



UNIVERSIDADE FEDERAL DE UBERLÂNDIA
FACULDADE DE ODONTOLOGIA



MAYRA RESENDE AZEVEDO

**EFEITO DO USO DOS CANABINOIDES NO TRATAMENTO DA DISFUNÇÃO
TEMPOROMANDIBULAR: UMA REVISÃO SISTEMÁTICA DE ESCOPO**

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TEMPOROMANDIBULAR: UMA REVISÃO SISTEMÁTICA DE ESCOPO**

Trabalho de conclusão de curso apresentado
a Faculdade de Odontologia da Universidade
Federal de Uberlândia, como requisito
parcial para obtenção do título de Graduado
em Odontologia

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SUMÁRIO

RESUMO.....	5
ABSTRACT	6
ARTIGO CIENTÍFICO	7
Abstract.....	8
Introduction.....	9
Materials and Methods.....	11
Results	16
Discussion	32
References.....	36
ANEXO I – Normas do Periódico Internacional The Clinical Journal of Pain.....	45

RESUMO

Os objetivos desta revisão de escopo foram avaliar os efeitos da cannabis e produtos derivados sintéticos no tratamento das disfunções temporomandibulares (DTM) e explorar os mecanismos potenciais subjacentes a esses efeitos em diferentes modelos de nocicepção relacionada à DTM. Foi realizada uma busca bibliográfica em cinco bases de dados para publicações até novembro de 2022. Foram incluídos estudos com dados de pacientes/animais submetidos a abordagens terapêuticas com uso de cannabis e seus produtos derivados sintéticos no tratamento de DTM. Doze estudos (nove estudos pré-clínicos, dois estudos observacionais e um estudo intervencional) foram incluídos na revisão de escopo. Os estudos pré-clínicos incluídos nesta revisão demonstraram que os compostos canabinoides são eficazes na redução do comportamento nociceptivo na ATM e no músculo masseter utilizando diferentes modelos animais. Além disso, todos os estudos incluídos avaliando a nocicepção da ATM induzida por formalina relataram que a antinocicepção induzida por um composto canabinoide (com ação agonista) foi mediada pela ativação central dos receptores CB1, mas não dos receptores CB2, na região da ATM. Os estudos observacionais e intervencionais relataram redução da dor, melhora da função e melhor qualidade de saúde com o uso da cannabis medicinal. Além disso, o uso da cannabis medicinal para a dor crônica parece ser uma alternativa eficaz ao uso de opioides e outros medicamentos para controle da dor associados a efeitos secundários indesejados. Conclui-se que o uso da cannabis e de seus produtos derivados sintéticos parecem ser eficazes na redução do comportamento nociceptivo na ATM e no músculo masseter. No entanto, mais estudos clínicos e mecanísticos são necessários para investigar completamente o potencial terapêutico dos compostos canabinoides na DTM.

Palavras chaves: Disfunções da articulação temporomandibular; canabinoides; músculo masseter.

ABSTRACT

The aim of this scoping review was to assess the effects of cannabis and its synthetically derived products on temporomandibular disorders (TMD) treatment and explore the potential mechanisms underlying these effects in various TMD nociception models. A bibliographic search was conducted in five databases were conducted for publications up to November 2022. Studies with data from patients/animals undergoing therapeutic approaches using cannabis and its synthetically derived products on TMD treatment were included. Twelve studies (nine pre-clinical studies, two observational studies and one interventional study) were included in the scoping review. The pre-clinical studies included in this scoping review demonstrated that cannabinoids compounds are effective in reducing nociceptive behavior in the TMJ and masseter muscle using different animal models. Moreover, all the included studies using formalin-induced TMJ nociception reported that cannabinoid agonist-induced antinociception in the TMJ region was mediated by the central activation of CB1 but not CB2 receptors. The observational and interventional studies reported pain reduction, improvement in function and better health quality with cannabis use. Furthermore, the use of cannabis for chronic pain appears to be an effective alternative to the use of opioids and other pain control drugs associated with unwanted side effects. In conclusion, the use of cannabis and its synthetically derived products seems to be effective in reducing nociceptive behavior in TMJ and masseter muscle. However, further clinical and mechanistic studies are necessary to completely investigate the therapeutic potential of cannabinoids compounds in TMD.

Keywords: Temporomandibular Joint Disorders; Cannabinoids; Masseter Muscle.

ARTIGO CIENTÍFICO ¹**EFFECTS OF CANNABINOIDS USE IN TEMPOROMANDIBULAR
DISORDERS: A SYSTEMATIC SCOPING REVIEW**

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Abstract

Objectives: the aim of this scoping review was to assess the effects of cannabis and its synthetically derived products on temporomandibular disorders (TMD) treatment and explore the potential mechanisms underlying these effects in various TMD nociception models. **Methods:** a bibliographic search in five databases were conducted for publications up to November 2022. Studies with data from patients/animals undergoing therapeutic approaches using cannabis and its synthetically derived products on TMD treatment were included. **Results and discussion:** twelve studies (nine pre-clinical studies, two observational studies and one interventional study) were included in the scoping review. The pre-clinical studies included in this scoping review demonstrated that cannabinoids compounds are effective in reducing nociceptive behavior in the TMJ and masseter muscle using different animal models. Moreover, all the included studies using formalin-induced TMJ nociception reported that cannabinoid agonist-induced antinociception in the TMJ region was mediated by the central activation of CB1 but not CB2 receptors. The observational and interventional studies reported pain reduction, improvement in function and better health quality with cannabis use. Furthermore, the use of cannabis for chronic pain appears to be an effective alternative to the use of opioids and other pain control drugs associated with unwanted side effects. In conclusion, the use of cannabis and its synthetically derived products seems to be effective in reducing nociceptive behavior in TMJ and masseter muscle. However, further clinical and mechanistic studies are necessary to completely investigate the therapeutic potential of cannabinoids compounds in TMD.

Keywords: Temporomandibular Joint Disorders; Cannabinoids; Masseter Muscle.

Introduction

Temporomandibular disorders (TMD) encompass a group of dysfunctions and disorders affecting the temporomandibular joints (TMJ), masticatory musculature, and associated structures [1]. TMD is characterized by pain in the muscles of mastication, reduced mandibular range of motion, TMJ pain, associated with joint noise with function, generalized myofascial pain, and a functional limitation or deviation of the jaw opening [2]. Considered the second most common musculoskeletal condition associated with pain and disability, the TMD overall prevalence was approximately 31% for adults/elderly and 11% for children/adolescents [3]

According to Diagnostic Criteria for Temporomandibular Disorders (DC/TMD), TMD can be divided in pain disorders and joint disorders [4]. Most pain disorders manifest as myofascial pain focused to the muscles of mastication [5]. Symptoms include chronic pain in the masticatory muscles, radiating pain to the ears, neck, and head [5]. Myofascial pain is also associated with muscle strain, spasm, and functional limitations. Bruxism, the common sleep disorder and parafunctional activity of the masticatory system, as well as clenching or other parafunctional habits, may be considered the major causes of myofascial pain [6]. Emotional stress also predisposes individuals to clenching and bruxism, contributing to myofascial pain [7].

The diagnosis of myofascial pain is based on the patient's history and physical examination. Radiographic studies can also serve as supplemental diagnostic tools [5]. Therapy goals for patients with myofascial pain focus on reducing pain and improving or restoring function [8]. Noninvasive modalities are often the first treatment option. Drug therapy is often prescribed as an adjunct for noninvasive or minimally invasive treatments with the aim of reducing pain and inflammation in the joint and/or muscles [8, 9]. The drugs most commonly used are nonsteroidal anti-inflammatory drugs (NSAIDs),

myorelaxants, corticosteroids, analgesics, benzodiazepines and tricyclic antidepressants [10]. However, all these drugs are associated with adverse effects as recently revised by Andre, Kang and Dym [8] which can restrict the pharmacologic therapy prescription for myofascial pain management.

Cannabis sativa is a natural plant usually smoked or ingested for recreational purposes. This plant is commonly called cannabis. Recently, both natural cannabis and synthetic-derived products have been proposed for medical use in the pain and inflammation management, particularly in cases where conventional treatments have proven ineffective [11, 12]. Cannabis contains more than 565 chemical compounds, with over 100 classified as cannabinoids. The primary cannabinoids are D9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN) [13, 14]. THC is the main active component of cannabis conferring both psychoactive and analgesic properties [11]. CBD also has an effect on pain control and exhibits anti-inflammatory properties [15].

