CBD in orofacial pain and TMD - a literature review

Karolina Walczyńska-Dragon (karolina.dragon@sum.edu.pl)
Medical University of Silesia in Katowice

Aleksandra Nitecka-Buchta
Department of Temporomandibular Disorders, Medical University of Silesia in Katowice

Stefan Baron
Department of Temporomandibular Disorders, Medical University of Silesia in Katowice

Article

Keywords:

Posted Date: November 7th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2184263/v1

License: Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: (Not answered)
CBD in orofacial pain and TMD - a literature review

Karolina Walczyńska-Dragon¹, Aleksandra Nitecka-Buchta¹, Stefan Baron¹
¹Department of Temporomandibular Disorders, Medical University of Silesia in Katowice, 2 Traugutta sq, 41-800 Zabrze, Poland; karolina.dragon@sum.edu.pl

Abstract:

Introduction: Temporomandibular disorders (TMD) and orofacial pain present therapeutic challenges. Interest in the use of CBD-based medications has outpaced the knowledge of its efficacy and safety in treating TMD. The objective of this review was to evaluate the effectiveness of CBD-based medications in individuals with TMD.

Materials and Methods: The PubMed, Embase, Scopus databases were examined. The search was filtered to include only papers published from 2007 to 2022. The main question was asked: Can CBD/Cannabis play an important role in the therapy of orofacial pain and TMD?

Results: After applying the inclusion and exclusion criteria and analyzing the abstracts, 31 articles were finally selected.

Conclusions: CBD should be taken into consideration in the therapy of masticatory muscles in patients with TMD and orofacial pain. Further research is needed for CBD administration.

1. Introduction

The first human use of Cannabis is reported to be 10,000 years ago, at the end of the Ice Age.¹ Through many years Cannabis flowers were used as an analgesic, anticonvulsant, and hypnotic, but in the nineteenth century a significant increase was reported in the use of Cannabis in medicine and research on its phytochemistry and pharmacology. The first characterization of cannabinol (CBN) was done in 1932, followed by the chemical synthesis of CBN and cannabidiol (CBD) in 1940.² In 1964, the psychoactive constituent of cannabis plant Δ9-THC was isolated and partially synthesized. Since then, cannabis has been used extensively in medicine.

Cannabis sativa L. is known to contain more than 565 chemical compounds that belong to different groups, such as flavonoids, dihydristilbens, phenantherenes. Cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC) are the two components found at the highest concentrations, and are the most represented phytocannabinoids in Cannabis sativa plants.³,⁴,⁵ They are produced in the plant in acid form and require a high temperature decarboxylation. There are also other cannabinoids in the plant, such as cannabigerol (CBG), cannabidivarin (CBDV),cannabichromene (CBC) and cannabidiol (CBDN). However, CBD which is an organic chemical compound present in hemp may develope a different activity compared with the psychotomimetic THC.⁶,⁷ The highest concentration of THC and CBD is in female cannabis inflorescence. Among the different species of cannabis, its use depends on the application and content of cannabinoids.

There is medical evidence showing that CBD may be effective in treatment of a wide range of disorders including epilepsy, Alzheimer's disease, Parkinson's disease, Huntington's disease, anxiety disorders including PTSD, depression, dystonia, Meige's syndrome, schizophrenia and psychosis,stroke and hypoxic-ischemic injury, spinal cord injury, inflammatory disorders, psoriasis, rheumatoid arthritis,a wide range of cancers across multiple organ system,
inflammatory bowel diseases, nausea, appetite suppressant and weight loss, bone formation, osteoporosis and fracture healing, hepatic encephalopathy and cirrhosis, cardiovascular diseases including hypertension, cardiomyopathy and myocardial ischemia, and diabetic complications. \(^{8,9,10,11}\)

Unlike THC, CBD does not have any psychoactive effect, scientists even confirmed its antipsychotic and anxiolytic effect and the reduction of some side effects of THC.\(^{12}\) Many researchers proved, that CBD possesses anti-inflammatory, anti-nociceptive and muscle relaxing properties.\(^{13}\) This is the reason why researchers are increasingly trying to find the way of using CBD in patients suffering from TMD and orofacial pain.

