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# Cannabis and Cannabinoid Medications for Treatment of Chronic Orofacial Pain: A Scoping Review

# Cannabis and Cannabinoid Medications for the Treatment of Chronic Orofacial Pain: A Scoping Review

## Short Title: Cannabinoids and Chronic Orofacial Pain

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KEYWORDS: *Cannabis, Cannabinoid, orofacial pain, Chronic pain*

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ABSTRACT

***Objectives****:* To collate and summarize existing evidence for the use of cannabis and cannabinoids to treat chronic orofacial pain (COP) by oral and maxillofacial surgeons (OMFS), oral medicine specialists (OMS), and orofacial pain specialists (OPS). ***Data:*** We systematically screened for sources including a measure of effect of a cannabinoid compound on pain in COP patients that might be treated by our target specialists. Sources were selected by two authors independently. Sources were summarized by country, publication date, objective(s), COP condition(s) studied, cannabinoid(s) studied, methods, results, limitations, and conclusions. A thematic analysis and word cloud were conducted to elucidate commonalities, emphases, and gaps amongst identified

sources. ***Sources:*** Retrieved from MEDLINE, EMBASE, Web of Science Core Collections, Dentistry and Oral Sciences, DARE, CCRCT, and US National Institute of Health and Controlled Trials Register. ***Study Selection****:* Of 705 retrieved titles, 8 met inclusion/exclusion criteria and were included for review. Included sources dealt with COP attributed to: head and neck cancer (3), multiple sclerosis-related trigeminal neuralgia-like symptoms (2), post-herpetic neuralgia (1), temporomandibular dysfunction (1), and primary burning mouth syndrome (1). Cannabinoids studied included: self-administered cannabis (3), topical N-palmitoyle-thanolamine (1), topical cannabis extract (1), cannabis sativa oil (1), nabiximols oromucosal spray (1), and nabilone (1). ***Conclusions:*** Most sources concluded their respective cannabinoid treatments to provide some therapeutic benefit for COP (6 of 8) and all concluded their treatments to be safe. Current research is wholistically focused, recording outcome measures for pain, anxiety, depression, quality of life, functional disability. Cannabinoids are most often studied as adjunctive and palliative treatments.
***Clinical significance****:* Cannabinoids are becoming increasingly accessible and might benefit many COP patients. Patients and clinicians require more and higher quality evidence to make confident and informed decisions regarding treatment of COP with cannabis or cannabinoids. This review summarizes current evidence for patients, clinicians, and future researchers.
KEYWORDS*: Cannabis, Cannabinoid, orofacial pain, chronic pain, THC, CBD*

## INTRODUCTION

Pain is most currently defined as: “An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” [1]. Pain can be viewed as acute or chronic with chronic pain defined as “pain that persists or recurs for more than 3 months” [2]. In chronic pain syndromes, pain is often the sole or leading complaint and requires special treatment and care [2]. Orofacial pain is an umbrella term used to define pain emanating from the head and neck region which may be of odontogenic or non-odontogenic origin [3]. Chronic orofacial pain (COP) is pain in the head and neck region that is chronic in nature [3]. Since COP is a definition based on anatomic location rather than pathophysiology, there are a wide range of diagnoses that fall within its scope. The pathophysiology of these conditions are varied and complex. Conditions resulting in COP may be of musculoskeletal, neurovascular, or neuropathic origin [3]. In addition, it is common for COP conditions to be complex and of multifactorial or idiopathic origins making treatment difficult [4]. Cannabis and cannabinoid medications are increasingly being used as a treatment option for refractory pain conditions with similar pathophysiology to many COP conditions [5]; in addition, research into the mechanisms of action for cannabinoid analgesics suggests they may be well-suited to treating refractory COP [4,6,7].

COP is a persistent unpleasant experience in a vital and intimate region of the body. It has a profound negative impact on quality of life for those who experience it [8]. COP can interfere with daily functions including speech, mastication, hydration, oral hygiene, sleep, and intimacy [9]. Severe physical and psychosocial sequelae are also common and may include dietary insufficiencies, social isolation, sleep deprivation, dental pathology, missed work or work cessation, depression, and drug abuse. [9, 10, 11].