In the human body, cannabinoids act on endocannabinoid system through two cannabinoid receptors: CB1, primarily found in the central nervous system, but also found in many peripheral tissues including trigeminal ganglion neurons, and CB2, which occurs mainly in the immune system [13]. Both receptors have been considered attractive therapeutic target for pain management, as they induce pain relief in various models of nociceptive, inflammatory, and neuropathic pain [16-18]. Considering, clinical [6] and pre-clinical studies [19-21] have investigated the effectiveness of the cannabinoids in managing pain associated with TMD.

In this scoping review, we assess the effects of cannabis and its synthetically derived products on TMD treatment and explore the potential mechanisms underlying these effects in various TMD nociception models.

Materials and Methods

Protocol

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews (PRISMA-ScR) guidelines [22] were used for reporting this study. A specific review question was elaborated by PICO (population; intervention; comparator; outcome): “Is the use of cannabinoids effective in controlling TMD-related pain?”.

Eligibility criteria

The following inclusion criteria were adopted based on the following PICO criteria: (P) Population: patients/animals with TMD; (I) Intervention: cannabinoids use; (C) Comparator: without cannabinoids use; (O) Outcome: pain reduction; (S) Study design: clinical studies [including randomized clinical trials (RCTs), controlled clinical studies, cohort studies (prospective or retrospective), case series, case reports) and animal studies reporting data about the use of cannabinoids for TMD-related pain control. Moreover, only articles in the English language were included.

Original research articles that did not follow all the criteria defined above were excluded from this scoping review. Moreover, letters to the editor, conference proceedings, protocol articles, historical reviews, in vitro studies (cellular models), and unpublished articles were also excluded.

Information sources and search

Bibliographic or literature search of PubMed, EMBASE, Web of Science, Scopus and Cochrane Library databases were conducted for publications up to November 2022. The search strategies were created using the Medical Subject Headings (MeSH) and Embase Subject Headings (Emtree). Boolean operators (AND and OR) combined the descriptors and improved the search strategy through different combinations, respecting each database syntax rules (Table 1). No filters were utilized in the search strategy.

The publications found in all electronic databases were transferred to the EndNote Program™ X9 version (Thomson Reuters, New York, NY, USA) to remove duplicate references. Then the results were exported to Rayyan QCRI software (Qatar Computing Research Institute, Doha, Qatar) for selection by titles and abstracts. The reference lists of the identified articles were also hand-searched for additional studies.

Table 1: Strategies for database search

Database	Search Strategy (November 2022)
PubMed/ MEDLINE	#1 ("Temporomandibular joint disorders"[All Fields] OR "Temporomandibular disorder"[All Fields] OR "Temporomandibular disorders"[All Fields] OR "Temporomandibular joint disease"[All Fields] OR "Temporomandibular joint diseases"[All Fields] OR "Temporomandibular joint dysfunction syndrome"[All Fields] OR ("Temporomandibular joint dysfunction syndrome"[MeSH Terms] OR ("temporomandibular"[All Fields] AND "joint"[All Fields] AND "dysfunction"[All Fields] AND "syndrome"[All Fields]) OR "Temporomandibular joint dysfunction syndrome"[All Fields] OR ("temporomandibular"[All Fields] AND "joint"[All Fields] AND "dysfunction"[All Fields]) OR "Temporomandibular joint dysfunction"[All Fields]) AND ("syndrom"[All Fields] OR "syndromal"[All Fields] OR "syndromally"[All Fields] OR "syndrome"[MeSH Terms] OR "syndrome"[All Fields] OR "syndromes"[All Fields] OR "syndrome s"[All Fields] OR "syndromic"[All Fields] OR "syndroms"[All Fields])) OR "Temporomandibular joint syndrome"[All Fields] OR "Temporomandibular joint syndromes"[All Fields] OR "joint syndrome temporomandibular"[All Fields] OR "syndrome temporomandibular joint"[All Fields] OR "syndrome tmj"[All Fields] OR "Temporomandibular dysfunction"[All Fields] OR "Temporomandibular joint dysfunction"[All Fields] OR "Temporomandibular Joint"[All Fields] OR "joint temporomandibular"[All Fields] OR "joints temporomandibular"[All Fields] OR ("joints"[MeSH Terms] OR "joints"[All Fields] OR "articular"[All Fields]) AND ("Temporomandibular joint disorders"[MeSH Terms] OR ("temporomandibular"[All Fields] AND "joint"[All Fields] AND "disorders"[All Fields]) OR "Temporomandibular joint disorders"[All Fields] OR ("temporomandibular"[All Fields] AND "disorder"[All Fields]) OR "Temporomandibular disorder"[All Fields])) OR "Articular temporomandibular disorders"[All Fields] OR ("joints"[MeSH Terms] OR "joints"[All Fields] OR "articular"[All Fields]) AND "temporomandibular"[All Fields] AND ("dysfunctional"[All Fields] OR "dysfunctionals"[All Fields] OR "dysfunctioning"[All Fields] OR "dysfunctions"[All Fields] OR "physiopathology"[MeSH Subheading] OR "physiopathology"[All Fields] OR "dysfunction"[All Fields])) OR ("joints"[MeSH Terms] OR "joints"[All Fields] OR "articular"[All Fields]) AND "temporomandibular"[All Fields] AND ("dysfunctional"[All Fields] OR "dysfunctionals"[All Fields] OR "dysfunctioning"[All Fields] OR "dysfunctions"[All Fields] OR "physiopathology"[MeSH Subheading] OR "physiopathology"[All Fields] OR "dysfunction"[All Fields])) OR "Dysfunction Syndrome"[All Fields] OR "TMD"[All Fields] OR "TMJ disease"[All Fields] OR "TMJ diseases"[All Fields] OR "TMJ disorders"[All Fields] OR "TMJ disorder"[All Fields] OR "TMJ pain"[All Fields] OR "TMJ"[All Fields] OR "TMJD"[All Fields] OR "Myofascial pain"[All Fields] OR ("facial pain"[MeSH Terms] OR ("facial"[All Fields] AND "pain"[All Fields]) OR "facial pain"[All Fields] OR ("pain"[All Fields] AND "myofascial"[All Fields])) OR "Myofascial Pain Syndrome"[All Fields] OR "pain syndrome myofascial"[All Fields] OR "pain syndromes myofascial"[All Fields] OR "syndrome myofascial pain"[All Fields] OR "syndromes myofascial pain"[All Fields] OR "Myofascial Trigger Point Pain"[All Fields] OR ("myofascial pain syndromes"[MeSH Terms] OR ("myofascial"[All Fields] AND "pain"[All Fields] AND "syndromes"[All Fields]) OR "myofascial pain syndromes"[All Fields] OR ("trigger"[All Fields] AND "point"[All Fields] AND "pain"[All Fields] AND "myofascial"[All Fields])) OR "Orofacial Pain"[All Fields] OR "Neuralgic Facial Pain"[All Fields] OR ("facial pain"[MeSH Terms] OR ("facial"[All Fields] AND "pain"[All Fields]) OR "facial pain"[All Fields] OR ("facial"[All Fields] AND "pain"[All Fields] AND "neuralgic"[All Fields])) OR ("facial pain"[MeSH Terms] OR ("facial"[All Fields] AND "pain"[All Fields]) OR "facial pain"[All Fields] OR ("pain"[All Fields]