The endocannabinoid system (ECS) is a crucial component of the musculoskeletal system's functioning. The ECS helps maintain physiological, emotional, and cognitive homeostasis, is a biological system that consists of endocannabinoids (neurotransmitters) and cannabinoid receptors (CB1 and CB2) expressed throughout the CNS (including the limbic system), and peripheral nervous system.\(^{14,15}\) The CB1 receptors control neurotransmitter release to avoid excessive neuronal activity. It leads to diminish anxiety, calming, reducing pain, and inflammation.\(^{14,16}\)

Temporomandibular disorders (TMDs) comprise a collection of conditions in the temporomandibular joint (TMJ), masticatory muscles and other related structures.\(^{17,18}\) TMD-related pain could be classified as acute or chronic, and patients may also experience limitations of jaw movements. Muscle pain may radiate to the head and neck region and produce other symptoms, such as tinnitus and earaches, soreness of eyes, headaches classified by patients as migraines and characteristic non-odontogenic toothache, especially reported by patients as toothache of all tooth one side of both arches. More often these non-specific symptoms are the result of masticatory muscles hyperactivity, so the first-line treatment for most TMD cases consists of occlusal splint therapy, physical therapy, behavioral modifications to change a patient's parafunctional habits and patient education.\(^{19}\)

Endocannabinoids like CBD are considered to regulate many physiological processes, like pain-sensation or inflammation. Thus, the present systematic review aimed to assess the efficacy of CBD used in reducing pain and other secondary outcomes associated with TMD.

2. Materials and Methods

A literature review was conducted to retrieve RCTs and reviews on the efficacy of cannabinoids in the treatment for TMD and orofacial pain. The databases searched were: PubMed, Embase, Scopus.

We followed the PRISMA guidelines for reporting systematic reviews that evaluate health care interventions.

The databases were searched from 1st May until 30th July, 2022. The search was filtered to include only papers published from 2007 to 2022, in both the Polish and English language. The following keywords were used in search to find proper articles: (CBD OR Cannabinoids OR Cannabis) AND (TMD OR temporomandibular disorders OR orofacial pain).
A preselection of the articles was made by one author who did the initial screen of abstracts, retrieved reports and excluded articles that clearly did not meet the inclusion criteria.

The following articles were included from the literature review:

<table>
<thead>
<tr>
<th>Population</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Studies describing the use of Cannabis/CBD in orofacial pain/TMD</td>
<td>Using CBD in general health problems beside orofacial pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application of Cannabis/CBD</td>
<td>None or any.</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination of facial pain, TMD by using Cannabis/CBD</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last 15 years.</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Two researchers then conducted an independent in-depth analysis of the remaining articles. During the formulation of the search strategy we asked a main question: Can CBD/Cannabis play an important role in the therapy of orofacial pain and TMD?

3. The results

By examining recent literature, we investigated the use of CBD and its potential role in orofacial pain management and TMD.
A total of 51 articles were found in the PubMed database, 21 articles in Scopus database, and 183 articles in Embase database. After applying the inclusion and exclusion criteria and analyzing the abstracts, 31 articles were finally selected (flowchart - Fig. 1).

Fig. 1. Flowchart for the review

There are many reports of observational studies, anecdotal reports, and even systematic reviews, but very few randomized clinical trials (RCTs), especially according to usage of pure CBD without any combination with THC.
In November 2017, The World Health Organization (WHO) announced that CBD in humans exhibits no evidence for abuse or dependence potential, and that there is no evidence of public health related problems associated with the use of pure CBD. In January 2018, the World Anti-Doping Agency removed CBD from their prohibited list, no longer banning use by athletes.