Pathology of odontogenic origin is the most common cause of orofacial pain for which patients seek professional help; however, odontogenic pain is nearly always of an acute nature and is treated effectively without cannabinoid medications. The prevalence of COP may be as high as 7% in the general population [12], but a statement regarding its exact prevalence is difficult

because of differing opinions on when pain qualifies as chronic and because universal inclusion criteria for orofacial pain do not exist [10]. What is known is that: chronic orofacial pain affects a relatively large proportion of the general population; certain populations including women and the elderly are affected disproportionately; and those that are affected suffer a substantial decrease in quality of life [8,10].

Cases of COP are often difficult to diagnose and treat [13] and are therefore often referred from general-practice dental or medical offices to specialists, most commonly oral and maxillofacial surgeons (OMFS), oral medicine specialists (OMS), or orofacial pain specialists (OPS). Options for treatment include limiting or avoiding exacerbating behaviours, diet modification, biofeedback, physical therapy, psychological therapy, appliance therapy, pharmacologic management, nerve blocks, trigger-point injections and varied surgical interventions [8,10]. Despite the variety of treatments available, patients and practitioners often report being dissatisfied and frustrated with available treatments [13]. Nerve blocks and surgical treatment options have varied success and present a level of physical risk to the patient [14]. Pharmacological management options, such as opiates, have limited success in managing chronic pain and may lead to dependence, addiction, drug tolerance, and other adverse effects [15]. A retrospective study looking at patients initially presenting with a COP diagnosis revealed that only 24% of attempts at managing pain were satisfactory for these patients and their respective attending clinicians [16]. Hence there is a need to explore alternate treatments for COP patients whose conditions are either refractory to traditional treatments or whose potential treatments (such as those associated with surgical interventions and opioid analgesics) carry a risk level that is unacceptable for patients. One such alternate option may be cannabinoid-based treatments.

While cannabis has been used holistically for the treatment of pain for millennia [17], only recently has there been a substantial increase in research on the analgesic properties of cannabis [18]. Research regarding the use of cannabis and cannabinoid medications for the treatment of chronic pain is also increasing [19]. Reviews on the use of cannabinoid medications for neuropathic pain have found encouraging results [5]. Given the similar pathophysiology between non-orofacial neuropathic pain conditions and several COP conditions, cannabinoid medications may be useful for treating COP conditions such as burning mouth syndrome, trigeminal neuralgia, and post-herpetic neuralgia [5]. In addition, studies aimed at assessing reasons patients access medical marijuana repeatedly report that patients use medical marijuana to relieve pain that is myofascial, arthralgic, or musculoskeletal in nature [20, 21, 22]. These findings suggest cannabinoids may be useful in relieving symptoms of TMD, the most common COP condition for which patients seek treatment [23]. To our knowledge there is a dearth of primary evidence for using cannabinoid medications to treat COP and thus the objective of this scoping review is to collate and summarize the evidence that exists regarding the use of cannabis and cannabinoid medications to treat COP conditions that fall within the scope of practice of OMFS, OMS, and OPS. The specific research question used to identify literature relevant to our objective was "What literature exists on cannabinoid-based treatments for COP falling within the scope of practice of OMFS, OMS, or OPS?". We intend to collate and summarize the available evidence to create a resource which makes clear the range and focus of current research for clinicians and patients alike, and to help guide future research in this area.

## MATERIALS AND METHODS

This scoping review was conducted following the Arksey and O'Malley framework for scoping reviews [25]. The methodology for our literature search, article screening, and analysis are reported using the preferred reporting items for systematic reviews and meta-analyses for scoping reviews (PRISMA-ScR) [26].

*Key Search Terms and Inclusion and Exclusion Criteria*

With the guidance of a health sciences librarian, a general search strategy for capturing as much literature relevant to our research question as possible was planned as follows.

A list of key terms associated with COP including specific diagnoses for which patients may develop chronic orofacial pain was compiled with the help of a certified oral medicine specialist. A list of key terms that would return sources dealing with cannabis or cannabinoids was developed. Here we considered cannabis or cannabinoid medications to be any prescribed or self-administered substance derived from a cannabis plant, synthetic cannabinoid, or endocannabinoid. Sources identified through searching databases for these key terms were reviewed and the lists of key terms were updated; this process continued until saturation was reached. The final lists of search terms to identify sources associated with COP and sources associated with cannabinoids are shown in Table 1. The results of each list were summed and sources present in both lists served as the body of literature eligible for screening. This general search strategy was adapted for best use for each electronic database searched. A detailed description of the search strategy used for each specific database is shown in Tables 2a-2e.

