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The use of tricyclic antidepressants in the treatment of temporomandibular joint disorders: Systematic review of the literature of the last 20 years

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Abstract

Many therapies have been proposed for the management of temporomandibular disorders, including the use of different drugs. However, lack of knowledge about the mechanisms behind the pain associated with this pathology, and the fact that the studies carried out so far use highly disparate patient selection criteria, mean that results on the effectiveness of the different medications are inconclusive. This study makes a systematic review of the literature published on the use of tricyclic antidepressants for the treatment of temporomandibular disorders, using the SORT criteria (Strength of recommendation taxonomy) to consider the level of scientific evidence of the different studies. Following analysis of the articles, and in function of their scientific quality, a type B recommendation is given in favor of the use of tricyclic antidepressants for the treatment of temporomandibular disorders.

Key words: *Temporomandibular disorders, tricyclic antidepressants, amitriptyline, orofacial pain.*

Introduction

Temporomandibular disorders (TMDs) is a collective term that includes disorders of the temporomandibular joint (TMJ), and of the masticatory muscles and their associated structures; characterized by pain, joint sounds, and restricted mandibular movement (1). Among other signs and symptoms, headaches and sleep disturbances can appear concomitantly (2).

The pathogenesis of the pain in TMDs remains unclear. Numerous factors, both physical, as well as biochemical and physiological have been related to the origin and evolution of this pathology; thus numerous types of treatment have been proposed in the literature, although with highly disparate results among the published studies (3-5).

Regarding pharmacologic therapy, the effects of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, muscle relaxants, anxiolytics, opioids and tricyclic antidepressants (TCAs) on TMDs have been studied among others, although with no conclusive results for any medication. However, in those cases where a TMD is associated with states of anxiety, depression and/or stress, the use of drugs may be clearly indicated (3,5-7). Other agents such as capsaicin in topical application or hyaluronic acid by intraarticular injection have

Table 1. Summary of evidence level 2 studies.

Authors and year	Publication	Type of study	Evidence	Results
Tversky et al. (1991) (14)	Oral Surg Oral Med Oral Pathol	Case control	Level 2	Depressive states are related with prognosis in patients with TMDs. Treatment should take into account both the physical and psychological problems of the patient.
Rizzatti-Barbosa et al. (2003)(9)	Cranio	Double blind clinical trial	Level 2	Amitriptyline at a dose of 25 mg / day significantly reduced pain and discomfort in comparison with a placebo in patients with TMDs.
List et al. (2003)(19)	J Orofac Pain	Systematic literature review	Level 2	The use of drugs for the treatment of chronic pain (TMDs, burning mouth syndrome, and atypical facial pain) is not based on scientific evidence criteria, therefore more randomized clinical studies are necessary to determine which drugs are truly effective.

also been studied, although there is insufficient scientific evidence to corroborate their effectiveness in treating TMDs (3,7,8).

Tricyclic antidepressants are the most studied regarding indication in the management and control of chronic pain in the orofacial area, as in the case of diverse musculoskeletal dysfunctions (myofascial pain and fibromyalgia) and other clinical entities such as primary headaches (migraine, tension type headaches, etc.), or certain neuropathies (diabetic neuropathy, atypical odontalgia, postherpetic neuralgia, traumatic trigeminal neuralgia, etc.) (9,10).

The aim of this article is to make a systematic review of the literature published on the use of TCAs for the treatment of TMDs in the last 20 years, considering their level of scientific evidence according to the principals of evidence-based dentistry.

Material and Methods

A MEDLINE search was made for articles published between the years 1988 and 2008. The MeSH (Medical Subject Heading) keywords and headings were used for "TMDs" to obtain a core bank of articles on this pathology. The literature identified was then limited to studies in humans and articles written in English. A similar search was made for "TRICYCLIC ANTIDEPRESSANTS." Both search strategies were in turn merged by means of the Boolean operator "AND", thus linking the articles on TMDs and TCAs. The same process was used in the COCHRANE database of the Cochrane Oral Health Group. Two authors analyzed the abstracts to verify that the articles obtained were pertinent to the topic under study. The irrelevant articles were discarded. Next, the same two authors independently stratified the scientific articles according to their level of scientific evidence using the SORT criteria (Strength of Recommendation Taxonomy) (11). Subsequently the authors compared their results; in the event of disagreement the results were discussed. If no consensus regarding the level of scientific evidence of a certain article was possible, a third author was included in the discussion. Subsequently, a recommendation was given for or against the use of this medication in the treatment of TMD according to the level of scientific evidence of the articles analyzed.