CBD is reported to be used in some medical conditions, including muscle hyperactivity and chronic pain. In human fascia and fascial fibroblasts CB1 and CB2 receptors were discovered. These receptors, with their localisation, may play an essential role in modulating inflammation and diminishing pain referred to masticatory muscles. Presence of cannabinoid receptors was proven in various oral tissues, which shows different directions in possibilities of orofacial pain treatment.

CBD was also proven to be safe and cause only mild adverse effects in humans, e.g., ataxia, sedation, nausea, headache or decreased appetite.

Due to its strong healing properties, many scientists searched for possible applications of CBD. Jakub Mlost et al. suggested a potential anti-nociceptive effect of CBD and CBD combined with other compounds in several pain-related diseases. They suggested, that several inflammatory-induced chronic pain models, CBD, may exert an analgesic and anti-inflammatory effects, also in orofacial pain. Preclinical and clinical studies highlight a potential anti-nociceptive effect of CBD in pain-related diseases. Min K. Lee et al. proved that the central administration of cannabinoids reduces inflammatory nociception in the TMJ. Cannabinoids are known to inhibit nociceptive transmission in the spinal cord, and the potency and efficacy of cannabinoids to produce antinociception are comparable to that of morphine. Authors suggest, that opioid and cannabinoid receptors function together within the same cell or neuronal circuit to produce antinociception and that modulation of one receptor system may lead to alterations in the activity of the other.

The administration of cannabinoid receptor agonists is also known to produce antinociception and reduce hypersensitivity in neuropathic and inflammatory pain models. Electrophysiological studies have demonstrated that cannabinoid receptor agonists inhibit nociceptive neuronal activity in the spinal trigeminal nucleus caudalis. Many clinical studies describe the efficacy of CBD and Δ9-THC co-administration, generally in doses of 2.5 mg CBD and 2.7 mg Δ9-THC in an oral mucosa spray. After treatment sessions, patients reported reduced pain, improved sleep quality, reduced insomnia and fatigue. Although, as far as we know, there were no studies based on pure CBD intraoral administration.

Scientists are still trying to find the best way of CBD application, to improve it's absorption. Wong et al. found that the trigeminal ganglion had both CB1 and CB2 receptors that innervate the rat masseter muscles and proved that intramuscular injection of CBD alone (5mg/ml) decreased mechanical sensitization and increased the mechanical threshold of masseter muscle mechanoreceptors. Therefore CBD injections might be successful for analgesic relief of myofascial pain syndrome without neurological side effects.

In another study with rats, electroacupuncture treatment was known to possess anti-inflammatory and antinociceptive effects in rat models of TMJ arthritis and it was suggested that effects of TMJ could be activated through cannabinoid receptors. In this study scientists
paid attention to endocannabinoid system as a different path for finding a solution for pain and inflammation reduction in TMD.\textsuperscript{31}

The positive effects of CBD were confirmed many years ago, encouraging clinical trials. A transdermal CBD-containing gel in patients with peripheral neuropathic pain mitigated pain, as well as cold and itchy sensations. CBD might be used clinically alone or in combination with other cannabinoids.\textsuperscript{32,33}

In a clinical trial of CBD skin application in adults Nitecka-Buchta et. al.\textsuperscript{33} showed that CBD may have analgesic activity in temporomandibular joint disorder. In that double-blind trial the application of CBD formulation over masseter muscle reduced the activity of masseter muscles and improved the condition of masticatory muscles in patients with myofascial pain. According to RCTs, three ways of CBD application to relief orofacial pain are administered-topical skin application, intramuscular injections, intraoral application-on mucosa. Future studies should confirm the clinical relevance to pain reduction and the best way of CBD administration in order to use CBD products effectively.