	AND "neuralgic"[All Fields] AND "facial"[All Fields])) OR "TMJ arthralgia"[All Fields] OR "disorder temporomandibular joint"[All Fields] OR "disorders temporomandibular joint"[All Fields] OR ("Temporomandibular joint disorders"[MeSH Terms] OR ("temporomandibular"[All Fields] AND "joint"[All Fields] AND "disorders"[All Fields]) OR "Temporomandibular joint disorders"[All Fields] OR ("joint"[All Fields] AND "disorder"[All Fields] AND "temporomandibular"[All Fields])) OR "joint disorders temporomandibular"[All Fields] OR "disorder tmj"[All Fields] OR "disorders tmj"[All Fields] OR "disorder temporomandibular"[All Fields] OR "disorders temporomandibular"[All Fields] OR "disease temporomandibular joint"[All Fields] OR "diseases temporomandibular joint"[All Fields] OR ("Temporomandibular joint disorders"[MeSH Terms] OR ("temporomandibular"[All Fields] AND "joint"[All Fields] AND "disorders"[All Fields]) OR "Temporomandibular joint disorders"[All Fields] OR ("joint"[All Fields] AND "disease"[All Fields] AND "temporomandibular"[All Fields])) OR ("Temporomandibular joint disorders"[MeSH Terms] OR ("temporomandibular"[All Fields] AND "joint"[All Fields] AND "disorders"[All Fields]) OR "Temporomandibular joint disorders"[All Fields] OR ("joint"[All Fields] AND "diseases"[All Fields] AND "temporomandibular"[All Fields])) OR "disease tmj"[All Fields] OR "diseases tmj"[All Fields])
	#2 ("Cannabis"[All Fields] OR "Cannabinoids"[All Fields] OR "Cannabi"[All Fields] OR "Marijuana"[All Fields] OR "Hemp"[All Fields] OR "Hemps"[All Fields] OR "receptors cannabinoid"[All Fields] OR "Endocannabinoids"[All Fields] OR "Cannab"[All Fields] OR "cbd"[All Fields] OR "thc"[All Fields] OR "Nabilone"[All Fields] OR "Nabiximol"[All Fields] OR "Sativex"[All Fields] OR "Dronabinol"[All Fields]) #1 AND #2
Embase	#1 temporomandibular AND ('joint'/exp OR joint) AND ('disorders'/exp OR disorders) OR (temporomandibular AND ('disorder'/exp OR disorder)) OR (temporomandibular AND ('disorders'/exp OR disorders)) OR (temporomandibular AND ('joint'/exp OR joint) AND ('disease'/exp OR disease)) OR (temporomandibular AND ('joint'/exp OR joint) AND ('diseases'/exp OR diseases)) OR (temporomandibular AND ('joint'/exp OR joint) AND dysfunction AND ('syndrome'/exp OR syndrome)) OR (temporomandibular AND ('joint'/exp OR joint) AND dysfunction AND syndromes) OR (temporomandibular AND ('joint'/exp OR joint) AND ('syndrome'/exp OR syndrome)) OR (temporomandibular AND ('joint'/exp OR joint) AND syndromes) OR (('joint'/exp OR joint) AND ('syndrome,'/exp OR syndrome,) AND temporomandibular) OR (('syndrome,'/exp OR syndrome,) AND temporomandibular AND ('joint'/exp OR joint)) OR (('syndrome,'/exp OR syndrome,) AND tmj) OR (temporomandibular AND dysfunction) OR (temporomandibular AND ('joint'/exp OR joint) AND dysfunction) OR (temporomandibular AND ('joint'/exp OR joint)) OR (('joint,'/exp OR joint,) AND temporomandibular) OR (('joints,'/exp OR joints,) AND temporomandibular) OR (articular AND temporomandibular AND ('disorder'/exp OR disorder)) OR (articular AND temporomandibular AND ('disorders'/exp OR disorders)) OR (articular AND temporomandibular AND dysfunction) OR (articular AND temporomandibular AND dysfunctions) OR (dysfunction AND ('syndrome'/exp OR syndrome)) OR tmd OR (tmj AND ('disease'/exp OR disease)) OR (tmj AND ('diseases'/exp OR diseases)) OR (tmj AND ('disorders'/exp OR disorders)) OR (tmj AND ('disorder'/exp OR disorder)) OR (tmj AND ('pain'/exp OR pain)) OR tmj OR tmjd OR (myofascial AND ('pain'/exp OR pain)) OR (('pain,'/exp OR pain,) AND myofascial) OR (myofascial AND ('pain'/exp OR pain) AND ('syndrome'/exp OR syndrome)) OR (('pain'/exp OR pain) AND ('syndrome,'/exp OR syndrome,) AND myofascial) OR (('pain'/exp OR pain) AND syndromes, AND myofascial) OR (('syndrome,'/exp OR syndrome,) AND myofascial AND ('pain'/exp OR pain)) OR (syndromes, AND myofascial AND ('pain'/exp OR pain)) OR (myofascial AND ('trigger'/exp OR trigger) AND point AND ('pain'/exp OR pain)) OR (('trigger'/exp OR trigger) AND point AND ('pain,'/exp OR pain,) AND myofascial) OR (orofacial AND ('pain'/exp OR pain)) OR (neuralgic AND facial AND ('pain'/exp OR pain)) OR (facial AND ('pain,'/exp OR pain,) AND neuralgic) OR (('pain,'/exp OR pain,) AND neuralgic AND facial) OR (tmj AND ('arthralgia'/exp OR arthralgia)) OR (('disorder,'/exp OR disorder,) AND temporomandibular AND ('joint'/exp OR joint)) OR (('disorders,'/exp OR disorders,) AND temporomandibular AND ('joint'/exp OR joint)) OR (('joint'/exp OR joint) AND ('disorder,'/exp OR disorder,) AND temporomandibular) OR (('joint'/exp OR joint) AND ('disorders,'/exp OR disorders,) AND temporomandibular) OR (('disorder,'/exp OR disorder,) AND tmj) OR (('disorders,'/exp OR disorders,) AND tmj) OR (('disorder,'/exp OR disorder,) AND temporomandibular) OR (('disorders,'/exp OR disorders,) AND temporomandibular) OR (('disease,'/exp OR disease,) AND temporomandibular AND ('joint'/exp OR joint)) OR (('diseases,'/exp OR diseases,) AND temporomandibular AND ('joint'/exp OR joint)) OR (('joint'/exp OR joint) AND ('disease,'/exp OR disease,) AND temporomandibular) OR (('joint'/exp OR joint) AND ('diseases,'/exp OR diseases,) AND temporomandibular) OR (('disease,'/exp OR disease,) AND tmj) OR (('diseases,'/exp OR diseases,) AND tmj)