Results

The MEDLINE search for TMDs provided a bank of 8,900 articles. The search for tricyclic antidepressants provided 19,571 articles. As previously mentioned, both searches were then cross-referenced. This provided a bank of 67 articles. Next, the abstracts of each article were analyzed to determine if they were pertinent to the topic under study. The search in the COCHRANE database provided no relevant articles that agreed with the search criteria of this study. After this process 11 relevant articles remained. These articles were critically analyzed and classified according to their level of scientific evidence.

This analysis produced 7 literature review articles, an article

presenting a clinical case (level 3), 1 study of treatment effectiveness (level 3), a double blind study with a small sample of patients (level 2), and a low quality (level 2) meta-analysis that included all the clinical studies in the literature on TCAs in the treatment of TMD.

Description of studies.

1. Pettengill CA, Reisner-Keller L (10).
Literature review. Evidence level 3.
2. Reisner-Keller L (12).
Literature review. Evidence level 3.
3. Dionne RA (13).
Literature review. Evidence level 3.
4. Tversky J, Reade PC, Gerschman JA, Holwill BJ, Wright J (14).
Case control study. Evidence level 2.
5. Harris M, Feinmann C, Wise M, Treasure F (15).
Literature review. Evidence level 3.
6. Denucci D, Dionne R, Dubner R (16).
Literature review. Evidence level 3.
7. Barker E, Blakely R (17).
Literature review. Evidence level 3.
8. Haas D (8).
Literature review. Evidence level 3.
9. Rizzatti-Barbosa CM, Nogueira MTP, de Andrade ED, Ambrosano CMB, de Barbosa JR (9).
Double blind clinical study (small patient sample and inconsistent results). Evidence level 2.
10. Plesh O, Curtis D, Levine J, McCall WD (18).
Pilot study on efficacy of treatment. Evidence level 3.
11. List T, Axelsson S, Leijon G (19).
Systematic literature review. Evidence level 2.

The results of studies with evidence level 2 are summarized in Table 1 (the literature reviews are excluded).
In accordance with the principals of evidence-based dentistry, the analysis produced a level B recommendation in favor of using TCAs in the treatment of TMDs. However, this result should be taken most cautiously since this recommendation is based on the only controlled study published so far, and which presents important methodological defects such as insufficient sample size and/or lack of homogeneity among the studied populations among others.

Discussion

Diverse signs and symptoms can be found in TMD, of which pain and joint dysfunction are the most frequent clinical findings (3,4,10,15,20). The chronic pain associated with TMDs is treated with peripheral analgesics (mainly NSAIDs), muscle relaxants, opioids and benzodiazepines (3,10,11,18). More recently TCAs, specifically amitriptyline, have been added to the therapeutic arsenal (14). Since the 1960s, TCAs have been accepted for the treatment of chronic pain syndromes (3,19,21,22). In this regard, Onghena and Houdenhove (23) demonstrated their efficacy in chronic pain in a metaanalysis that compiled 39 quality scientific studies (controlled clinical studies with placebo).
Publications are scarce on the specific case of using TCAs in TMDs. Our search found only 11 studies that fulfilled our criteria, most being literature reviews based on studies of the efficacy of these antidepressant medications, specifically amitriptyline, for the control of chronic pain of other origins such as diabetic or postherpetic neuropathies and primary headaches, among others.
For most authors (9,15,24), the analgesic effect of TCAs is due to the serotonin and noradrenaline reuptake inhibition at synaptic level in the central nervous system (CNS). The blocking of these two amines increases their concentration and availability in the synaptic space of the nerve endings in the posterior horn of the spinal cord (involved in the transmission of pain) favoring or prolonging the inhibitory action in the transmission of this pain (10,23).
Nevertheless, this would only provide a partial explanation of the action mechanism by which TCAs produce an effect in the management of chronic pain. Other theories have been proposed that suggest that an interaction of TCAs would exist with the endogenous opioids and the spinal adrenergic system, although the specific physiologic bases of this interaction are unknown (25).
It has also been suggested that since most patients who suffer chronic pain usually have associated depressive states, in many cases related with some type of disturbance in sleep patterns, the pain could be indirectly decreased due to the change in these patterns, especially in those patients with a depletion in serotonin levels in the CNS (9,10). The study by Tversky et al. (14) which indicates that depressive states play a crucial role in the therapeutic response of patients with TMDs would confirm this hypothesis, since chronic pain leads to mood changes in the patient, and therefore an evaluation of the psychological status before any treatment planning would be mandatory. However, the specific physiologic bases of the mechanism by which TCAs provide an analgesic effect are unknown (10).
According to some authors (8,10), the use of TCAs in patients with TMDs, besides being effective in the control of pain, reduces the number of sleep disturbances, extending stage IV or delta sleep, and considerably reducing REM sleep. They are effective in the treatment of the night bruxism associated with these sleep disturbances and, due to the sedative action, would induce a muscle relaxing action at central level. Therefore, according to these authors, their use would be indicated when other treatments (splints, physiotherapy, etc.) have been ineffective (10) or they can be administered simultaneously (18). However, no scientific study exists that demonstrates the efficacy of these medicines in any of the above-mentioned cases.
The doses of TCAs used for pain management are usually much lower (10 to 20 times) than those used to control depression (8). For the specific case of amitriptyline, which continues to be the most used TCA in the management of

