The knowledge of prescription and the pharmacological role in temporomandibular disorders for dental surgeons: literature review

O conhecimento da prescrição e o papel farmacológico em disfunção temporomandibular para os cirurgiões-dentistas: revisão de literatura

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ABSTRACT

BACKGROUND AND OBJECTIVES: The temporomandibular disorder (TMD) is an anatomical-functional disorder that affects the muscles of chewing, the temporomandibular joint (TMJ) or both structures. It is one of the most common orofacial pain of non-dental origin with a prevalence of 5% to 7% of the population, being considered a public's health problem. The main symptom of TMD is pain and, when chronic, it affects the quality of life. The drug classes that are commonly used in this condition are antidepressants, anticonvulsants and muscle relaxants that modulate symptomatology in these subjects. The aim of this study was to review the literature about main drugs used to control TMD, its mechanisms of action and effectiveness as well as the possible causes of TMD.

CONTENTS: Literature was searched in the following databases: Pubmed, Scielo and Lilacs with a time sample from 2010 to 2021. As inclusion parameter, were selected literature's review and systematic articles, randomized clinical cases, placebo-controlled and double-blind studies with the TMD theme, considering pharmacological treatment's aspects. As exclusion parameter, articles in which the outcome was not the TMD, congress abstracts and personal opinions were rejected. After the articles' selection, reading of titles and abstracts, 09 articles were selected, consisting of reviews and clinical studies relevant to the subject.

CONCLUSION: The pharmacological approach has demonstrated its positive effects in the management of TMD-related chronic pain, with more effective results when associated with other therapies, due to its multifactorial characteristic.

Keywords: Orofacial pain, Pharmacological treatment, Temporomandibular joint disorders,

RESUMO

JUSTIFICATIVA E OBJETIVOS: A disfunção temporomandibular (DTM) é uma desordem anátomo-funcional que afeta os músculos da mastigação, da articulação temporomandibular (ATM) ou ambas as estruturas. É uma das dores orofaciais mais comuns de origem não dentária, com prevalência de 5% a 7% da população, sendo considerada um problema de saúde pública. O principal sintoma da DTM é a dor que, quando crônica, afeta a qualidade de vida. As classes de fármacos mais comumente empregadas nessa condição são os antidepressivos, anticonvulsivantes e relaxantes musculares, que modulam os sintomas nesses pacientes. O objetivo deste estudo foi revisar a literatura acerca dos principais fármacos utilizados no controle da DTM, seus mecanismos de ação e eficácia, bem como as suas possíveis causas.

CONTEÚDO: Buscou-se na literatura artigos científicos nas bases de dados: Pubmed, Scielo e Lilacs, com a amostra temporal de 2010 a 2021. Como parâmetro de inclusão, foram selecionados artigos de revisão de literatura e sistemática, casos clínicos randomizados, estudos placebo-controlados e estudos duplo-cegos com a temática DTM, considerando aspectos do tratamento farmacológico. Como parâmetro de exclusão, artigos em que o desfecho não era a DTM, resumos em congressos e opiniões pessoais foram rejeitados. Após a seleção dos artigos, leitura de títulos e resumos, 9 artigos foram selecionados, consistindo em revisões e estudos clínicos pertinentes ao assunto.

CONCLUSÃO: A abordagem farmacológica demonstrou efeitos positivos no manejo da dor crônica por DTM, tendo resultados mais eficazes quando associada a outras terapias, em virtude de sua característica multifatorial.

Descritores: Dor facial, Transtornos da articulação temporomandibular, Tratamento farmacológico.

INTRODUCTION

Temporomandibular disorder (TMD) is an anatomical-functional disorder of the masticatory muscles, the temporomandibular joint (TMJ) or both associated structures[1-7], often characterized

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HIGHLIGHTS

- Psychosocial changes act as amplifying factors for chronic pain in TMD and contribute negatively to its control.
- Pharmacological therapy combined with other therapies enhances the chances of controlling chronic TMD pain.
- The use of medicinal cannabinoids has shown promising results in the management of chronic pain in TMD patients.