	#2 'cannabis'/exp OR cannabis OR 'cannabinoids'/exp OR cannabinoids OR cannabis OR 'marijuana'/exp OR marijuana OR 'hemp'/exp OR hemp OR hems OR (receptors,AND ('cannabinoid'/exp OR cannabinoid)) OR 'endocannabinoids'/exp OR endocannabinoids OR cannabis OR cbd OR thc OR 'nabilone'/exp OR nabilone OR 'nabiximol'/exp OR nabiximol OR 'sativex'/exp OR sativex OR 'dronabinol'/exp OR dronabinol #1 AND #2
Web of Science	#1 (((((((((((((((ALL=((Temporomandibular joint disorders))) OR ALL=((Temporomandibular disorder))) OR ALL=((Temporomandibular disorders))) OR ALL=((Temporomandibular joint disease))) OR ALL=((Temporomandibular joint diseases))) OR ALL=((Temporomandibular joint dysfunction syndrome))) OR ALL=((Temporomandibular joint dysfunction syndromes))) OR ALL=((Temporomandibular joint syndrome))) OR ALL=((Temporomandibular joint syndromes))) OR ALL=((Temporomandibular joint dysfunction))) OR ALL=((Temporomandibular joint dysfunction))) OR ALL=((Temporomandibular Joint))) OR ALL=((Articular temporomandibular disorder))) OR ALL=((Articular temporomandibular disorders))) OR ALL=((Articular temporomandibular dysfunction))) OR ALL=((Articular temporomandibular dysfunctions))) OR ALL=((Myofascial pain))) OR ALL=((Myofascial Trigger Point Pain))) OR ALL=((Orofacial Pain)) #2 (((((((((((((((ALL=((Cannabis))) OR ALL=((Cannabinoids))) OR ALL=((Cannabi))) OR ALL=((Marijuana))) OR ALL=((Hemp))) OR ALL=((Hemps))) OR ALL=((Receptors, Cannabinoid))) OR ALL=((Endocannabinoids))) OR ALL=((Cannab))) OR ALL=((cbd))) OR ALL=((thc))) OR ALL=((Nabilone))) OR ALL=((Nabiximol))) OR ALL=((Sativex))) OR ALL=((Dronabinol)) #1 AND #2
Scopus	#1 (ALL ((temporomandibular AND joint AND disorders) OR (temporomandibular AND disorder) OR (temporomandibular AND disorders) OR (temporomandibular AND joint AND disease) OR (temporomandibular AND joint AND diseases) OR (temporomandibular AND dysfunction) OR (temporomandibular AND joint AND dysfunction) OR (temporomandibular AND joint) OR (joint, AND temporomandibular) OR (joints, AND temporomandibular) OR (articular AND temporomandibular AND disorder) OR (articular AND temporomandibular AND disorders) OR (articular AND temporomandibular AND dysfunction) OR (articular AND temporomandibular AND dysfunctions) OR (disorder, AND temporomandibular AND joint) OR (disorders, AND temporomandibular AND joint) OR (joint AND disorder, AND temporomandibular) OR (joint AND disorders, AND temporomandibular) OR (disorder, AND temporomandibular) OR (disorders, AND temporomandibular) OR (disease, AND temporomandibular AND joint) OR (diseases, AND temporomandibular AND joint) OR (joint AND disease, AND temporomandibular) OR (joint AND diseases, AND temporomandibular))) #2 (ALL ((cannabis) OR (cannabinoids) OR (cannabis) OR (marijuana) OR (hemp) OR (hems) OR (receptors, AND cannabinoid) OR (endocannabinoids) OR (cannab) OR (CBD) OR (thc) OR (nabilone) OR (nabiximol) OR (sativex) OR (dronabinol))) #1 AND #2
The Cochrane Library	#1 "Temporomandibular joint disorders" OR "Temporomandibular disorder" OR "Temporomandibular disorders" OR "Temporomandibular joint disease" OR "Temporomandibular joint diseases" OR "Temporomandibular joint dysfunction syndrome" OR "Temporomandibular joint dysfunction syndromes" OR "Temporomandibular joint syndrome" OR "Temporomandibular joint syndromes" OR "Joint Syndrome, Temporomandibular" OR "Syndrome, Temporomandibular Joint" OR "Syndrome, TMJ" OR "Temporomandibular dysfunction" OR "Temporomandibular joint dysfunction" OR "Temporomandibular Joint" OR "Joint, Temporomandibular" OR "Joints, Temporomandibular" OR "Articular temporomandibular disorder" OR "Articular temporomandibular disorders" OR "Articular temporomandibular dysfunction" OR "Articular temporomandibular dysfunctions" OR "Dysfunction Syndrome" OR "TMD" OR "TMJ disease" OR "TMJ diseases" OR "TMJ disorders" OR "TMJ disorder" OR "TMJ pain" OR "TMJ" OR "TMJD" OR "Myofascial pain" OR "Pain, Myofascial" OR "Myofascial Pain Syndrome" OR "Pain Syndrome, Myofascial" OR "Pain Syndromes, Myofascial" OR "Syndrome, Myofascial Pain" OR "Syndromes, Myofascial Pain" OR "Myofascial Trigger Point Pain" OR "Trigger Point Pain, Myofascial" OR "Orofacial Pain" OR "Neuralgic Facial Pain" OR "Facial Pain, Neuralgic" OR "Pain, Neuralgic Facial" OR "TMJ arthralgia" OR "Disorder, Temporomandibular Joint" OR "Disorders, Temporomandibular Joint" OR "Joint Disorder, Temporomandibular" OR "Joint Disorders, Temporomandibular" OR "Disorder, TMJ" OR "Disorders, TMJ" OR "Disorder, Temporomandibular" OR "Disorders, Temporomandibular" OR "Disease, Temporomandibular Joint" OR "Diseases, Temporomandibular Joint" OR "Joint Disease, Temporomandibular" OR "Joint Diseases, Temporomandibular" OR "Disease, TMJ" OR "Diseases, TMJ" in All Text

	#2 "Cannabis" OR "Cannabinoids" OR "Cannabis" OR "Marijuana" OR "Hemp" OR "Hemps" OR "Receptors, Cannabinoid" OR "Endocannabinoids" OR "Cannab" OR "CBD" OR "thc" OR "Nabilone" OR "Nabiximol" OR "Sativex" OR "Dronabinol" in All Text #1 AND #2
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Selection of sources of evidence

Two investigators (L.C.S. and C.F.B) made the initial search for the evaluation of titles and abstracts independently using the previous eligibility criteria. Irrelevant studies were excluded, and the full text of the articles included based on title and abstract were independently read and evaluated according to selection criteria (L.C.S. and C.F.B). Disagreements between reviewers were resolved by discussion including a third investigator (D.A.F.A) for the final decision. The articles excluded in the full-text analysis were listed separately, and the reasons for exclusion were specified.

Data charting process and items

Two investigators (L.C.S. and C.F.B) independently read all studies and extracted the following data for animal studies: (a) animal type; (b) TMD model; (c) experimental groups; (d) methods of pain evaluation and (e) main outcomes. For clinical studies, the data extracted were: (a) study type; (b) patients' number, gender and mean age in each group; (c) medical history; (d) TMD treatment protocol; (e) methods of pain evaluation; (f) follow-up and (g) main outcomes. After completing the data extraction, disagreements were discussed and resolved through consensus with the third reviewer (D.A.F.A).

Synthesis of results

A logical and descriptive summary of the results was made based on the review objective and question. A table was developed describing the characteristics of the included studies and the key information relevant to the review question.

Results

Selection of sources of evidence

In the electronic search, a total of 2370 hits were found, being 2184 unique citations. A total of 30 studies were evaluated as full-text copies and 18 of these studies were excluded based on priori criteria (Figure 1). The exclusion motivation for each excluded study was shown in Table 2. The remaining 12 studies (9 pre-clinical studies, two observational studies and one interventional study) were included in the scoping review.

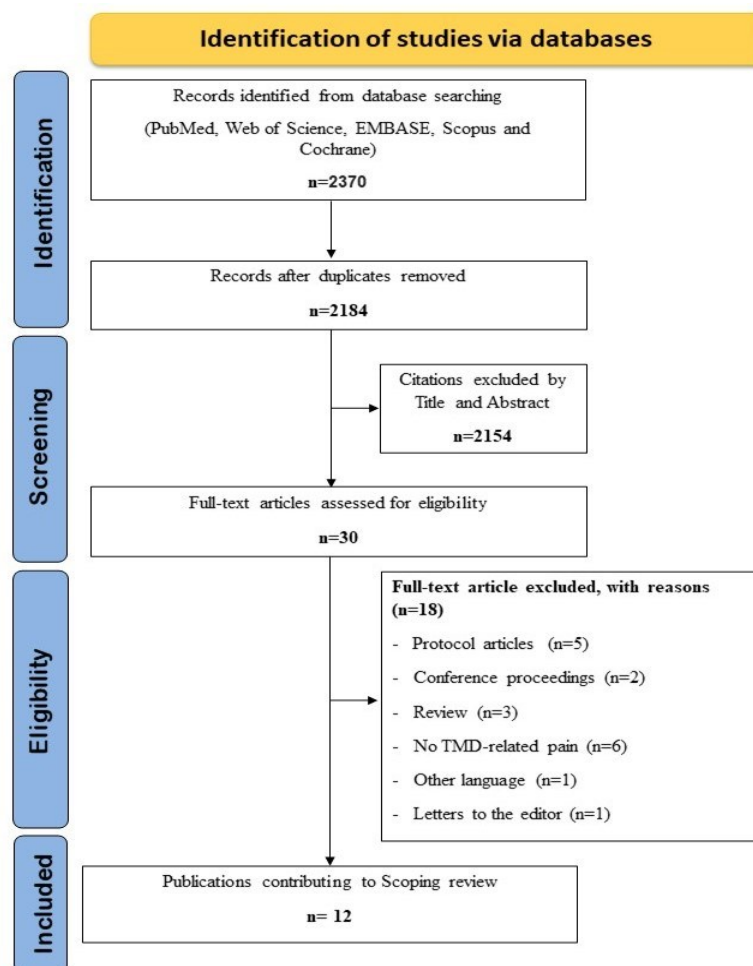


Figure 1: Literature search flowchart.

Table 2 - Articles excluded with the reasons after evaluating the full text.

