

## **Acupuncture and expression of neurotransmitters in temporomandibular disorders: Systematic review**

### **Acupuntura e expressão de neurotransmissores em desordens temporomandibulares: Revisão sistemática**

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#### **ABSTRACT**

Temporomandibular disorders (TMD) is a common condition of chronic orofacial pain. Acupuncture is a therapeutic method of traditional Chinese medicine (TCM) and some studies to get understand the mechanisms of action and molecular basis involved in this approach therapeutic. We propose to verify in the current literature on the integration of neurotransmitters expression in treat temporomandibular joint disorders by acupuncture in adulthood. A predefined protocol was used and registered on PROSPERO. This qualitative review of the literature analysed international scientific publications in several databases that used the following keywords: Temporomandibular Joint Disorders OR Acupuncture OR Neurotransmitter. Then, in the study selection phase, the eligible texts were read in full to determine their final inclusion or exclusion. The pre-established selection criteria in the protocol determined the inclusion or exclusion of studies during the selection phase. Although to know the diverse effects of acupuncture are intrinsically linked at the cellular and molecular level there is not yet any paper about this in adulthood, but there is a publication about the relationship between TMD and Acupuncture Treatment. There are no studies in the literature that correlate the temporomandibular disorders, acupuncture therapy and neurotransmitters in humans.

**Keywords:** Acupuncture, Neurotransmitters, Temporomandibular Disorders.

## RESUMO

As desordens temporomandibulares (DTM) são uma condição comum de dor orofacial crônica. A acupuntura é um método terapêutico da medicina tradicional chinesa (MTC) e alguns estudos para compreender os mecanismos de ação e a base molecular envolvidos nesta abordagem terapêutica. Propomos verificar na literatura atual sobre a integração da expressão dos neurotransmissores no tratamento dos distúrbios da articulação temporomandibular por acupuntura na vida adulta. Um protocolo pré-definido foi utilizado e registrado no PROSPERO. Esta revisão qualitativa da literatura analisou publicações científicas internacionais em diversas bases de dados que utilizaram as seguintes palavras-chave: Distúrbios Temporomandibulares das Articulações OU Acupuntura OU Neurotransmissor. Em seguida, na fase de seleção do estudo, os textos elegíveis foram lidos na íntegra para determinar sua inclusão ou exclusão final. Os critérios de seleção pré-estabelecidos no protocolo determinaram a inclusão ou exclusão dos estudos durante a fase de seleção. Embora para conhecer os diversos efeitos da acupuntura estejam intrinsecamente ligados a nível celular e molecular, ainda não há nenhum artigo sobre isso na vida adulta, mas há uma publicação sobre a relação entre TMD e o Tratamento da Acupuntura. Não há estudos na literatura que correlacionem as desordens temporomandibulares, a terapia da acupuntura e os neurotransmissores em humanos.

**Palavras-chave:** Acupuntura, Neurotransmissores, Transtornos Temporomandibulares.

## 1 INTRODUCTION

Temporomandibular disorder (TMD) refers to clinical problems in the masticatory muscles, in the temporomandibular joints and musculoskeletal structures associated with the head and neck [1] and are recognized as common conditions of orofacial pain [2,3]. Studies considering that between 40% and 75% of the population of Brazil presents at least one sign of TMD, such as the presence of joint sounds in Temporomandibular Joint (TMD); and 33% have at least one symptom such as, facial or TMD pain [4]. The symptoms characterized chiefly by pain in the muscle and/or temporomandibular joint (TMD), TMD noises, restriction of mandibular movements, and deviation or limitation of mouth opening [2,5–7]. Many clinicians consider persistent pain in the general orofacial region not clearly identifiable as headache to be TMD [3]. Clinical studies have specifically evaluated that comorbid pain is extremely common [2], with >50% of TMD patients reporting headache/migraine, neck pain, joint pain, and low back pain, while only 17% report pain isolated in the face and jaw [8].

The sensorial abnormalities can be observed in somatic and neuropathic pain patients and may be underlying neuroplastic changes. The pain in masticatory system can

also cause sensorial dysfunction due to chronification and become at least in part neuropathic; may be a secondary cause of pain in such patients [2,9]. The symptomatology of orofacial pain has been characterized with the most prevalent symptoms being both current and previous incidences of persistent multifocal pain, coupled with a host of additional somatic complaints, including sleep disturbance, memory problems, fatigue, and mood disorders [9]. The innervation the craniofacial tissues are branches of the trigeminal (V) sensory nerve and can be supplied by other cranial nerves or cervical nerves. They have an extensive somatosensory area in the central nervous system (CNS) and this region is site the most common acute and chronic pain conditions [10].