pain associated with TMDs, the recommended posology varies between 25 and 150 mg daily, proposed by Pettengill and Reisner-Keller (10) and Kreisberg (24). The treatment begins at a low dose (between 10 and 25 mg day) increasing gradually until obtaining a considerable decrease or the total disappearance of the patient's symptoms (10,13,22,24). In this regard, Plesh et al. (18) carried out a pilot study in 25 patients investigating the efficacy of amitriptyline at low doses (between 10 and 30 mg) in reducing pain in 2 groups of patients with chronic temporomandibular pain (myofascial pain and arthralgias). From the results obtained they concluded that amitriptyline in low doses is effective in reducing pain. However, they found that the pain reduction is better at 6 weeks than one year after commencing therapy, especially in the myofascial pain group, although they do not justify this fact.

Rizzatti-Barbosa et al. (9) published a double-blind study in which they sought to verify the efficacy of amitriptyline in chronic pain management in TMD on a sample of 12 women medicated over 14 days. The authors concluded that amitriptyline at a dosage of 25 mg / day is effective in reducing pain and discomfort in chronic temporomandibular pain. However, no greater analgesic effect is obtained when using amitriptyline in higher concentrations (50-75 mg / day), although the side effects are greater.

Studies by Sharav et al. (26) and McQuay et al. (27,28) obtained similar results to those of the above, but should be considered with caution since the sample size is inadequate and there are numerous methodological errors.

In contrast to these conclusions, Dionne (13) suggests that the analgesic effect of amitriptyline is no higher than with a placebo, attributing this to the psychogenic factor present in many cases and to the difficulty for the patient to measure subjective sensations of pain and discomfort. On the other hand, Zitman et al. (29) indicate that an improvement in the symptoms exists, but is smaller than expected.

None of the studies found in the literature can be classified as scientific evidence level 1 according to the SORT criteria. The best quality scientific study found in the literature corresponds to a systematic review which aimed to analyze the randomized clinical studies published in the MEDLINE, Cochrane Library, EMBASE and Psych Litt databases to determine the efficacy and the safety of the drug therapies used in the treatment of TMDs (they included rheumatoid arthritis and burning mouth syndrome) (19). The authors found 11 studies that included 368 patients in total. The effectiveness in the management of pain in TCAs was demonstrated in only one of the studies. These authors concluded that there is no scientific evidence to demonstrate the efficacy of any drug in the control of TMDs, and therefore more randomized controlled studies would be necessary to obtain consistent results for each of the therapies. The above study cannot be considered as level 1 of the SORT criteria because limitations in the selection criteria prevent it from being considered a metaanalysis.

Conclusions

Publications on the use of TCAs for the treatment of TMDs are scarce, most are literature reviews that extrapolate the results obtained with these drugs in other chronic pain pathologies in different areas of the body to pain in the orofacial area.

According to the principals of evidence-based dentistry, there is currently a scientific evidence level B in favor of using TCAs for the treatment of TMDs. No studies on this topic exist that fulfill the conditions for classification as scientific evidence level 1 according to SORT criteria. This means that the results published in the literature should be analyzed with caution since none have sufficient scientific basis, either because the sample size is inadequate, methodological defects are present, for example the lack of homogeneity of the populations studied, or, as commented above, because the results are extrapolated.

There are no scientifically sound studies that demonstrate the effectiveness of TCAs in the treatment of TMDs, therefore, more controlled clinical trials are necessary to demonstrate this hypothetical efficacy, and to assess the dose required for each pathology type and its associated side effects, among other parameters.

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