Author/Year	Exclusion reasons
Baron, Lucas, Eades and Hogue [23]	No TMD-related pain
Nct [24]	Protocol article
Nct [25]	Protocol article
Nct [26]	Protocol article
Nct [27]	Protocol article
Nct [28]	Protocol article
Cornelison, Allen, Mohite, Chellboina and Durham [29]	Conference proceedings
Durham, Hawkins and Hyde [30]	Conference proceedings
Elikottil, Gupta and Gupta [31]	Review
Vivanco-Estela, Dos-Santos-Pereira, Guimaraes, Del-Bel and Nascimento [32]	Myofascial pain related to Parkinson's disease
Haviv, Georgiev, Gaver-Bracha, Hamad, Nemirovski, Hadar, Sharav, Aframian, Brotman and Tam [33]	No TMD-related pain
Heiliczzer, Wilensky, Gaver, Georgiev, Hamad, Nemirovski, Hadar, Sharav, Aframian, Tam and Haviv [34]	No TMD-related pain
Hensen [35]	Review
Pavanini, Lauriola, Mottola and Cocchi [36]	Other language
Rodriguez, Ouyang and Kandasamy [37]	Review
Sessle [38]	Letter to the editor
Zubrzycki, Janecka, Liebold, Ziegler and Zubrzycka [39]	No TMD-related pain

Characteristics of sources of evidence

For in vivo studies (9 studies) (Table 3), the majority used rats (8 studies; 6 studies used male rats and 2 studies used female rats) and only one study used mice. As TMD experimental model, 3 studies used formalin-induced TMJ nociception, 3 studies used acute muscle pain (by hypertonic saline injection in the masseter), 2 studies used Nerve growth factor (NGF)-induced sensitization in the masseter muscle and one study used Complete freund's adjuvant (CFA) into the masseter muscle. Four studies evaluated the WIN 55,212-2 compound (WIN), a synthetic non-subtype-selective cannabinoid CB1 and CB2 agonist, two studies evaluated the THC compound, two studies evaluated the CBD compound, one study evaluated CBN compound and one study evaluated the Cannabichromene (CBC) compound. Regarding the pain evaluation methods, 3 studies evaluated the number of scratches and the duration of scratching, 3 studies evaluated the

total number of hind paw shakes, two studies evaluated in vivo electrophysiology and one study evaluated the face rubbing and head flinching.

From the observational and interventional studies included (3 studies) (Table 4), two studies (1 cross-sectional study and 1 case series) used online questionnaires to evaluate medical cannabis use in chronic pain management. Patients with DTM were included in both studies. Only one interventional study [classified as a randomized clinical trial (RCT)] evaluated the myorelaxant effect of CBD after the transdermal application in patients with myofascial pain.

Synthesis of results

Pre-clinical studies

The studies included evaluating the effect of the cannabinoid agonist WIN 55,212-2 (WIN) showed that cannabinoid-induced antinociception in the TMJ region is mediated by the central activation of CB1 but not CB2 receptors [19, 20, 40]. On the other hand, Robles, Arias and Fontelles [41] reported that both CB1 and CB2 receptors are capable of reducing the nociceptive shaking behavior induced by hypertonic saline in the masseter muscle.

In addition, the central blockade of COX-2 pathways enhanced the antinociceptive effects mediated by activation of CB1 receptor, as reported in Ahn, Choi, Yeo, Woo, Lee, Yang, Jeon, Park and Mokha [19]. However, intracisternal pretreatment with naloxone (opioid receptor antagonist) did not affect cannabinoid-induced antinociception. Similarly, Lee, Choi, Yang, Jeon, Kyung, Kwon, Park, Bae, Mokha and Ahn [20] demonstrated that the central activation of a cannabinoid receptor enhances antinociception produced by intracisternally administered group II or III metabotropic glutamate receptors (mGluRs) agonists in the TMJ region. In Burgos, Pascual, Martín and

Goicoechea [40], WIN induced an antinociceptive effect in the TMJ region equivalent to morphine and superior to other analgesic drugs (indomethacin and ketamine). The studies also reported that intracisternal administration of WIN did not affect motor functions [19, 20, 40].

The THC antinociception effect was confirmed in two different models of muscle pain [12, 42]. Moreover, no impairment of motor functions was reported after THC utilization [12, 42]. However, contradictory results were reported regarding the CB1/CB2 receptors activation by THC. Bagüés, Martín and Sánchez-Robles [12] reported that when THC was administered systemically, its antinociceptive effect was antagonized by the selective CB1 cannabinoid antagonist in the masseter muscle. On the other hand, the CB2 receptor seems to be responsible for the antinociceptive effect of THC after its local administration in the masseter muscle. In Wong, Hossain and Cairns [42] study, the THC was able to reverse the NGF-induced mechanical sensitization of muscle mechanoreceptors through the activation of CB1 receptors but not CB2 receptors.

Wanasuntronwong, Kaewsrirung, Rotpenpian, Arayapisit, Pavasant and Suprongsinchai [21] showed that the antinociceptive effects of CBD induced by acute orofacial nociception induced by CFA was mediated by vanilloid receptor 1 but not by calcitonin gene-related peptide (CGRP). In Wong and Cairns [43] study, intramuscular injections of non-psychoactive cannabinoids CBD, CBN and their combinations reversed NGF-induced sensitization in behavioral and electrophysiology experiments. Low concentration CBD (1 mg/ml) enhanced the ability of CBN to reverse NGF-mechanical sensitization, whereas the higher concentration of CBD (5 mg/ml) appeared to decrease the effectiveness of CBN.

Observational and interventional studies

Both studies using online questionnaire applied in patients with chronic pain (including TMD) described that medical cannabis promoted pain reduction, improvement in function and better health quality [44, 45]. In the Boehnke, Scott, Litinas, Sisley, Williams and Clauw [44] study, the participants reported replacing opioids and other pain medications with medical cannabis due to improvement in symptom management and fewer adverse side effects. Similarly, Lynch, Young and Clark [45] published that the majority of cannabis users were able to decrease the use of other medications associated with side effects. In addition, no serious adverse events associated with cannabis use were reported in this study, and patients declared that the benefits of using cannabis compensated for the side effects in every case.

In a parallel-group RCT, NITECKA-BUCHTA et al. (2019) assessed the myorelaxant and antinociceptive effect of CBD after transdermal application in patients with myofascial pain. The CBD oil was applied over masseter muscle twice a day for up to a period of 14 days. Afterwards, the CBD promoted a reduction in pain intensity of masseter muscles during resting position and improves the condition of the muscle in patients with myofascial pain.

Table 3: Characteristics of the pre-clinical studies included in the scoping review according to the PICO strategy (population, intervention, comparison and outcome).

Author (Year)	Study Purpose	Sample/Animal type/	TMD model	Experimental protocol	Methods of pain evaluation	Main outcomes
Ahn, Choi, Yeo, Woo, Lee, Yang, Jeon, Park and Mokha [19]	To investigate the participation of central COX pathways in modulating the antinociceptive effects of intracisternally administered cannabinoid on nociception induced by inflammation of the TMJ in freely moving rats.	280 male Sprague–Dawley rats	Formalin-induced TMJ nociception	All drugs were intracisternally administered. Experimental protocol 1 (n=8 per group) Saline Formalin Vehicle + Formalin 10 µg WIN 55,212-2 + Formalin 30 µg WIN 55,212-2 + Formalin Experimental protocol 2 (n=8 per group): Formalin Vehicle + 30 µg WIN 55,212-2 + Formalin 10 µg AM251 + WIN 55,212-2 + Formalin 10 µg AM251 + Vehicle + Formalin 10 µg AM630 + WIN 55,212-2 + Formalin 100 µg AM630 + WIN 55,212-2 + Formalin 100 µg AM630 + Vehicle + Formalin Experimental protocol 3 (n=8 per group): Formalin Vehicle + 30 µg WIN 55,212-2 + Formalin 30 µg Naloxone + WIN 55,212-2 + Formalin	Number of scratches and the duration of scratching.	1. 30 µg of WIN (synthetic non-subtype-selective CB1/2 receptor agonist) attenuated the number of scratches and duration of scratching compared with the vehicle; 2. Neither vehicle nor 10 or 30 µg of WIN affected motor functions; 3. 10 µg of AM251 (CB1 receptor antagonist) or 100 µg of AM630 (CB2 receptor antagonist) not affect the scratching behavior; 4. 10 µg of AM251 blocked WIN induced antinociception, while 10 or 100 µg of AM630 did not alter WIN induced antinociception; 5. Naloxone (opioid receptor antagonist) did not block the effect produced by WIN; 6. 10 µg of WIN produced an effect following 30 µg of indomethacin (non-selective COX1/2 inhibitor) or NS-398, (selective COX-2 inhibitor) or acetaminophen (ATAP; COX-3 inhibitor), but not SC-560 (selective COX-1 inhibitor); 7. Pretreatment with NS-398 (selective COX 2 inhibitor) significantly enhanced the