There is a growing literature on the structural, functional, and neurochemical alterations that are present in the brains of TMD patients. The targets for the development of effective therapeutic is knew the peripheral chemical mediators, ion channels, receptors and intracellular processes involved in the activation or sensitization of the nociceptive afferents. Imbalances in the neurotransmitters known to play a role in causing the pain of the disorder are contributing to the comorbid pain conditions and to disturbances with sleep, affect, memory, and other realms of function [3]. There are indicate that neurotransmitter levels are altered in TMD [11].

Many different therapies, some conservative and reversible, others irreversible, have been advocated for patients with TMD and therapy by acupuncture demonstrating clinical success have been published however the underlying neuromodulator systems mechanisms of acupuncture treatment for it are unclear. Much work has been done to focus their efforts on acupuncture research to better understand the underlying mechanisms and scientific basis of acupuncture as well as to explore the roles and contributions of endogenous systems [12,13]. This way, centralized and peripheral components of pain have been appointing although the Chinese Medicine consider the diagnosis of the patient's energy alteration, which lead to the specific selection of points of treatment for individual syndromic profile or pattern [14]. When first discovery that acupuncture stimulates the secretion of the endogenous opioid endorphin [15] establishes the neural model of acupuncture mechanism so it may also result in the activation of other neural pathways as well as the secretion of other neurotransmitters [12].

Considering that nowadays, a growing number of researchers have begun to focus their efforts on to know the relation of neurotransmitters involved in endogenous systems

to explain the action of acupuncture in temporomandibular dysfunction, the aim this review was approach what have been showed in scientific literature about it.

## **2 MATERIALS AND METHODS**

The protocol of this systematic review was published online (<https://www.crd.york.ac.uk/prospero/>) on PROSPERO (an international database of prospectively registered systematic reviews, registration number CRD42019135901. Two reviewers (Vilela, M.C.R. and Matos, R.J.B.) independently and concomitantly conducted this study using the pre-established protocol. A third evaluator (Cunha, D.A.) was consulted in the case of disagreement between the reviewers. This systematic review was performed in two phases: study selection and data collection. The studies were selected in two stages. First, searches of the PubMed, Biblioteca Virtual, Science Direct, Web of Science, LILACS, Scopus, CINAHL and Bireme were conducted from June to August 2019. For the search filters, the following descriptors were used in the MeSH terms: “Temporomandibular disorders OR Temporomandibular Joint Disorders OR TMD Diseases OR Temporomandibular dysfunction OR Temporomandibular Pain OR Craniomandibular Disorder” additionally “Acupuncture OR Pain Acupuncture OR Acupuncture Treatment OR Acupuncture Analgesia OR Acupuncture Therapy” and “Neurotransmitters agents OR Receptor, Neurotransmitter OR Neurotransmitter OR Neuromodulators”. The studies were selected based on the titles and abstracts. In the second stage of the study selection phase, the eligible texts were read in full to determine their final inclusion or exclusion. Reference lists from the primary studies were also searched to track further studies. The pre-established selection criteria in the protocol determined the inclusion or exclusion of studies during the selection phase.

To be included in the study, and article had to meet the following conditions: 1) it was an original article from experimental studies using humans models; 2) it was a study that used the acupuncture to treat temporomandibular dysfunction in adulthood; 3) it was a study that evaluated the expression of neurotransmitters in the temporomandibular dysfunction. No language or publication period was established. However, a search filter was activated to show only studies performed on adulthood models. Articles that used other techniques to temporomandibular disorders therapy were excluded.