CBD is known to be an inverse agonist at the CB2 receptor, which may contribute to its anti-inflammatory effects. By the work of Mengjie et al.\textsuperscript{34} CBD can act on the CB2 receptors to inhibit the inflammatory state, whereas a portion of its effects is realized by binding TRPV1, G protein-coupled receptor 55, and 5-HT-1A other than the CB mechanism. Due to CBD topical administration, a low level of oxidative and nitrosative stress was also observed.

In a clinical trial by Vivanco-Estela et.al.\textsuperscript{35} authors suggest a distinct treatment effect depending on sex-related differences. Researchers proved, that male rats reduced allodynia and hyperalgesia responses in orofacial region compared to female, acute treatment with the smaller and intermediate doses of CBD (10 and 50 μg) injected locally in masseter muscle decreases orofacial allodynia in female and the intermediate and higher doses of CBD (50 and 100 μg) reduced orofacial allodynia in male. Acute treatment with the 3 CBD doses injected locally in the masseter muscle decreased orofacial hyperalgesia in both female and male rats, with the better responses in male rats. This research work shows a potential way of CBD administration in patients with orofacial pain.

Amongst many other symptoms, patients with TMD often suffer from a low quality of sleep. Furthermore, obstructive sleep apnea (OSA) is presumably associated with chronic pain disorders including temporomandibular disorder.\textsuperscript{36,37,38,39} Authors emphasize that the association between sleep disordered breathing and TMD requires further study and may provide novel insight into the complex interactions between sleep and pain-regulatory processes.

The quality of sleep was evaluated in a research by Golanska et. al.\textsuperscript{40} Authors suggest, that temporomandibular myofascial pain syndrome is affected by the combined action of the limbic, autonomic, endocrine, somatic, nociceptive, and immune systems. Due to the complexity of the problem, monotherapy is usually insufficient and patients are looking for alternative solutions, such as the CBD administration.

In other research it was shown that 79.2\% of all patients suffering from myofascial pain had decreased anxiety and 66.7\% had improved sleep after one month of CBD treatment.\textsuperscript{41,42}

4. Conclusions
Orofacial pain, which is one of the most common causes of chronic pain, is related to musculoskeletal disorders and temporomandibular disorders (TMDs). TMD is resulting in pain and dysfunction that involves the masticatory muscles, the temporomandibular joint, and associated structures.

Diagnostics and treatment of TMD is a long and difficult process and sometimes splint therapy, botox, hyaluronic acid or physiotherapy are insufficient. CBD formulations are a promising form of masticatory muscles therapy in patients suffering from TMD and could be an effective alternative to the most commonly used therapies. Further research is necessary to achieve the most effective way of CBD administration in orofacial pain.

5. Author Contributions
Conceptualization: K.W-D. (Karolina Walczyńska-Dragon); methodology: S.B. (Stefan Baron); resources: A.N-B. (Aleksandra Nitecka-Buchta), K.W-D. (Karolina Walczyńska-Dragon); writing—original draft preparation: K.W-D. (Karolina Walczyńska-Dragon); writing—review and editing: S.B. (Stefan Baron); supervision: S.B., A.N-B (Stefan Baron, Aleksandra Nitecka-Buchta). All authors have read and agreed to the published version of the manuscript.

6. Funding: The authors did not receive specific funding but the research study was performed as part of the employment in the Medical University of Silesia in Katowice, Poland. Manuscript publishing charges were also covered by the Medical University of Silesia in Katowice, Poland.
References:


14. Vivanco-Estela AN, Dos-Santos-Pereira M, Guimaraes FS, Del-Bel E, Nascimento GCD. Cannabidiol has therapeutic potential for myofascial pain in female and male parkinsonian...


35. Vivanco-Estela AN, Dos-Santos-Pereira M, Guimaraes FS, Del-Bel E, Nascimento GCD. Cannabidiol has therapeutic potential for myofascial pain in female and male parkinsonian rats. Neuropharmacology. 2021 Sep 15;196:108700. PMID: 31698733; PMCID: PMC6912397.