The key search terms in Table 1 formed the basis of our inclusion and exclusion criteria. Since we were primarily interested in finding literature that could most directly aid in decision making for patients, clinicians, and researchers regarding the use of cannabis and cannabinoid medications for treating COP, we initially included literature sources if they contained some outcome measure for cannabis or cannabinoid medication(s) as treatment for pain. Articles were included if they studied outcomes for chronic pain (defined as such by the author(s) of the article in question, or if the condition underlying the pain was of a chronic nature). Additionally, sources were only included if the symptoms or conditions being treated could potentially fall within the scope of practice of OMFS, OMS, or OPS. If the independent reviewers were unsure whether to include an article based on this criterion, the decision was made by a licensed oral medicine specialist who was part of the research team. All routes of administration were included. Sources were included from the maximum ranges of publication dates for each database. Both published articles and grey literature including unfinished studies were searched. Sources were excluded if full texts were not available in English or if animal models were their primary focus. A list of inclusion and exclusion criteria are available in Table 3.

*Search Strategy*

Using the search strategies outlined in Tables 2a - 2e, the following electronic databases were searched: Medline, Embase, Web of Science Core Collection, Dentistry and Oral Sciences, The Database of Abstracts of Reviews of Effects (DARE), The Cochrane Central Register for Controlled Trials, and The U.S. National Institutes of Health Clinical Trial Register. The literature search took place between June 1, 2021, and June 11, 2021. From this initial list of sources duplicates were removed to create the list to undergo title and abstract review.

Two independent reviewers were provided the above list in the form of an Excel document and an initial meeting was held for the two reviewers to calibrate regarding inclusion and exclusion criteria. The reviewers independently assessed all titles and abstracts for eligibility for full-text review, then reviewed full-texts for final analysis against our inclusion and exclusion criteria. Full texts were accessed through the University of Saskatchewan Library or through loaning

agreements with other institutions. In one case the full text for an article was purchased specifically for this study. References from all sources selected for full-text review were searched for additional relevant literature. After title and abstract screening and again after full-text review, results were compared between reviewers and any disagreements regarding inclusion and exclusion were discussed. If no decision could be reached whether to include or exclude a source, a third independent reviewer was to make the decision. No sources required the third reviewer. This process led to the final list of sources for data extraction. Interrater level of agreement and Cohen's Kappa statistic were calculated at both stages of the screening process.

*Data extraction table, theme analysis, and word cloud*

A data extraction table was created to record relevant information from each of the sources selected for data extraction. The columns of this table include country and year of publication, title, objective(s) of study, COP condition(s) studied, cannabinoid(s) studied, methods overview, relevant results, limitations, and relevant conclusions drawn (see Table 4).

To summarize and analyze the focus and content of included sources, a theme analysis was carried out. The two reviewers read each source and independently developed a list of topics that appeared in at least one of the sources. Topics were considered to be any element of the literature that spoke to the focus, goals, limitations, clinical implication, clinical significance, or interpretation of findings of a source. The reviewers met to compare topic lists, level of agreement was recorded, and disagreements were discussed to arrive upon a single finalized topic list. Disagreements on inclusion or exclusion of a topic that could not be settled between the two reviewers were to go to a third independent reviewer; however, the third reviewer protocol was not needed. Once the final list of topics was created and level of agreement recorded, the reviewers reread each of the sources and coded each topic from the final list as either present (1) or not present (0) in each individual source. In a similar process to that described above for establishing the final list of topics, the reviewers met to compare data, and record and discuss any disagreements. Once again, use of a third independent reviewer was not necessary. After the data set for the presence of identified topics was finalized, a member of the research team who had no previous involvement with the analysis process reviewed the data set and grouped topics together if they were seen, in the reviewer's judgment, to center around a common theme.

We created a word cloud to find, visualize, and communicate words that commonly appeared in the titles and abstracts of selected sources. The word cloud was generated using the free online word cloud generator available at worditout.com (see Figure 4). All text from all titles and abstracts was entered into the word cloud generator. All words with no meaning outside the context of the sentences in which they appeared were removed. The list was "cleaned" to combine upper- and lower-cases or singular and pluralized versions of the same words. Similarly, acronyms and words belonging to a single term were combined. Examples of this include "multiple sclerosis" and "MS" to "multiple-sclerosis," or "QOL" and "quality of life" to "quality-of-life."