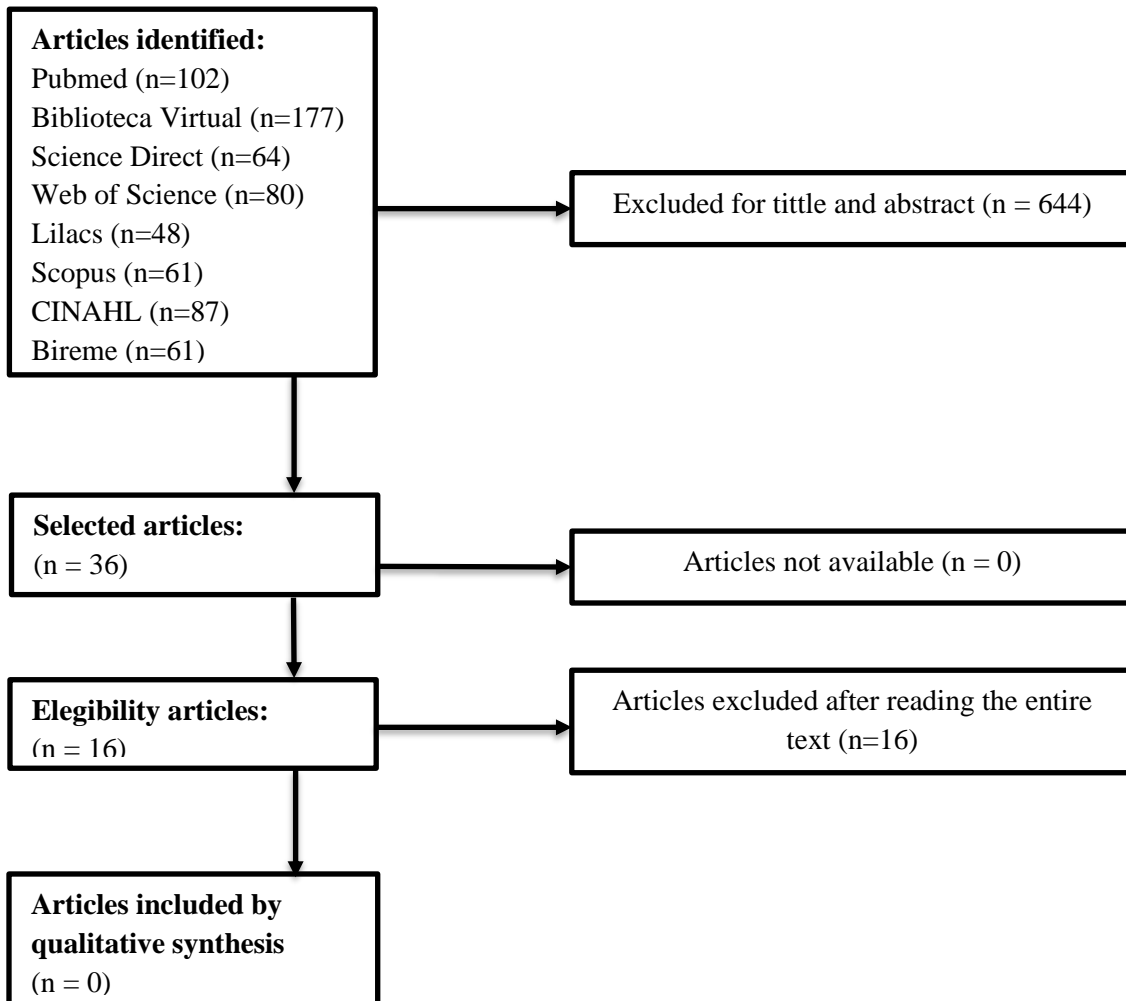
Selection studies was carried out in three stages: the collection of study characteristics, the collection of results and the collection of the components used to evaluate the interferences. The following study characteristics were collected for

qualitative synthesis: the study population, the acupoint, the intervention time, the techniques used for analysis, the molecular and/or cellular results and the behavioural outcomes.

### 3 RESULTS

A total of 680 studies, 16 met the inclusion criteria based on the title and abstract. Finally, no one studies were included in this review after applying the inclusion and exclusion criteria (as defined in the materials and methods section) and fully reading the eligible texts. Unfortunately, in the literature the knowledge about neurotransmitters is not direct TMD. No one paper was published related acupuncture and therapeutics effects and neurotransmitter in adulthood (Figure 1).

Figure1. Flowchart of the bibliographic search and selection of studies for the systematic review.



However, the relationship between TMD and acupuncture is pointed out in seventeen articles published in the Pubmed (n = 15) and Science Direct (n = 2) databases. The tool for pain diagnosis in most studies was the VAS scale [7,16–23], Table 1.

Other assessment methods such as Algometry [24], assessment of pain / tenderness of musculature on pressure [19] and computerized electrical pulp tester [20] are used in pain assessment. Among the selected works, two studied the patterns of Qi imbalance in patients with TMD [16,25]. Bergstro et al [26] made a follow-up study of subjective symptoms of temporomandibular disorders in patients who received acupuncture and / or interocclusal appliance therapy 18-20 years earlier. Most of the patients reported a lasting improvement in their symptoms, Table 1.