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by chronic condition[8]. It is one of the most common orofacial pains of non-dental origin[9].

Considering the world population, about 70% of people have at least one sign of TMD, but only a small portion needs treatment, considering the painful symptoms[4], which have a prevalence of 5% to 7% in the global population[5,6,10], and is considered a public health problem[5].

TMD etiology is multifactorial, complex and encompasses physical, behavioral, social and physiological factors that play important roles in the development of thedisorder[2,5]. TMD, when chronic, affects quality of life and behavior of the patient[4].

The main symptom of TMD is pain, either in the face, TMJ region and/or head[3], which makes it a guiding factor for seeking medical treatment[1,2]. Other important signs include joint noises and limited mouth opening[3,4,11].

Several therapeutic approaches have been reported, although there is no consensus as to the choice of treatment for this condition[2,6]. The treatments include therapeutic-behavioral management, physical therapy, psychotherapy, occlusal therapy, patient reassurance and education, surgical management and/or pharmacotherapy[1]. Multidisciplinarity is successful in TMD management[9].

Pharmacological management, among the non-surgical ones, is one of the first choice conducts for TMD, when the focus is to remove the patient from pain chronicity[1]. The drug classes most commonly employed in this condition are antidepressants, anticonvulsants, muscle relaxants, which, in minimal and optimal concentrations, modulate pain in TMD patients by different mechanisms[1].

The present study is justified by the importance of the dental surgeon (DS) in knowing the prescription and the pharmacological role related to TMD in order to prevent the aggravations resulting from the disorder and to control the dysfunction, not with the purpose of curing the patient, but to help him/her manage the chronic pain and get him/her out of a crisis situation[1]. The main objective was to review the literature on the pharmacological role of the main drugs used by DS in TMD control.

CONTENTS

TMD is classified according to the affected structures: of intra-articular or intracapsular origin, also called arthrogenic TMD, and of extra-articular origin, or myogenic TMD, when associated with the masticatory muscles[7].

There are several causes that contribute to internal TMJ derangements, either inflammatory or mechanical, namely: osteoarthritis, hypermobility, capsular inflammation, and traumatic lesions, and the disk displacement is a common finding in the population[12,13].

Musculoskeletal causes result from muscle tension, fatigue, and spasms, and are considered to be the most commonly associated with TMD, characterized by presence of trigger points (TP) or referred pain, which are activated or potentiated by parafunctional habits, psychological and emotional conditions, and poor posture[12].

Parafunctional habits

Among parafunctional habits, bruxism, characterized by clenching and grinding of the teeth and tensioning the jaw muscles, is a factor that results in excessive and prolonged muscle tension around the TMJ, leading to joint overload[4,14,16], and has been widely studied as a possible risk factor[4].

Some signs and symptoms are common in bruxism, such as: pain, muscle sensitivity, morning headaches and fatigue[15]. Bruxism has two circadian manifestations: sleep bruxism (SB) and awake bruxism (AB)[16]. SB is characterized as rhythmic or phasic and non-rhythmic or tonic and is referred by repetitive horizontal or eccentric teeth grinding movements. AB is characterized by repetitive or sustained movements with touching or non-touching of the teeth and is referred by vertical or centric loads[16].

The correlation between bruxism and TMD signs is based on the general notion of excessive and repetitive use of the TMJ, whose exacerbated actions result in functional abnormalities[4]. Bruxism is generally more associated with muscle disorder, but this parafunction can culminate in joint changes/disc dislocation[4]. This parafunction can affect the bone remodeling of the mandibular condyle and degrade bone cartilage, contributing to the development of TMJ osteoarthritis[4].

Despite this, there is no correlation between bruxism and chronic pain, since the identification of the nature of pain is not specified, giving rise to a series of painful conditions[15]. Central mechanisms are essential for bruxism development, and psychological factors may exacerbate it[15].

Cognitive and psychiatric disorders: stress and anxiety

Psychosocial alterations, depression, anxiety, stress and somatization are closely related to limitations related to intensity and duration of pain[16,17]. These variables converge to a negative adjustment or a worse pain coping in individuals with chronic pain[18].