## RESULTS

Implementing our search strategy yielded 8 sources for analysis [27 – 34]. A summary of the results at each stage of the review process is available in Figure 1. There was 95.6% agreement between reviewers regarding articles eligible for full text review (Cohen's kappa = 0.64), and 99.5% agreement regarding articles for final inclusion and data extraction (Cohen's kappa = 0.80).

*Summary of articles by objectives*

As a direct result of our search protocol, all 8 sources reviewed contained data on the effect of a cannabinoid medication on COP falling within the scope of practice of OMFS, OMS, or OPS. However, pain was the primary outcome of interest for only half of the included sources [27, 29, 32, 33]. 2 of the remaining 4 sources were primarily concerned with quality of life [28, 30] and 2 were primarily focused on determining for which symptoms patients self-medicated with cannabinoids. [31, 34]. 5 sources endeavored to record adverse effects of the respectively studied cannabinoid treatments [27,29,30,32,33], but only 1 listed recording adverse effects of the cannabinoid treatment as a main objective [30].

*Summary of articles by year of publication*

Despite searching all years catalogued by each database, no eligible articles were found published before 1997 [34]. In fact, 6 out of 8 sources reviewed were published within the last 6 years [27-33], while the remaining source was published in 2009 [27]. This indicates a relatively recent increase in research related to cannabinoids for treatment of COP which is not surprising given the overall increased interest in cannabinoid medication that has come with recent legal changes in North America and other parts of the world [18].

*Summary of articles by condition studied*

All sources assessed treatment of COP attributed to a specific diagnosis, no studies assessed the effect of cannabinoid medication on COP related to multiple or unknown diagnoses. 3 sources studied COP caused by head and neck cancer and treatment of head and neck cancer [28, 30, 32]. 2 sources studied multiple sclerosis (MS) related trigeminal neuralgia-like pain [33, 34]. 1 source assessed the effect of cannabinoid medications on primary burning mouth syndrome [29] and 1 on post-herpetic neuralgia [27]. All sources could be divided into 3 broad groups based on the general pathophysiology of the underlying condition: 4 studied neuropathic COP [27, 29, 33, 34], 3 studied cancer and cancer treatment related COP [28, 30, 31], and 1 studied COP caused by TMD of primarily musculoskeletal or myofascial origin [32]. 4 of the 8 sources recorded outcomes of cannabinoid treatment on patients whose COP conditions were refractory to other forms of treatment [27, 29, 31, 33].

*Summary of articles by cannabinoid studied*

6 out of 8 sources made use of phytocannabinoids, cannabinoids organically derived from a cannabis plant, in one form or another [28, 29, 31, 32, 33, 34]. 3 of these studies used plant extracts with known composition: 6.3% THC: 8% CBD in oil taken as sublingual drops for primary burning mouth syndrome [29], 7.3% CBD in a cholesterol based topical ointment for treatment of masseter muscle related TMD [32], and the 1:1 CBD to THC oromucosal spray (Nabiximols) for MS-related trigeminal neuralgia-type pain [33]. In the remaining 3 sources studying phytocannabinoids, there was no specification of composition or plant strain [28, 31, 34]. In one of these studies the route of administration was exclusively smoked cannabis [34], while the other two sources studying non-specific phytocannabinoids set no exclusions based on route of administration [28, 31]. Of the two sources not using phytocannabinoids, one studied the effect of topical application of the endogenous cannabinoid receptor agonist N-palmitoylethanolamine on post-herpetic neuralgia related pain [27] and the other studied the effect of the synthetic cannabinoid Nabilone on the quality of life of head and neck cancer patients [30].

*Summary of article methods*

The experimental design and data collection methods were diverse among the 8 sources under analysis. Of 8 sources, 4 were trials: 2 were randomized double blinded placebo-controlled trials

[30, 32], two were open label (OL) trials with no control group [27, 29]. 4 studies were observational in design; of these 1 was a prospective case match-controlled study [28], 2 were cross-sectional questionnaires [32, 34], and 1 was a case study [33]. In general, there was little information provided on sampling methods. 5 studies reported recruiting patients from a single care center [28 – 32], 1 of which stated that sampling was random (60 out of 87 possible patients), but later shows that the 27 patients not selected for the sample were excluded based on a priori exclusion criteria [32], while the remaining 3 articles did not specify sampling methods [27, 33, 34]. 1 of the articles that did not specify their sampling protocol did, however, take a sample from MS patients in both the United States and the United Kingdom [34].

