No	4 pertes de vue	Uncertain
Rizzatti B[20]	No	Inadequate	No	No	High
Rizzatti B[13]	Adequate	Not clear	No	3 losses of sight	Uncertain
Alajbeg I[19]	Adequate	Not clear	No	No	Uncertain
Inchingolo F[18]	No	Not clear	No	Yes	Uncertain
Haviv Y[16]	Adequate	Not clear	No	Yes	Uncertain
Plesh O[14]	Adequate	Not clear	No	No	Uncertain
Ivkovic N[15]	Adequate	Not clear	No	Yes	Uncertain

The description of the articles included in our review was carried out according to the PICO criteria (Participants/Intervention/Comparison/Outcomes), the studies were listed according to the type of intervention: Administration of anxiolytics and antidepressants alone or in combination with occlusal splints. And cognitive behavioral therapy.

-Impact of the administration of anxiolytics and antidepressants alone: (Table 1)

The studies carried out by Corry R et al. [10], Pablo Kimos et al. [11], Gv Pramod et al. [12], Célia M et al. [13], O Plesh et al. [14], N ivkovic et al. [15] and Yaron Haviv et al. [16] aimed to evaluate the effectiveness of anxiolytics and antidepressants alone in the treatment of temporomandibular disorders. Cory R et al. [10] show that cyclobenzaprine is more effective than clonazepam, that the reduction in pain over time is more marked for the group treated with cyclobenzaprine. The average improvement reported by the cyclobenzaprine group was twice that of the other two groups. After the intervention period, 61% (25 of 41) of participants achieved a PSQI score >5, indicating that poor sleep quality was not relieved by treatment.

Pablo Kimos et al. [11] show that there is a significant difference between the two groups, the experimental group presents a higher improvement on the different variables evaluated; the reduction in pain intensity, reduction in muscle sensitivity and interference of the disorder with life activities are more marked for this group. After 4 and 8 weeks of treatment, the experimental group showed a significant reduction compared to the control group. The evaluation of the experimental group after 12 weeks showed the stability of the results obtained in terms of pain intensity and muscle sensitivity, unlike the score for interference of the disorder with daily activities which experienced an increase.

-Impact of the administration of anxiolytics and antidepressants in combination with cognitive-behavioral therapy: (Table 2)

The objective of the study conducted by Patricia dos et al. [17] is to highlight the effectiveness of the combination of cognitive behavioral therapy with anxiolytics and antidepressants for the treatment of temporomandibular disorders. Continuous evaluation of the group treated with amitriptyline and CBT shows a significant reduction in the different variables measured. The results of this study suggest that adding cognitive behavioral therapy to anxiolytics and antidepressants results in a reduction in pain and depression as well as an improvement in quality of life and sleep.

-Impact of the administration of anxiolytics and antidepressants in combination with occlusal splints: (Table 3)

The studies carried out by F.INCHINGOLO et al. [18], IVA Z et al. [19] and Celia M et al. [13]. Aimed to evaluate the effectiveness of anxiolytics and antidepressants in combination with the wearing of occlusal splints.

Bias was assessed using the tool recommended by the Cochrane Handbook for Systematic Reviews of Interventions online guide "The Handbook" adapted by Higgins et al. in 2011 [8], the tool in question is used to estimate the risk of bias in meta-analyses and systematic literature reviews bringing together randomized clinical trials.

Discussion

-Impact of the administration of anxiolytics and antidepressants alone:

All studies included in our research except the study conducted by Cory R et al. [10] concluded that the administration of anxiolytics and antidepressants was effective in significantly improving pain scores. However, this conclusion should be qualified since the tool for measuring pain intensity was the visual analog scale which is a subjective tool. While, in study [14], pain perception was assessed by the McGill questionnaire which may be a source of bias, given that patients might be inclined to report a greater degree of satisfaction with their treatment [20,21].

Furthermore, these results were harmonious with those of the literature; Martin R. et al. [22] supported our results through their systematic review which confirms that the use of anxiolytics and antidepressants to treat temporo-mandibular disorders results in long-term improvements in pain. This is explained by the mechanism of action of tricyclic and tetracyclic antidepressants which act primarily as serotonin and norepinephrine reuptake inhibitors by blocking the serotonin transporter and consequently

the norepinephrine transporter. This results in an extracellular elevation of these neurotransmitters. The analgesic effect of antidepressants results from inhibition of neurotransmitter reuptake in the central nervous system.

As for the meta-analysis carried out by Onghena and Houdenhove [23], which studies 39 controlled clinical trials to evaluate the analgesic effect of antidepressants in chronic pain management, she concluded that patients suffering from pain chronic and who received antidepressants as treatment had less pain than 74% of patients suffering from chronic pain who received a placebo.