Patients with muscle pain associated with joint disorders experience more advanced stages of depression and somatization of TMD symptoms[4,17]. A study[18] revealed that the profile of patients with chronic TMD shows an impaired emotional state and reports moderate and high levels of somatization and depression[18].

Although myogenic pain is directly related to TMD, a study using functional brain imaging found that the central nervous system (CNS) triggers a range of information that is converted into muscle pain, i.e., muscle pain is regarded as a secondary process[19]. Moreover, TMJ muscle and/or joint dysfunction is usually related to preexisting psychopathological factors[19].

The COVID-19 pandemic (SARS-COV2 virus), especially during the lockdown period (social isolation), was a scenario whose hindrances changed the routine and the personal, emotional, financial and/or social life of many subjects[20].

A cohort study[20] addressed the impact of COVID-19 on psychological distress, pain sensitivity characteristics, pain severity and quality of life of individuals with chronic TMD[20]. In that study, findings were obtained, which ratified and reinforced the role of stress as an amplifier agent of CNS sensitization,

as well as anxiety, depression, chronic pain and pain-related disabilities/limitations[20].

Case-control evidence elucidated significantly higher scores of stress, anxiety and catastrophizing (exaggerated reactions to worldly threats) in TMD patients compared to asymptomatic patients[17], in addition to elucidating the contribution of these cognitive/psychiatric disorders to pain maintenance[20]. Moreover, oral health quality may also be affected as a result of psychological changes, leading to harmful habits[21].

A study[17] highlighted the importance of some physiological markers in psychosocial disorders, such as markers of the hypothalamic-pituitary-adrenal (HPA) axis, which regulate stress and different bodily functions. In this study, the HPA axis was addressed as a cross-sectional cohort survey of 60 TMD patients. This sample was subjected to clinical questionnaires, medical and socioeconomic history, lifestyle factors, and an anxiety and depression scale. In addition, from the morning saliva analysis of these participants, significant findings of cortisol and cortisone, hormones released in response to stressful events, were obtained in TMD patients, compared to control group, corroborating the role of stress as a potential risk factor for the development of TMD.

Just as psychological factors interfere in the development of TMD, there are several discussions whose analysis also address TMD symptoms as causal phenomena in influencing the development of psychic changes, i.e., there is a feedback of psychosocial, biological and physical factors[4].

The etiology and pathogenesis of TMD are still poorly understood, so comprehending its causes in each patient is essential to identify and control the potential factors involved in this dynamic disorder[4].

Neuroimmune interactions, temporomandibular dysfunction and chronic pain

Neuroimmune interactions in painful TMD have had emerging scientific evidence. Inflammatory mediators play an essential role in TMJ sensitization, and neurogenic inflammation may exacerbate TMJ dysfunction in TMD and potentiate neuronal excitability, leading to pain and the chronic condition of the disorder[22], amplifying CNS sensitization and the protective muscle twitch reflex[8].

Neurogenic inflammation is a condition in which the release of proinflammatory cytokines and interleukins alter the viscosity of the synovial fluid, which leads to insufficient lubrication and nutrition of cartilage and articular disc. This process occurs by stimulating the opening of calcium channels, the sensitization of slowly conducting amyelin C fibers, and the secretion of substance P, an inflammation-related neurotransmitter, and calcitonin gene-related peptide (CGRP), which exerts a vasodilatory effect leading to the appearance of cardinal signs[8].

In the inflammatory process, it is normally expected that the reaction to nociceptive stimuli decays with time, but this mechanism can be accentuated and establish a central activity and, consequently, chronify pain. The rAMPA (alpha-amino--3-hydroxy-5-methyl-isoxosol-4-propionic acid) and rNMDA (N-methyl-d-aspartate) receptors, located in the synaptic cleft, are responsible for the pathophysiology of pain chronification. They allow sodium entry and depolarization of the membrane. The rNMDA, of long-lasting activation and blocked by magnesium at rest, allows the entry of sodium in conditions in which the nociceptive stimulus recurs or exceeds the baseline threshold for changes in pain quality, i.e., stimuli considered harmful or not harmful, when persistent, activate the rNMDA and, consecutively, trigger the process of pain chronification[8].