About the therapy approach five them used acupuncture and occlusal splint [18,21,24,27,28], five acupuncture and sham acupuncture [16,19,22,23,29]; Wang and Zhang [30] clinical therapeutic effects of acupuncture combined with magnetic therapy; Zhou and Zhao[31] compared the therapeutic effect acupuncture in combination with ultrasound therapy; Widersrtöm-Noga et al,[20] Widersrtöm-Noga et al, (1998) stimulated somatic afferents in patients orofacial muscular pain either manual acupuncture either TENS. Dry needling in classically recognized acupuncture points ("acupuncture") was compared with dry needling in skin areas not recognized as acupuncture points in patients with myofascial pain [17] and Huang et. al. [32] tested whether laser acupuncture was effective for the treatment of TMD, Table 1.

Table 1. Studies investigating the correlation between TMD and acupuncture in adulthood.

RESEARCHS	BASE DE DADOS	APROACHING BY DIAGNOSTIC	TERAPEUTIC APPROACHING	RESULTS
<i>Zhou and Zhao, 2004</i>	PUBMED	–	<i>Treatment: Acupuncture+Ultrasound</i>	<i>Better results in a shorter treatment course.</i>
<i>Wang and Zhang, 2009</i>	PUBMED	–	<i>Treatment: Acupuncture+Magnetic therapy</i>	<i>Better than that of the simple magnetic therapy</i>
<i>Bergstro et al., 2008</i>	PUBMED	–	<i>Evaluate (18-20 years after treatment: Acupuncture+occlusal splint</i>	<i>Most of the patients reported a lasting improvement in their symptoms</i>

List and Helckimo, 1992	PUBMED	By Helkimo	Treatment: Acupuncture+occlusal splint	Similar results
List et al., 1992	PUBMED	–	Treatment: Acupuncture+occlusal splint	Acupuncture better than the occlusal splint therapy
Goddard et al., 2002	PUBMED	VA	Treatment: Acupuncture+dry needling	Both acupuncture and dry needling reduced pain
Zotelli, et al., 2017	PUBMED	Ryodoraku VAS / RDC /	Treatment: Acupuncture+sham acupuncture	- Reduced pain in both groups - Increased the unassisted mouth opening limitation without pain -Preserved the Yin energy in the Treatment Group. -Decreased equally in both groups Yang energy.
List, 1992	PUBMED	Algometer in the masticatory muscles	Treatment: Acupuncture+occlusal splint	Similar results
Grillo et al., 2015	PUBMED	Electromyographic VAS, Millimeter ruler.	Treatment: Acupuncture+occlusal splint	Similar results
Schmid-Schwap et al., 2006	PUBMED	VAS Assessment of pain/tenderness of musculature on pressure Electronic Axiography	Treatment: Acupuncture+sham laser	Similar results
Widersrtöm-Noga et al., 1998	PUBMED	Computerized electrical pulp tester VAS Psychometric forms.	Treatment: Acupuncture+TENS	Only acupuncture increased pain threshold
List et al., 1993	PUBMED	Pressure pain threshold, clinical dysfunction score, and visual analog scale measures were used to evaluate patients before, immediately after, and 6 months after treatment.	Treatment: Acupuncture+occlusal splint	The improvements resulted immediately with acupuncture At the 6-month follow-up, no significant differences

Shen et al., 2009	PUBMED	VAS	Treatment: Acupuncture+Sham acupuncture	Acupuncture is better than sham acupuncture
Smith et al., 2007	PUBMED	Pain VAS and Functional VAS	Treatment: Acupuncture+Sham acupuncture	Acupuncture is better than sham acupuncture
Shen and Goddard, 2007	PUBMED	Functional VAS	Treatment: Acupuncture+Sham acupuncture	Only acupuncture increased pain threshold
Zotelli et al., 2018	SCIENCE DIRECT	Ryodoraku method	Evaluate energy in TMD subjects	-Pattern of Qi deficiency - Imbalance in the kidney and bladder and in the energetic planes Shao Yin (heart/kidney) and Shao Yang (triple energizer/gall bladder).
Huang et al., 2014	SCIENCE DIRECT	VAS	Treatment: Laser acupuncture	Decreased pain

#### 4 DISCUSSION

Results presented in comparative studies between acupuncture and occlusal splint, four pointed to similar clinical results in pain reduction [18,21,24,27]. showed that acupuncture gave better subjective results than occlusal splint therapy. Although, perpetuation of the therapeutic effect of acupuncture and occlusal plaques was observed in subjects after 18 and 20 years of treatment, and most patients reported definite improvement of their symptoms [26].