In 5 studies cannabinoid medication was administered by researchers to patients who were not using medical marijuana at the time of the study [27, 29, 30, 33, 34]. 3 studies involved patients who were self-medicating with cannabinoid products. Each of these 3 studies reported a higher prevalence of prior medical or recreational use of marijuana than the general population [28, 31, 34]. Dosage and duration were meticulously reported in the studies where researchers administered cannabinoid medications to the patients [27, 29, 30, 33, 34], but poorly reported, if at all, in studies of self-medicating patients [28, 31, 34]. Doses tested are difficult to compare because the routes of administration and cannabinoid compounds were heterogeneous. Of the recorded regimens the duration of treatment ranged from 2 weeks [27, 32] to 7 weeks [30]; with no specified end date for the case study [33]. Data collection was generally done through validated questionnaires and/or visual analogue scales (VAS) for pain. 2 studies used questionnaires of their own design either as adjuncts to validated questionnaires and a VAS for pain [31], or as the only means of data collection [34]. 1 study used surface electromyography (sEMG) to record the effect of topical CBD ointment on masseter muscle activity along with a VAS for pain [32].

*Summary of article results*

Results of the identified 8 sources were mixed. 3 sources compared pain scores between a group of COP patients taking a form of cannabinoid medication and a control group, 1 of which found no statistically significant difference in pain scores between groups [30], while 2 found statistically significantly lower average pain scores in their respective treatment groups [28, 32]. 5 sources reported changes in the magnitude of pain attributed to use of a cannabinoid medication: 1 source found that only 1 out of 4 chronic post herpetic neuralgia patients found clinically significant pain alleviation (89%) [27]; a second source found statistically significant reductions in pain represented by averaged VAS scores and a number of validated questionnaires with use of cannabis sativa oil for treatment of primary burning mouth syndrome [29]; 2 separate studies sent questionnaires to head and neck cancer patients and to patients with MS-related trigeminal neuralgia type pain, with 83% and 73% of respondents to these questionnaires noting cannabis-related alleviation of head and neck pain and neuropathic facial pain, respectively [29, 34]; the final source, a case study of a male patient suffering from refractory MS-related trigeminal neuralgia type pain found complete amelioration of symptoms from an oromucosal spray containing cannabis extracts [33]. 4 sources indicated that symptoms of depression and anxiety, both strongly associated with COP, may improve with use of the cannabinoid compounds tested [28, 29, 31, 34]. 5 out of 8 sources collected data on adverse effects related to the use of the studied cannabinoid compounds [27, 29, 30, 32, 33]. 2 sources discussed possible negative consequences of cannabinoid use but did not record data for adverse effects [31,34]. Of the 5 sources that recorded specific adverse effects of treatment, 3 found no adverse effects at all [27, 30, 32] while the remaining two studies recorded dizziness, gait unsteadiness,

drowsiness/fatigue, and headache as the most common adverse effects of their respective treatments [29, 33]. No adverse effects occurred that were severe enough to require study participants to discontinue treatment [27 – 34]. 1 source discussed possible negative consequences of treatment due to the psychosocial stigmas surrounding cannabis use [34], while another mentioned possible carcinogenic effects of smoking cannabis [31].

*Summary of article limitations*

The identified literature contained limitations. Poor generalizability of results due to sampling and heterogenous data reporting was a common problem. Sample sizes were generally small, ranging between n = 4 and n = 30 for trials, and n = 1 and n = 112 for observational studies [27 – 34]. Some studies had over-representation of male participants [28, 30, 31]. The observational studies reviewed reported over representation of previous/recreational marijuana users in their respective study groups [28, 31, 34], and sampling was done out of apparent convenience in most cases. Over representation of previous/recreational marijuana users may have lead to a decrease in recorded adverse effects because individuals who felt adverse effects would be less likely to use marijuana recreationally.