Although the pathophysiological mechanisms of pain in patients with chronic TMD remain unknown, it is believed that changes in brain activity, amplified pain perception, immune and neuroendocrine interactions, as well as genetic predisposition may be factors involved in this process[22].

Diagnosis

The diagnosis of TMD is essentially clinical and is usually made through the evaluation of the medical history, physical examination and, in some cases, imaging tests that can be useful when the clinical findings do not provide sufficient information regarding TMJ[12].

Anamnesis is essential for the initial diagnosis. Diagnosis, in most cases, requires the analysis of imaging exams, either by computed tomography (CT), to evaluate TMJ hard tissues, or by nuclear magnetic resonance (NMR), to analyze temporomandibular region soft tissues, due to the difficulty in reaching a precise and correct diagnosis[14].

Panoramic radiography can be useful for initial diagnosis, by excluding odontogenic causes and by evaluating temporomandibular joints. CT scans can reveal severe degenerative joint disease and eliminate possible causes of orofacial pain, such as fractures and dislocations. A NMR is the ideal exam to investigate TMD, but despite its high sensitivity and specificity to evaluate TMJ structures, its use was eventually reduced due to high cost and the relevance given to conservative treatments[12,13].

The Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD), updated to Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) is considered a systematized tool, with clinical examinations and questionnaires that indicate predisposing factors for the disorder[23].

As for DC/TMD, the symptoms indicated as criteria are systemic, psychological, or structural, such as: fibromyalgia, which is typical in muscular pain or discomfort in the jaw, neck, and shoulder girdle, internal TMJ disorders, and degenerative joint diseases[23].

The TMD diagnostic criteria are based on axis I, referring to physical symptoms, and axis ll, referring to psychosocial symptoms[18]. With the update of DC/TMD criteria, it was possible to use the axes for both research and clinical purposes[18]. The clinical findings include difficulties in opening the mouth, sensitivity in the masticatory muscles and neck or shoulder region, in addition to possible associations with bruxism[12]. For these factors, it is necessary to perform a physical examination, such as palpation of the TMJ and masticatory muscles, to identify the presence of painful symptoms[12].

TMJ evaluation can be optimized by light palpation on the anterior wall of the auditory canal[12]. Sounds in the mandibular

movements, suggestive of crackles, noises or clicks, are signs of an internal derangement and are best auscultated with the aid of a stethoscope. TMJ crepitations may suggest the diagnosis of osteoarthritis, as they are related to articular surface rupture[12].

Pharmacological therapy

It is considered a support therapy, directed to relief of pain and disorder, characterized by methods that aim to change patient's symptoms, usually without effect on the cause of the disorder. In the face of a diverse range of therapeutic interventions, there does not seem to be the most correct conduct, but the most indicated, as well as for the drugs aimed at each patient's demand in an individualized and judicious manner[19].

The choice of drug is related to pain intensity, frequency and duration[23]. Since there is no consensual treatment protocol[23] and because the wide array of drugs, there is a certain degree of clinical uncertainty in TMD control[19].

Pharmacological therapy in patients with TMD is a challenge, as it is still largely empirical and has few studies demonstrating the efficacy of pharmacological agents. One of the limitations is that several studies have a significant placebo effect, and the randomized studies exhibit a small sample size for patients with the disorder[24].

Therefore, it is important that DSs, in view of the use of drugs, knows how to prescribe them, rationalize them, and know each one thoroughly in the process of pain prevention and TMD control[25].

This research conducted a literature review from scientific articles published in the Pubmed, Scielo, and Lilacs databases between the years 2010 to 2021. Terms in Portuguese and English were used for a general search for titles and, consequently, abstracts. Inclusion criteria were literature review articles, systematic reviews and randomized, placebo-controlled and double-blind clinical cases that addressed TMD, taking into account mainly aspects of pharmacological treatment. Exclusion criteria were articles in which the outcome was not TMD, conference abstracts, and personal opinions. After the selection of articles, all abstracts were read and those listed pertinent to the subject were separated for reading of the full text for summarization and start of the literature review.