However, the results of the study conducted by Cory R et al. [10] show that the cyclobenzaprine is more effective than clonazepam in the treatment of temporomandibular disorders. As such, this conclusion appears to be in conflict with other studies that demonstrated the analgesic effect of anxiolytics in the treatment of disorders of the temporomandibular joint. Indeed, Singer E et al. [24] in their study characterized by the administration of Diazepam, Ibuprofen and a placebo in 39 patients concluded that relief pain in these patients is attributed to diazepam.

The authors of studies [17,19], which measured the interference of TMJ disorder with the life activities of patients before and after treatment, concluded that the administration of anxiolytics and antidepressants allows an improvement in quality of life. However, in the study conducted by Kimos Pablo et al. [11], improving the quality of life appeared from the 8 weeks of treatment. However, this improvement is not maintained at the 12th week. This contradiction could be due to the presence of an uncertain risk of bias in the following sections: Attrition bias (data incomplete results), Bias in measuring results given the subjectivity of the tool measurement. Studies do not seem to agree on the benefits of administering anxiolytics and antidepressants on quality of life. Hence the need to carry out other studies in order to judge the real action of these molecules.

-Impact of the administration of anxiolytics and antidepressants in combination with cognitive-behavioral therapy:

As for the trial carried out by Patricia Calderon et al. [17] demonstrated that the association between amitriptyline and cognitive-behavioral therapy makes it possible to potentiate the effectiveness and improve the results, by reducing more significantly the intensity of the pain. Therefore, cognitive-behavioral therapy can be considered as an effective adjuvant to anxiolytics and antidepressants in the treatment of temporomandibular disorders.

These results are in agreement with those listed in the systematic reviews of Aggarwal et al. [25] and Randhawa Kristi et al. [26]; reported that cognitive- behavioral therapy reduces pain in patients with TMJ disorders. While Liu et al. [27], were unable to determine the effectiveness of cognitive-behavioral therapy in the management of TMJ disorders.

In accordance with the literature, the association of standard conservative treatment with cognitive-behavioral therapy, which is a psychotherapy focused on the patient's erroneous and negative thoughts and beliefs, makes it possible to increase the effectiveness of the treatment and accelerate healing and prevent relapses. In light of the above, the addition of brief cognitive-behavioral therapy to anxiolytics and antidepressants for the treatment of patients suffering from TMJ disorders, makes it possible to improve the results obtained in a manner more important. However, a single study remains insufficient to judge the real action of this association, it will therefore be necessary to support it with other trials for more conclusive results.

-Impact of the administration of anxiolytics and antidepressants in combination with occlusal splints:

For the study conducted by Rizzatti-Barbosa C. and coll [20], the combination of occlusal splints, benzodiazepine and an anti-inflammatory reduced the intensity and severity of symptoms. But a follow-up period of 21 days remains insufficient to have a clear long-term conclusion. Hence the need to conduct other studies with a longer follow-up period.

Conclusion

At the end of this systematic review, we can draw the following conclusions: Temporomandibular dysfunction corresponds to a lack of adaptation of the masticatory system, increased by a psychological disorder. They form an extremely polymorphic clinical entity, which preferentially affects young people and more specifically women.

The multitude of symptoms of these disorders results from the large number and the entanglement of biological, structural and psychosocial cofactors involved in the triggering and evolution of these dysfunctions.

Many treatment modalities are available for the treatment of these pathologies namely; orthotics, physical therapies, occlusal therapies, surgery or pharmacological treatment. Among the flowering of treatment methods offered, pharmacotherapy occupies a special place in the therapeutic arsenal of temporo-mandibular dysfunction.

Given the cyclical evolution of this pathology, and the stressed terrain often found, it appears useful to offer patients a therapeutic complement to treat both the symptom and the terrain. With this in mind, the administration of anxiolytics and antidepressants in patients suffering from temporomandibular disorders makes it possible to increase the effectiveness of the treatment by reducing the intensity of pain, improving function and acting on the psyche.

Our review shows the importance of the psychological component, often neglected by practitioners when treating patients suffering from temporomandibular disorders, which are pathologies linked to the interaction of multiple factors. In this way, the dentist must

be able to analyze the patient as a whole by adopting a broader therapeutic approach including a biopsychosocial model.

However, the disparity of the results of the studies and the absence of scientific evidence forming a consensus do not allow clear conclusions to be drawn. Added to this is the small size of the populations studied which does not allow the results to be extrapolated.

Following this observation, further studies are required, with a longer observation period and a large sample size in order to provide a better analysis of the effectiveness of anxiolytics and antidepressants in the treatment of temporo- mandibular dysfunction.

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