Only 2 of the trials reviewed utilized blinding [30, 32] and only 3 studies utilized comparison to a control group [28, 30, 32]. Given that there is a popular public belief that cannabis and cannabinoid medications have strong analgesic potential [34], the lack of blinding may have led to over-reporting of the magnitude of effect the cannabinoid compounds had on COP due to a placebo effect. 1 source cited uncertainty regarding the correct dosage of the tested cannabinoid medication to administer to participants as a limitation, going on to suggest that the dose given may have been too low and that trials to establish correct dosing are needed [30]. Accurately recording dose and type/strain of cannabis or cannabinoid medication used is extremely difficult in studies of self-medicating participants, as was noted to be the case for 3 sources using an observational methodology [28, 31, 34].

*Summary of relevant conclusions drawn*

75% (6 of 8) of sources concluded that the cannabinoid compound(s) studied were effective in reducing pain in COP patients [27 – 34]. All sources studying phytocannabinoids indicated in their conclusions that these medications appeared to be encouragingly successful in reducing pain in the COP patients studied [28, 29, 31, 32, 33, 34], while the sources studying a synthetic cannabinoid (Nabilone) and an endocannabinoid supplement (N-palmitoylethanolamine) concluded clinical failure of their respective treatments to alleviate COP [27, 30]. With respect to COP conditions, 2 out of 3 sources studying HNC [28, 31], 3 of the 4 sources studying neuropathic COP [29, 33, 34], and the single source studying a musculoskeletal condition [32] concluded cannabinoid treatments were effective in reducing chronic pain. Finally, all sources studying patients who self-administered/self-titrated their cannabinoid regiments concluded that the treatment was effective in reducing COP [28, 31, 34].

*Thematic Analysis*

132 topics were identified for our final list of topics (Table 5). Of these 132 topics, 110 were initially identified by both reviewers, 10 additional topics were identified by reviewer 1 but not by reviewer 2, 12 additional topics were identified by reviewer 2 but not by reviewer 1. Table 6 shows the total number of topics present in each source as well as the level of agreement between reviewers.

It was found that all 132 topics fit within 15 identified themes. Table 5 shows the list of themes with respective underlying topics and the number of sources in which each topic was present. The number of sources in which at least one topic is present for each theme is displayed in

Figure 2, and the total number of times a topic belonging to each theme was coded as present in our body of literature is displayed in Figure 3.

The process of identifying and categorizing topics according to theme helped identify and illustrate the overall content and emphasis of literature available for review. Most sources included content on most themes, with 80% (12/15) of themes being present in at least 7/8 articles. The most heavily emphasized theme after "study design descriptors" was "adjunctive or first line therapy," therapies attempted prior to treatment with the studied cannabinoid medication. Research on cannabinoids for COP is heavily focused on use of cannabinoids as adjunctive, non-first-line therapeutics. In fact, only one source studied cannabinoid medication as a first line therapy [32]. The theme "current or historical legality" figured least prominently with only half (4/8) of our sources containing topics within this theme [28, 31, 32, 34] and only 5 such topics identified in the entire body of literature reviewed.

Despite the a priori requirement for inclusion in this study that a source must measure the effect of a cannabinoid medication on pain, other outcome measures such as "physical outcome measures," "functional outcome measures," and "emotional/ psychosocial/ mental/ cognitive outcome," were emphasized equally or more heavily than "pain outcome measures," based on the analysis of themes. In addition, "therapeutic potentials of cannabinoids cited but not tested" emerged as a distinct theme.

*Word Cloud*

A word cloud was created using the titles and abstracts from each of the 8 sources reviewed (see Figure 4). The word cloud showed the most commonly appearing words to be "patients," "pain," "quality of life," "treatment," "cannabis," and "marijuana." The word cloud identified two etiologies of COP for which most research on cannabinoid medication exists, "head and neck cancer," and "neuralgia," which agrees with observations made from the data extraction table. Finally, the word cloud identified two common co-morbidities which accompany chronic pain in COP, "anxiety," and "depression." These findings, along with the prominence of the phrase "quality of life," agree with those of the theme analysis which show that the current body of literature focuses on the overall potential benefit of cannabinoid medication for COP rather than on the modulation of pain alone.

## DISCUSSION

The question we sought to answer with this scoping review was "What literature exists on the use of cannabinoids to treat COP falling within the scope of practice of OMFS, OMS, or OPS?". Our search identified 8 relevant sources exposing, as suspected, a dearth of information related to the use of cannabis or cannabinoid medications for treatment of COP. A larger body of literature for the use of cannabis and cannabinoids for generalized chronic pain, and research on the use of these medications to treat other conditions [19] provide some guidance and encouragement for those looking to treat COP with cannabinoids, but there is a clear need for more research specific to treating COP with cannabis or cannabinoids medications.