RESULTS

Among the articles that underwent title analysis and abstract analysis, 9 relevant articles were selected according to the established inclusion criteria. Among these, 6 correspond to randomized clinical studies, 5 of which were double-blind. In addition, one corresponds to a literature review and two correspond to systematic reviews with meta-analysis, considering randomized and placebo-controlled clinical trials. The studies have little variation in sample size, with the smallest equal to 35 and the largest equal to 60. The selected articles are shown in Table 1.

Table 1. Studies that have demonstrated or evaluated pharmacological therapy in temporomandibular dysfunction

Authors	Goal	Methodology	Results
Alencar et al.[26]	Compare the effectiveness of adding CYC, TZA or placebo to patient education and a self-care management program for patients with myofascial pain and who specifically present jaw pain on awakening.	45 patients in this 3-week study, diagnosed with myofascial pain, were randomly assigned to one of three groups: placebo group, TZA 4 mg group, or CYC 10 mg group. The patients were evaluated for changes in pain intensity, frequency, and duration.	All three groups had reduced pain symptoms and improved sleep quality based on comparison of pre-treatment and treatment scores. However, no significant differences were observed between the groups at post-treatment assessment.
Mujakperuo et al.[1]	To evaluate the effectiveness of pharmacological interventions alone and in combination with non-pharmacological therapy on pain relief in patients with chronic TMD.	Randomized controlled trials in which a pharmacological agent was compared with placebo for pain control in TMD patients.	There is insufficient evidence to support or disprove the effectiveness of the reported drugs for the treatment of pain due to TMD. There is a need for more well-conducted randomized controlled studies in the management of TMD.
Häggman-Henrikson et al.[27]	Conduct a health technology assessment (HTA) including a review with meta-analysis of randomized clinical trials to evaluate the treatment effectiveness, health economics, and ethical aspects of pharmacological treatments in patients with chronic orofacial pain.	Randomized controlled trials were included for treatment in patients ≥18 years old with chronic orofacial pain. The patients were divided into subgroups: muscular TMD and joint TMD.	The study summarizes the current evidence, although limited by the small number of studies that can be included, which reduces the generalizability of the results. Even with these limitations, the meta-analysis allowed to observe that the muscle relaxant cyclobenzaprine showed a positive effect in the treatment of TMD muscle pain.
Calderon et al.[30]	To evaluate the effectiveness of cognitive-behavioral therapy (CBT) and the use of amitriptyline in patients with chronic temporomandibular disorders.	47 women (mean age = 35.4 years) with chronic TMD were included in the study and divided into 4 groups: amitriptyline; amitriptyline and CBT; placebo and CBT, and placebo alone (control). Patients were treated for 7 consecutive weeks. Follow-up assessments were done at 1st, 7th and 11th week of treatment. The presence and severity of pain, depression levels, quality of life and sleep were measured.	All three groups showed improvement, although there were no statistically significant differences. At the end of the control, the positive results remained for the CBT + Amitriptyline group in TMD. They also showed that this association is effective in reducing depression levels and improving quality of life.

Continue...

Table 1. Studies that have demonstrated or evaluated pharmacological therapy in temporomandibular dysfunction – continuation