				Experimental protocol 4 (n=8 per group): Formalin Vehicle + 10 µg WIN 55,212-2 + Formalin 30 µg SC-560 + 10 µg WIN 55,212-2 + Formalin 30 µg NS-398 + 10 µg WIN 55,212-2 + Formalin 30 µg Indomethacin + 10 µg WIN 55,212-2 + Formalin 30 µg ATAP + 10 µg WIN 55,212-2 + Formalin		antinociceptive effects of WIN compared with the vehicle-treated group.
				Experimental protocol 5 (n=8 per group): Vehicle + WIN 55,212-2 NS-398 + WIN 55,212-2		
Bagüés, Martín and Sánchez-Robles [12]	To study the anti-nociceptive effect of systemic or locally administered THC in two different rat models of acute muscular pain, and to evaluate the role of the CB1 and CB2 receptors in this effect, using selective antagonists, AM251 and AM630, respectively	Male Wistar rats	Acute muscle pain (by hypertonic saline injection in the masseter)	Systemic drugs administration: i.p. Local drugs administration: i.m (masseter).	Total number of hind paw shakes.	1. Systemic drugs administration: 1A: THC significantly reduced the hind paw shaking; 1B: Animals were pretreated with the selective antagonists only AM251 (CB1 receptor antagonist) was able to antagonize the antinociceptive effect of THC; 2. Local drugs administration: 2A: THC reduced the hind paw shaking in a dose-dependent manner;
				Experimental protocol 1 (systemic): Vehicle THC (0.5 mg/kg) THC (1 mg/kg) THC (3mg/kg)		
				Experimental protocol 2 (systemic): THC (1 mg/kg) THC (1 mg/kg) + AM251 (0.5 mg/kg) THC (1 mg/kg) + AM630 (0.5 mg/kg)		

				Experimental protocol 3 (local): Vehicle THC (0.0125 mg/kg) THC (0.05 mg/kg) THC (0.1 mg/kg) Experimental protocol 4 (local): THC (0.1 mg/kg) THC (0.1 mg/kg) + AM251 (0.04 mg/kg i.m.) THC (0.1 mg/kg) + AM251 (0.5 mg/kg i.p.) THC (0.1 mg/kg) + AM630 (0.04 mg/kg i.m.)		2B: Only the AM630 (CB2 receptor antagonist) prevented the antinociceptive effect of THC; The i.p. administration of THC did not induce motor impairment at the doses of 1 and 3mg/kg, but locomotor activity was significantly reduced with the administration of 5mg/kg.
Burgos, Pascual, Martín and Goicoechea [40]	To evaluate the systemic effect of the cannabinoid agonist WIN 55,212-2 and two antagonists (SR141716A and SR144528) on two different models of inflammatory orofacial pain, and to compare the antinociceptive effectiveness of WIN with other well-known	Male Wistar rats	Formalin-induced orofacial or TMJ nociception	All drugs were administrated before formalin administration (i.p.) Saline solution WIN 55,212-2 (WIN; 0.5 and 1 mg/kg) SR141716A (SR1; 1 mg/kg) + WIN SR144528 (SR2; 1 mg/kg) + WIN Morphine (2, 5 and 10 mg/kg) Naloxone (1 or 2 mg/kg) +	Nociceptive behaviors (face rubbing and head flinching)	1. WIN (synthetic non-subtype-selective CB1/2 receptor agonist) at 1 mg/kg induced an antinociceptive effect; 2. Only the SR1 (CB1 receptor-selective antagonist) prevented WIN-induced antinociception; 3. Neither the cannabinoid receptor antagonists, SR1 and SR2 (CB2 receptor-selective antagonist), nor the cannabinoid vehicle, elicited any significant effect; 4. WIN at 1 mg/kg showed similar efficacy to morphine;

	analgesic drugs such as morphine, indomethacin, and ketamine.			Morphine (5 or 10 mg/kg) Indomethacin (2.5, 5 mg/kg) Ketamine (25, 50 mg/kg)		5. Indomethacin (NSAID) and ketamine (NMDA antagonist) were less effective than the cannabinoid agonist.
Cumella, Hernández-Folgado, Girón, Sánchez, Morales, Hurst, Gómez-Cañas, Gómez-Ruiz, Pinto, Goya, Reggio, Martin, Fernández-Ruiz, Silva and Jagerovic [46]	To synthesize, characterize, and test a chromenopyrazoles library designed analogously to the classical cannabinoid cannabiniol for cannabinoid activity.	Male Wistar rats	Acute muscle pain (by hypertonic saline injection in the masseter)	All drugs were administrated i.p. after masseter injection Vehicle Compound 13a (at 1 and 3 mg/kg ⁻¹)	Number of shakes	The nociceptive behavior was decreased by i.p. administration of compound 13a (at 1 and 3 mg/kg ⁻¹), suggesting that 13a is active in this pain model acting at CB1 receptors located outside the CNS.
Lee, Choi, Yang, Jeon, Kyung, Kwon, Park, Bae, Mokha and Ahn [20]	To evaluate cannabinoid modulation in antinociceptive roles of mGluRs	344 male Sprague–Dawley rats	Formalin-induced TMJ nociception	All drugs were intracisternally administered. Experimental protocol 1 (n=8 per group) Formalin Vehicle + Formalin WIN 55, 212-2 (3, 10 or 30µg) + Formalin Experimental protocol 2 (n=8 per group) Vehicle + Formalin WIN 55, 212-2 (3µg) + Formalin	Number of scratches and the duration of scratching.	1. 30 µg of WIN attenuated the scratches number; 2. 3 µg of WIN or 100 nmol of APDC did not affect the formalin-induced TMJ nociceptive behavior; 3. 30 µg dose of WIN 55,212-2 produced a slight but non-significant motor impairment; 3. APDC (100 nmol; group II mGluR agonist) significantly reduced the

				APDC (100 nmol) + Formalin APDC (100 nmol) + Vehicle + Formalin APDC (100 nmol) + WIN 55, 212-2 (3µg) + Formalin APDC (100 nmol) + WIN 55, 212-2 (3µg) + Vehicle + Formalin APDC (100 nmol) + WIN 55, 212-2 (3µg) + LY341495 (0.5 nmol) + Formalin Experimental protocol 3 (n=8 per group) Vehicle + Formalin WIN 55, 212-2 (3µg) + Formalin L-AP4 (30 nmol) + Formalin L-AP4 (30 nmol) + Vehicle + Formalin L-AP4 (30 nmol) + WIN 55, 212-2 (3µg) + Formalin L-AP4 (30 nmol) + WIN 55, 212-2 (3µg) + Vehicle + Formalin L-AP4 (30 nmol) + WIN 55, 212-2 (3µg) + CPPG (75 nmol) + Formalin		nociceptive behavior in the presence of 3 µg WIN; 4. The antinociceptive action of APDC in the WIN-treated group was blocked by pretreatment with LY341495 (group II mGluR antagonist); 5. Neither pretreatment with 30 nmol L-AP4 (group III mGluR agonist) nor 3 µg WIN altered the scratching behavior; 6. Administration of 30 nmol L-AP4 and 3µg WIN significantly reduced the number of scratches as compared with the vehicle; 7. Antinociception, produced by the combined administration of L-AP4 and WIN was blocked by pretreatment with CPPG (group III mGluRs antagonist).
Robles, Arias and Fontelles [41]	To test if cannabinoids (CB) could be considered as a potential therapeutic alternative for muscle pain and to investigate the contribution of the different subtypes of CB receptors.	Male Wistar rats	Acute muscle pain (by hypertonic saline injection in the masseter)	Systemic drugs administration: i.p. Local drugs administration: i.m (masseter). Experimental protocol 1 (systemic): Vehicle WIN 55,212-2 (0.25 mg/kg) WIN 55,212-2 (0.5 mg/kg) WIN 55,212-2 (1 mg/kg) WIN 55,212-2 (3 mg/kg)	Total number of hind paw shakes.	1. WIN significantly reduced the hindpaw shaking in a dose-dependent manner in systemic and local administration; 2. AM 251 (CB1 receptor antagonist) and AM 630 (CB2 receptor antagonist) antagonized WIN antinociceptive effect in systemic and local administration.

Experimental protocol 2 (systemic):

Vehicle
 WIN 55,212-2 (1 mg/kg)
 WIN 55,212-2 (1 mg/kg) + AM251 (0.5 mg/kg)
 WIN 55,212-2 (1 mg/kg) + AM630 (0.5 mg/kg)

Experimental protocol 3 (local):

Vehicle
 WIN 55,212-2 (0.0125 mg/kg)
 WIN 55,212-2 (0.01875 mg/kg)
 WIN 55,212-2 (0.025 mg/kg)

Experimental protocol 4 (local):

Vehicle
 WIN 55,212-2 (0.01875 mg/kg)
 WIN 55,212-2 (0.01875 mg/kg)
 + AM251 (0.02 mg/kg i.m.)
 WIN 55,212-2 (0.01875 mg/kg)
 + AM630 (0.04 mg/kg i.m.)