Comparative work between acupuncture and placebo using sham lasers has yielded similar clinical results [19], but three other studies with a comparative approach between acupuncture and placebo have shown that real acupuncture is more effective than false approaches [22,23,29].

Although most of the positive results were recorded with real acupuncture, Goddard et al[17] experimented with dry needling in acupuncture points ("acupuncture") and compared with dry needling in skin areas not recognized as acupuncture points in patients with myofascial pain. They found that both acupuncture and dry needling reduced



pain evoked by mechanical stimulation of the masseter muscles in myofascial pain patients.

The patterns of Qi imbalance in patients with TMD were analyzed by Ryodoraku and concluded that volunteers with TMD presented a pattern of Qi deficiency, and the most prevalent imbalance patterns identified were in the kidney and bladder coupled meridians and in the energetic planes Shao Yin (heart / kidney) and Shao Yang (triple energizer / gall bladder)[25]. When comparing the effects of real acupuncture and sham acupuncture, Zotelli et al., (2017) evaluating pain score and energetic quality of subjects found that acupuncture points used were effective in reducing pain in both groups, although there were increasing the unassisted mouth opening limitation without pain and preservation of Yin Energy only in the treatment group. The Yang energy decreased equally in both groups.

Considering the influence of anxiety and mood variation on pain threshold scores [20] conducted a comparative study between acupuncture and TENS and found that following acupuncture, the group average pain threshold (PT) increased significantly, whereas no significant change was observed following low-TENS. Higher scores on trait anxiety and stress was significantly correlated with a low PT that increasing following only acupuncture.

Another therapeutic approach to the treatment of TMD following Chinese medical standards is laser acupuncture, which shows good results in the literature [32]. Studies that used acupuncture associated with another therapeutic approach such as ultrasound therapy [31] and magnetic therapy [30] achieved improved effects with the combination of techniques.

The pain is brought about by chemical substances, produced in inflammatory lesions that act on the pain receptors and these are termed pain related mediators [3,10,15].

In TMD dysfunction acupuncture has been the alternative technique that improve clinical signs on the patients [16,18]. There is much work about the mechanism of acupuncture, although there is no unified theory of acupuncture mechanism and details about it are still unclear [12]. It was found that acupoints located on the meridians, exhibited rich innervation mainly in the deep tissues, clearly indicating that the acupoints on all of the meridians were innervated by peripheral nerves [15]. Functional acupoint specificity is crucial to the clinical efficacy of acupuncture treatment, whether acupuncture needling at a peripheral acupoint produces distinct patterns of brain

responses remains controversial. Diverse signal molecules can be mediating acupuncture effects, such different kinds opioid peptides, glutamate, GABA ( $\gamma$ -Aminobutyric acid) enkephalin, dynorphin, substance P, BDNF (brain-derived-neurotrophic factor), dopamine and endocannabinoid system [12,13,15,33].

Neuroimaging have helped us make significant advances in our understanding of chronic pain pathogenesis [34,35]. Functional magnetic resonance imaging studies can reveal how specific neural responses interacted with stimulation at different acupoints, building the neurologic basis of treatment of pain by acupuncture [3]. In the TMD, the understanding of the mechanism of action of acupuncture is also permeated by the understanding of the substances involved in the healing of and repair processes. Research needs to be developed to shed light on this understanding, and perhaps the use of Functional Magnetic Resonance Imaging (fMRI) may be a good way to go. Published studies have presented solid evidence showing the effects of acupuncture in treatment of TMD subjects, further, the neurotransmitter specifically involved in this therapeutic approach in cases of TMD in adulthood are not yet known. Investigations need to be made in order to elucidate this issue. In addition, it is necessary to know about mechanisms main of neurotransmission to assist in acupuncture treatment of musculoskeletal disorders.

## **5 CONCLUSION**

Published studies have presented solid evidence showing the effects of acupuncture in treatment of TMD subjects, further, the neurotransmitter specifically involved in this therapeutic approach in cases of TMD in adulthood are not yet known. Investigations need to be made in order to elucidate this issue. In addition, it is necessary to know about mechanisms main of neurotransmission to assist in acupuncture treatment of musculoskeletal disorders.

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### **ARTICLE HIGHLIGHTS**

- Studies show effects of acupuncture in treatment of TMD;
- It isn't clear about the neurotransmitters directly involved in therapeutic acupuncture to TMD;

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