Authors	Goal	Methodology	Results
List and Axelsson[29]	Assess the methodological quality of published SRs on TMD management.	The systematic reviews were searched in the Pubmed, Cochrane, and Bandolier databases between 1987 and September 2009.	There is evidence that amitriptyline is effective in relieving TMD pain.
Gauer and Semidey[9]	To review the literature on the therapeutic management of TMD patients.	The literature review used the key terms: temporomandibular joint disorders, temporomandibular disorders, headache, diagnosis, acupuncture, treatment, occlusal plates, occlusal adjustment, pharmacotherapy, randomized controlled trials, meta-analysis, botulinum toxin, differential diagnosis, biofeedback, cognitive behavior therapy, physical therapy, and classification. Searches on the Cochrane Library, UpToDate, Essential Evidence databases were also included.	Muscle relaxants may prove beneficial if a muscle component is involved. Antidepressants are considered to be first-line therapy in chronic pain associated with TMD. Gabapentin is considered to be very effective for chronic pain.
Sugimine et al.[32]	To verify the efficacy of pregabalin for endogenous analgesia, especially in patients with pain (low endogenous analgesia).	59 healthy subjects were randomly assigned to a pregabalin group or a placebo group and 50 of them completed the study. The correlation of initial CPM with the change in CPM was compared between the pregabalin and placebo groups.	CPM significantly affected the pregabalin group, but not the placebo group (pregabalin group $p < 0.001$; placebo group: $p = 0.56$) which indicate that pregabalin has a greater endogenous analgesic effect in individuals with lower original endogenous analgesia.
Pramod et al.[2]	To evaluate and compare the analgesic efficacy of placebo and diazepam in patients with temporomandibular disorder.	35 patients with a diagnosis of temporomandibular dysfunction were recruited. The patients were randomly placed in one of two groups, placebo or diazepam. Mean pain intensity was recorded with the visual analog scale (VAS) at pre-treatment, at the weekly interval until completion of a three-week trial, and at the post-treatment visit at week eight of baseline.	A statistically significant ($P < 0.01$) decrease in temporomandibular dysfunction pain in the placebo group (65%) and a statistically significant ($P < 0.001$) decrease in the diazepam group (72%) were observed on the VAS after three weeks of treatment. Intergroup comparison showed no statistically significant difference between the groups.
Nitecka-Buchta et al.[36]	To evaluate the efficiency of the myorelaxation effect of cannabidiol after transdermal application in patients with myofascial pain.	60 TMD patients were randomly divided into 2 groups. Group 1 received transdermal cannabidiol and group 2 received topical placebo. Masseter muscle activity and pain intensity were measured by surface electromyography and VAS, respectively, for 14 days with topical applications twice daily.	In group 1, masseter activity decreased significantly, being 11% in the right and 12.6% in the left masseter muscles. In group 2, masseter activity was recorded as 0.23% in the right masseter muscle and 3.3% in the left. Pain intensity on the VAS was significantly decreased in group 1: 70.2%, compared to group 2: 9.81%.

CYC = Cyclobenzaprine; TZA = Tizanidine; CPM = Conditioned pain modulation; TMD = Temporomandibular dysfunction.

DISCUSSION

Pharmacological therapy, as an adjuvant intervention in TMD control, aims to relieve the pain symptomatology, control and remove the patient from a chronic crisis condition[1]. In 90% of the selected studies,[1,2,9,26-30] TMD was found to be chronic. Therefore, it is essential to know and understand the pathophysiological mechanisms of neurogenic inflammation in TMD[8].

The main pharmacological classes investigated were: muscle relaxants, anticonvulsants, antidepressants, and cannabinoids, which in stipulated minimum amounts, modulate pain[1,2,9,26-30,32,36,37]. In most cases of TMD patients, management consists of a multidisciplinary approach, given the complexity of the disorder, whether cognitive-behavioral, psychological, emotional and/or psychiatric[2,5,9]. Discussion of these factors brings the understanding of the psychosocial changes somatization and how each patient faces the TMD in the chronic picture, being usually a negative adjustment to the disorder condition, once it has action in the CNS[18].

The contribution of daily environmental changes in personal, emotional and financial life is deemed to have a major impact on TMD patients quality of life, with high stress, anxiety, and catastrophizing scores in relation to pain maintenance correlated with chronic TMD and, consequently, oral quality of life, affecting self-care[4,17,20]. Although there are not many studies crossing chronic pain, TMD and somatization, it is relevant to consider and deepen the view on such complex interaction in the face of daily activities[16].