Wanasuntronwong, Kaewsrisung, Rotpenpian, Arayapisit, Pavasant and	To investigate the efficacy and mechanisms of CBD on orofacial nociception induced by CFA.	Male <i>Mus musculus</i> mice	CFA into the masseter muscle	All drugs were injected into the right masseter muscle (n=6 per group) Experimental protocol 1: Sham CFA (10 µl) CBD (0.5 mg/10 µl) + CFA	Number of scratches and the duration of scratching.	1. At the 50 % inhibitory concentration (3 mg), CBD exerted antinociceptive effects on spontaneous pain-like behaviors and c-fos expression in several brain areas associated with pain pathways;
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Suprongsinchai [21]				CBD (1 mg/10 µl) + CFA CBD (3 mg/10 µl) + CFA CBD (5 mg/10 µl) + CFA CBD (10 mg/10 µl) + CFA Experimental protocol 2: Sham CFA (10 µl) CGRP antagonista (5nM/10 µl) + CFA CGRP antagonista (5nM/10 µl) + CBD (3 mg/10 µl) + CFA Vanilloid receptor 1 antagonist (1µm/10 µl) + CFA Vanilloid receptor 1 antagonist (1µm/10 µl) + CBD (3 mg/10 µl)+ CFA		2. Injection with a vanilloid receptor 1 antagonist before treatment with CBD showed no difference compared with normal saline injection; 3. Reduction in c-fos expression in each brain area associated with pain was observed in the group receiving CGRP antagonist injected before treatment with CBD.
Wong, Hossain and Cairns [42]	To investigated whether intramuscular injection of THC could decrease NGF-induced sensitization in masseter muscle.	Female Sprague–Dawley rats	NGF-induced sensitization in masseter muscle (model of myofascial TMD)	All drugs were locally administrated into the masseter. Vehicle (PBS; 10 µl) NGF (25µg/mL) NGF (25µg/mL) + THC (1 mg/mL) NGF (25µg/mL) + THC (1 mg/mL) + AM251 (10mg/mL) NGF (25µg/mL) + THC (1 mg/mL) + AM630 (10mg/mL)	In vivo electrophysiology.	1. CB1 and CB2 receptors are expressed by trigeminal ganglion neurons that innervate the masseter muscle and also, on their peripheral endings; 2. Intramuscular injection of THC attenuated NGF-induced mechanical sensitization; 3. Co-administration of the CB1 antagonist AM251 blocked the effect of THC on masseter muscle mechanoreceptors while the CB2 antagonist AM630 had no effect.

Wong and Cairns [43]	To investigated whether local intramuscular injection of non-psychoactive cannabinoids including CBD, CBN, and CBC or their combinations could reduce NGF-induced sensitization in masseter muscle.	Female Sprague–Dawley rats	NGF-induced sensitization in masseter muscle (model of myofascial TMD)	Vehicle (PBS; 10 µl) NGF (25µg/mL) NGF (25µg/mL) + CBD (1 and 5 mg/ml) NGF (25µg/mL) + CBN (1 mg/ml) NGF (25µg/mL) + CBC (1 mg/ml) NGF (25µg/mL) + CBD/CBN (1:1 or 5:1 mg/ml)	In vivo electrophysiology.	1. CBD (5 mg/ml) or CBN (1 mg/ml) decreased NGF-induced mechanical sensitization; 2. Combinations of CBD/CBN induced a longer-lasting reduction of mechanical sensitization than either compound alone; 3. CBD (5 mg/ml), CBN (1 mg/ml) and the combination of CBD/CBN (1:1 mg/ml) increased the masseter muscle mechanoreceptors mechanical threshold; 4. Combining CBD/CBN (5:1 mg/ml) at a higher ratio reduced the duration of this effect which may indicate an inhibitory effect of higher concentrations of CBD on CBN.
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COX: Cyclooxygenase; TMJ: Temporomandibular joint; THC: Tetrahydrocannabinol; i.p.: Intraperitoneally; i.m.: Intramuscularly; NSAID: Non-Steroid Anti-inflammatory Drug; CNS: Central nervous system; mGluRs: Metabotropic glutamate receptors; CFA: Complete Freund's adjuvant; CGRP: Calcitonin gene-related peptide NGF: Nerve growth factor; TMD: Temporomandibular disorders; CBD: Cannabidiol; CBN: Cannabinol; CBC: Cannabichromene.

Table 4: Characteristics of the observational and interventional studies included in the scoping review according to the PICO strategy (population, intervention, comparison and outcome).

Author (Year)	Study type	Study Purpose	Number of participants	Age	Number of male (M) and female (F)	Medical history	TMD treatment protocol	Methods of pain evaluation	Follow up	Main outcomes
Boehnke, Scott, Litinas, Sisley, Williams and Clauw [44]	Cross-sectional study	To report the online survey applied to medical cannabis users with chronic pain about pain management, health, and pain medication use.	1.321 medical cannabis users 84 participants with TMD	49.8 ± 13.9 years*	M=540* F=781*	*Opioid (n=207) Benzodiazepine (n=163) NSAID (n=393) Gabapentanoide (n=154) DMARD (n=39) SNRI (n=118) SSRI (n=160) Other (n=202)	NI	Online questionnaire	Not applied	1. Medical cannabis users with chronic pain reported substituting cannabis for opioids and other pain medications, as well as reporting decreased pain and improved health after using cannabis; 2. The two most common reasons for substitution were improved symptom management and fewer adverse side effects.

Lynch, Young and Clark [45]	Case series	To report descriptive data on 30 patients using medicinal marihuana for chronic pain management.	30 medical cannabis users One participant with TMD	45 years (31-61 years)*	M=18 F=12*	NI	Dosage: 1 to 5 g per day (average dose 2.5 g per day)* Route: smoke (n=30); smoke plus oral (n=9) and oral primarily (n=2)* Not informed for TMD	Online questionnaire	Medicinal marihuana used for 1 to 5 years	1. Ninety-three percent of patients reported moderate or greater pain relief; 2. Side effects were reported by 76% of patients (increased appetite and a sense of well-being, weight gain, and slowed thoughts); 3. Patients reported that the benefits of using marihuana outweighed the side effects in every case; 4. Fifteen patients (70%) were able to decrease the use of other medications that had been causing side effects (e.g., NSAIDs, opioids, and antidepressants); 5. No serious adverse events were reported with the marihuana use; 6. Ninety-five percent of patients reported
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subjective improvement in function;

7. Fifty percent of patients reported previous recreational use of marihuana at some point in their lives.

Nitecka-Buchta, Nowak-Wachol, Wachol, Walczyńska-Dragon, Olczyk, Batoryna, Kempa and Baron [6]	RCT	To evaluate the efficiency of the myorelaxant effect of CBD after the transdermal application in patients with myofascial pain.	60 participants with myofascial pain	Experimental group: 23.2 ± 1.6 years Control group: 22.6 ± 1.86 years	Experimental group: 23.2 ± 1.6 years Control group: 22.6 ± 1.86 years	Experimental group: M=12 F=18 Control group: M=15 F=15	CBD topical application (20% CBD oil) Twice a day for up to 14 days	VAS for pain Masseter muscle activity (sEMG)	Days 0 and 14	Masseter muscle reduces sEMG activity and pain intensity of masseter muscles during resting position and improves the condition of the muscle in patients with myofascial pain.
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*Data not informed for TMD participants; NSAID: Nonsteroidal Anti-inflammatory drugs; DMARD: Disease-modifying antirheumatic drug; SNRI: Serotonin norepinephrine reuptake inhibitors; SSRI: Selective serotonin reuptake inhibitors; NI: Not informed; RCT: Randomized Clinical Trial; CBD: Cannabidiol; VAS: Visual Analogue Scale; sEMG: Surface electromyography.

Discussion

In general, the pre-clinical studies included in this scoping review demonstrated that cannabinoids compounds are effective in reducing nociceptive behavior in TMJ and masseter muscle using different animal models. This effectiveness has been confirmed by observational [44, 45] and interventional studies [6] which reported pain reduction, improved function, and better health quality with cannabis use. Moreover, the use of cannabis for chronic pain appears to be an effective alternative to the use of opioids and other pain control drugs associated with unwanted side effects.

Formalin-induced TMJ nociception was successfully utilized in three included studies [19, 20, 40] as a TMJ model of inflammatory pain to assess nociceptive and antinociceptive responses. Additionally, hypertonic saline injection in the masseter muscle was the most frequent model of acute muscle pain in the included studies [12, 41, 46]. This experimental method has been widely adopted because the quality of the induced pain is comparable to clinical muscle pain with localized and referred pain [47, 48]. On the other hand, NGF-induced sensitization in masseter muscle was also used by two included studies [42, 43] to mimic the tender points observed in the craniofacial regions of TMD patients [49, 50]. Only one study reported the use of CFA to promote a series of inflammatory processes in masseter muscle [21]. CFA induce acute thermal and mechanical hypersensitivities for 1–2 h [42, 51].

CB receptors belong to the family of G-protein coupled receptors, physiologically activated by endocannabinoids [52]. Both CB receptor subtypes lead to the inhibition of adenylate cyclase, which reduces the formation of the intracellular messenger substance cyclic adenosine monophosphate (cAMP) [6]. Expression of both CB1 and CB2 receptors was observed in trigeminal ganglion neurons innervating the masseter muscle, suggesting that these receptors can be targeted for masticatory muscle pain [42]. In fact, Robles, Arias and Fontelles [41] reported that both CB1 and CB2 receptors can reduce the nociceptive behavior promoted

by hypertonic saline injection in the masseter muscle after WIN systemic and local administration.

On the other hand, all the included studies using formalin-induced TMJ nociception reported that WIN-induced antinociception in the TMJ region was mediated by the central activation of CB1 but not CB2 receptors [19, 20, 40]. These contradictory results can be associated with the different tests and tissues used (TMJ formalin test versus hypertonic saline injection in the masseter muscle). However, the innervation is trigeminal in all these cases [41].

For THC, Bagüés, Martín, and Sánchez-Robles [12] demonstrated that the CB2 receptor seems to be responsible for the antinociceptive effect of local THC administration in masseter muscle and CB1 receptor is associated with THC systemic administration. However, Wong, Hossain, and Cairns [42] showed that local THC administration was able to reverse the NGF-induced mechanical sensitization through the activation of CB1 receptors, but not CB2 receptors. One potential explanation for the difference between both studies is that NGF-induced mechanical sensitization is not associated with significant tissue inflammation, therefore it might be expected that CB2 receptor activation (primarily expressed in immune cells) would have a limited effect in this model of myofascial pain sensitivity [42, 53]. It is also important to highlight that the difference in the involvement of CB1 and CB2 receptors on the analgesic effect of WIN compound and THC can be explained by the differences between the pharmacodynamic and pharmacokinetic profiles of these compound, as WIN is a synthetic compounds and THC is a natural derivative of cannabis [54, 55]

Vanilloid receptor 1 and CGRP are receptors in the peripheral ganglion that are crucial for sensory input modulation. Wanasuntronwong, Kaewsrising, Rotpenpian, Arayapisit, Pavasant and Suprongsinchai [21] showed that the antinociceptive effects of CBD were mediated by vanilloid receptor 1 but not by CGRP. It is suggested that cannabidiol is an agonist of vanilloid receptor 1, acting by displace capsaicin from vanilloid receptor 1 and increasing

intracellular calcium levels in heterologous cells overexpressing vanilloid receptor 1 [56-58]. Therefore, continued binding of the cannabidiol–vanilloid receptor 1 complex might cause nociceptive sensitization [21, 59].

The combined prescription of cannabinoids and other compounds to improve pain management has also been proposed for orofacial pain treatment [19, 20]. Of particular note is the prescription of COX inhibitors, which promote analgesic effects by suppressing prostaglandin synthesis in the periphery [60]. As demonstrated by Ahn, Choi, Yeo, Woo, Lee, Yang, Jeon, Park, and Mokha [19], the central blockade of COX-2 pathways enhances the antinociceptive effects mediated by CB1 receptors activation in inflammation-induced TMJ nociception. This result emphasizes the therapeutic potential of combined administration of cannabinoids with COX inhibitors in TMD pharmacologic treatment. However, in the same study, it was demonstrated that the effects of cannabinoids reducing inflammatory pain in the TMJ region do not involve crossover utilization of opioid receptor pathways. Likewise, Lee, Choi, Yang, Jeon, Kyung, Kwon, Park, Bae, Mokha and Ahn [20] also showed the successful combination of sub-analgesic doses of group II or III mGluRs agonists with sub-analgesic doses of cannabinoids in the treatment of inflammatory pain associated with TMJ. The group II and III mGluRs act to inhibit glutamate release through presynaptic autoreceptors at central synapses [61-63] and possibly interact with cannabinoid receptors in presynaptic terminals. According to the authors, the combination of both compounds ensures the cannabinoids administrations at doses not associated with undesirable motor dysfunction [20].

The use of cannabinoids has significant central nervous system side effects including immobility, catalepsy, or hypo-locomotion responses [64]. Moreover, the psychoactive effect of THC limits its use in clinical practice [6]. To address these effects, the local tissue administration of these drugs targeting peripheral receptors was proposed as a treatment for TMD. All pre-clinical studies included in this scoping review demonstrated the efficacy of

cannabinoids local administration using different models of nociceptive behavior in TMJ and the masseter muscle. In line with these findings, an RCT showed that local application of a CBD oil promoted a reduction in pain intensity of masseter muscles during resting position and improved the condition of the muscle in patients with myofascial pain [6]. The transdermal administration proposed in the study allowed a constant drug release at the application site for a longer period of time, minimizing the adverse effects associated with higher systemic drug concentrations. Furthermore, CBD's highly polar chemical structure enhances skin absorption in humans [65].

The main limitation of this scoping review is associated with the limited number of interventional studies included. Only one RCT was included [6], however, the sample size and follow-up period of this study were limited, and further high-quality research is needed to confirm the efficacy of topical application of CBD in the treatment of myofascial pain. Additionally, both observational studies included in this scoping review involved patients with TMD in the sample. Nevertheless, individual results for these patient groups were not described, making it challenging to extrapolate the findings to TMD patients. Moreover, contradictory results were observed for the role of CB1/CB2 in masseter muscle pain management. Therefore, more well-designed clinical trials are required to support the therapeutic effectiveness of cannabinoids in TMD pharmacological treatment.

In conclusion, the use of cannabis and its synthetically derived products appear to be effective in reducing nociceptive behavior in the TMJ and masseter muscle. Nonetheless, further clinical and mechanistic studies are necessary to thoroughly investigate the therapeutic potential of cannabinoid compounds in TMD.

Conflict of Interest: No conflict of interest.

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Legends

Figure 1: Literature search flowchart.

ANEXO I – Normas do Periódico Internacional The Clinical Journal of Pain

The Clinical Journal of Pain - Online Submission and Review System

INSTRUCTIONS FOR AUTHORS

The Clinical Journal of Pain publishes original articles in the following forms: *Clinical investigations*: Present results of original clinical research. *Case reports*: **Case reports will no longer be accepted for publication in *Clinical Journal of Pain* and thus no submission for case reports will be accepted as of June 13, 2013.** *Reviews*: Comprehensive surveys covering a broad area. They consolidate old ideas and may suggest new ones. They must provide a critique of the literature. *Special articles*: On subjects not easily classified above (e.g., articles on history, education, demography, ethics, socioeconomics, etc.). *Letters to the editor*: These may offer criticism of published material, but must be objective, constructive, and educational. A few references, a small table, or relevant illustrations may be used.

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General format: Submit manuscripts in English as a Word file. Double space all copy, including legends, footnotes, tables, and references.

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The Clinical Journal of Pain does not have a required number of words for the text. Please treat your subject thoroughly but not excessively. Perusing several back issues to familiarize yourself with typical accepted article length is recommended.

Abbreviations: For a list of standard abbreviations, consult the *Council of Biology Editors Style Guide* (available from the Council of Science Editors, 9650 Rockville Pike, Bethesda, MD 20814) or other standard sources. Write out the full term for each abbreviation at its first use unless it is a standard unit of measure.

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Journal article

1. Prager J, Jacobs M, Johnson KJ. Evaluation of patients for implantable pain modalities: medical and behavioral assessment. *Clin J Pain* 2001;17:206-214.

Book chapter

2. Todd VR. Visual information analysis: frame of reference for visual perception. In: Kramer P, Hinojosa J, eds. *Frames of reference for pediatric occupational therapy*. Philadelphia: Lippincott Williams & Wilkins, 1999:205-256.

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Software

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Online journals

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Database

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Figures:

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- Cite figures consecutively in your manuscript.
- Number figures in the figure legend in the order in which they are discussed.
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