These findings were corroborated by a study that evaluated clinical conditions, lifestyle, stress, anxiety, and morning saliva levels, which showed the presence of significant cortisol in patients with chronic TMD, ratifying stress as a potential risk factor for TMJ

muscle and/or skeletal dysfunction development and amplification of CNS sensitization[17].

Pharmacological approach in chronic temporomandibular dysfunction

Among the muscle relaxants, cyclobenzaprine is widely used against TMD, and it acts by inhibiting the serotoninergic pathway under 5-HT2 serotonin receptors. Thus, by acting from the CNS, it suppresses nerve impulses that result in musculoskeletal pain relief[23].

Tizanidine and cyclobenzaprine were effective in improving muscle pain symptoms associated with self-care management, but not superior to the placebo administered in the study[26] (Table 1). This finding reveals that in addition to the good response to the association of therapies for pain management, the multiplicity of TMD aspects should be considered, in view of the psychological factors that affect TMJ dysfunction development and can modulate pain according to the way of coping with the symptomatological condition[18] and the presence of inflammatory mediators[22].

Similarly, in one study[1], muscle relaxants were not significant compared to placebo, contrary to another study[27], which showed, despite limitations, positive results for myogenic TMD (Table 1). This contrasting results in different studies reveals not only the plurality of TMD aspects, but also the difficulty in making the correct diagnosis, empirical therapeutic experience and small sample "n".

Cyclobenzaprine associated with self-care management was shown to be superior compared to diazepam and placebo[28] (Table 1). This finding not necessarily reveal that diazepam does not provide positive effects, because it has inhibitory effects potentiated through the action on GABA adrenergic receptors (gamma-aminobutyric acid), which mitigate the effects on muscles, but it refers to the mechanism of action that the muscle relaxant has to suppress muscle spasm associated with care management by cognitive behavioral therapy (CBT), which increases the chances of pain remission due to therapies connection.

The adverse effects evidenced in studies with tizanidine, cyclobenzaprine, and placebo were drowsiness, dry mouth, and fatigue. These are effects that resolve transiently within a few days. For drowsiness the percentiles for tizanidine, cyclobenzaprine, and placebo were 73%, 53%, and 13%, respectively. For dry mouth they were 79%, 60%, and 33%, respectively, and for fatigue they were 20%, 27%, and 20%, respectively[26].

Amitriptyline has proven effective and safe for TMD control, even with some limitations of studies[23]. Amitriptyline acts by inhibiting the reuptake of serotonin and norepinephrine, prolonging the analgesic effects due to the accumulation of these monoamines in the synaptic cleft[23] and providing analgesic effects in minimal and optimal amounts[23].

A systematic literature review (SLR)[29] evidenced the efficacy of amitriptyline compared to placebo, as well as another study[30], but in this case associated with CBT. In the SLR, 3 clinical studies were covered, with different results, with one being superior to placebo, one moderate in improving TMD-related pain and another with little improvement when comparing amitriptyline to placebo, an inert substance[29] (Table 1). In general, amitriptyline has desirable and appropriate effects for pain control through its analgesic effects and, when associated with other therapy, further increases the success rates of pain control, justified by the management of chronic pain, which is usually multifactorial.

Antidepressants are already used by many patients for several disorders, including chronic pain and psychiatric disorders[30]. When associated with other drugs, they can increase the adverse risks that require approaches in the oral cavity, given their repercussions. Tricyclic antidepressants (TCAs), such as amitriptyline, are the most relevant for oral cavity[30].

Amitriptyline doses above 25 mg tend to provide greater analgesic effects, but with greater adverse effects[31]. TCAs have a strong inhibitory influence on salivary secretion, due to their anticholinergic effects[19,34], which provides an ideal dry mucosa environment for the incidence of oral infections such as candidiasis, periodontal disease, and dental caries[30], in addition to salivary gland infections[31], and for the serotonergic syndrome when associated with cyclobenzaprine or tizanidine[27], which induce an increase in blood pressure and heart rate, and a feeling of uneasiness.

With regard to anticonvulsants in the studies analyzed, gabapentin, despite being more commonly used in peripheral neuropathic pain, was used in patients with chronic TMD pain and was superior to placebo[1,9] (Table 1). Gabapentin showed significant results compared to placebo for pain symptoms, hyperalgesia of the masticatory muscle and the impact of chronic daily myalgia[9]. This shows the analogous action to the neurotransmitter GABA, but in the $GABA_B$ receptor, which allows the opening of $Ca^{++}$and K^+ channels, which induce neuronal hyperpolarization, relaxing the masticatory muscles[23].

In addition, pregabalin was found in only one study, but in individuals with acute TMD, which demonstrated the effectiveness of this drug in producing analgesia in individuals with a lower capacity to modulate pain levels[32] (Table 1). Pregabalin normally inhibits excitatory neurotransmitter release by binding to the alpha 2 subunit of calcium channels[32].

CPM (Conditioned Pain Modulation) and DNIC (Diffuse Noxious Inhibitory Control) assess an individual's ability to reduce or inhibit pain and measure endogenous analgesia[32]. These measurements were used for the subjects administered with placebo and pregabalin[32]. The data revealed that pregabalin has a more effective endogenous analgesic effect for individuals with less ability to modulate pain, i.e., in addition to the drug relying on endogenous analgesia[32], it is typical of those who have chronic pain and have CPM with reduced efficiency, as in case of TMD[35].

Pregabalin compared to placebo elucidated some adverse effects such as: dizziness, 13% for pregabalin group and 0% for placebo; headache, 29% for pregabalin group and 12% for placebo; and dry mouth, 4% for pregabalin and 0% for placebo[32].

One study[2] revealed that diazepam 5 mg showed no statistically significant difference in analgesia over placebo[2] (Table 1). This confirms that placebo can be considered an important agent in strategy management in patients with TMD[2]. On the other hand, when mouth opening is analyzed, it was noted that diazepam group prevailed in the first 3 weeks and stabilized by 5 weeks, i.e., in a short period of intervention there was an improvement in mouth opening and muscle sensitivity[2]. Anticonvul-

sants should be prescribed with caution, because their indiscriminate use causes dependence[33].

The use of medicinal cannabinoids is widely discussed for their anti-inflammatory effects and for their antinociceptive properties[36]. Cannabinoids act on receptors related to the CNS (CB1) and the immune system (CB2), with applicability in chronic pain, improving mood and conferring sedation and relaxation[36,37].

From *Cannabis sativa* leaf, two substances of clinical importance are obtained: cannabidiol, which is non-psychoactive, since it does not alter memory and cognition, and delta 9-tetrahydrocannabinol (THC), which is psychotensive, and therefore its use is limited[36,38].

A study[36] showed a significant reduction in Group 1 regarding muscle activity and pain intensity in the masseter muscle compared to Group 2 regarding myofascial pain (Table 1).

Despite the limitation of publications of articles with cannabidiol targeting TMD-related pain, it was observed that due to the lipophilic nature of the substance, the transdermal route was the most appropriate choice, in view of the reduced systemic bioavailability by the inhalation route (31%) and oral aerosol route (6%)[36]. In addition, the transdermal route allows administration for a longer time in minimal amounts effective at the site of application, which reduces adverse effects, improves efficacy and patient safety[36].

CONCLUSION

The DS is an important agent in acquisition of knowledge about the prescription and pharmacological role of TMD central control drugs. Therefore, they must know not only the risk factors, but also the most common drugs for symptom control, providing safety in the rationalization, given the chronicity of the condition, in order to prevent aggravations, as well as having support, comprehension and enough experience for diagnosis, monitoring, referral and individualized approach.

Pharmacological therapy has shown its analgesic efficacy in controlling pain in patients with TMD, mainly chronic, associated with stress, anxiety, and neurogenic interactions, despite the few clinical studies with centrally acting drugs and with a quality methodology available in the literature, requiring more published studies.

AUTHORS' CONTRIBUTIONS

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Data Collection, Research, Methodology, Writing - Preparation of the Original, Writing - Review and Editing
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Project Management, Writing - Review and Editing, Supervision, Visualization
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