Our specific objective was to collate and summarize the evidence that exists regarding the use of cannabis and cannabinoid medications to treat COP conditions that fall within the scope of practice of OMFS, OMS, or OPS. The limited amount of research we identified did contain some interesting trends: (1) a holistic focus of most sources with respect to outcomes measured, (2) an interest in cannabinoids as palliative and adjunctive medications for cases refractory to other treatments, and (3) an interest in the safety and tolerability of cannabinoid medications. Our review process also highlighted several gaps and limitations in the literature, in addition to its scarcity, which include: (1) heterogenous study designs and data collection methods, (2) poor

sampling and a need for blinding in most studies, and (3) a lack of knowledge regarding effective doses, compounds, and routes of administration for COP patients.

Research on cannabinoids for COP is concerned with investigating several potential benefits these medications may provide including but not limited to pain reduction. Most sources reviewed included outcome measures in addition to effect on pain. Though the a priori inclusion criterion for our review stated that an outcome measure assessing the effect of a cannabinoid on chronic pain must be present, our analysis revealed several other outcome measures as themes more heavily emphasized within the included sources. A list of themes describing various outcome measures ranked in order of least to most often represented in the literature is as follows: "Pain outcome measures," "physical outcome measures," "emotional/ psychosocial/ mental/ cognitive outcome measures," and "functional outcome measures" (see Figure 3). In agreement with these findings, our word cloud displays the words "depression," "anxiety," and the phrase "quality of life" prominently. The tendency of the literature on cannabinoids for COP to be more holistically focused aligns with research on the use of cannabinoid medications to benefit patients with other chronic conditions such as MS and irritable bowel disorder [35] and is likely of more interest to patients and clinicians dealing with unsatisfactorily treated COP [13]. Of the sources that recorded results specifically for anxiety, depression, and overall quality of life, 3 out of 4 found evidence to support the claim that cannabinoids helped improve each outcome measure [28 – 31]. While no robust conclusions can be drawn, these results are encouraging, especially considering that the study which found no evidence that cannabinoids helped reduce anxiety and depression and improve quality of life listed a concern that they administered too low a dose to their test group to be of therapeutic benefit [32]. In the context of Loeser's adaptation of the biopsychosocial model to chronic pain, suffering is described as the negative emotional sequelae of pain and includes anxiety, fear, hopelessness, and depression [36]. Loeser states that "it is suffering, not pain, which brings patients into doctor's offices in hopes of finding relief. [36]. The potential for cannabinoids to not only provide analgesia but also help ease anxiety and depression should make them a very enticing option for clinicians and patients battling refractory cases of COP.

Cannabinoids are being studied as palliative rather than curative agents for COP. Half (4 of 8) of our sources studied cannabinoids for COP specifically refractory to other treatment modalities [27, 29, 32, 33]. Further, the theme "first line or adjunctive therapies used," coded as present when any treatment modality was tried prior to or simultaneously with the tested cannabinoid, was present in all 8 sources and was identified a total of 40 times, making it the second most frequently identified theme during our analysis. 3 out of the 4 sources specifically studying cases refractory to other available treatment concluded that the cannabinoid tested was useful in alleviating COP [27, 29, 32, 33]. Given that first line therapies aimed at curing etiologic conditions underlying COP often prove unsuccessful [37], there is a need for additional palliative medications to alleviate pain and increase quality of life in patients whose COP remains refractory to other treatments. Patients and clinicians are also commonly dissatisfied with current treatment options such has surgery or opiate medications due to their associated risks [37]. Our sources indicated that cannabinoid medications may be able to help some COP patients whose conditions are not satisfactorily controlled with other treatments; this raises the question of whether cannabinoids are safer or more acceptable than other adjunctive or second line therapies. The treatment decision of any clinician when determining whether to prescribe a medication comes down to their assessment of the risk-benefit ratio in each individual case [38]. Even if the benefit is uncertain or minimal, a medication may still be justly prescribed if the associated risk

is very low, especially in situations where other treatments have failed to yield satisfactory results [38]. For this reason, clinicians may consider prescribing cannabinoids for cases of COP, especially those refractory to other treatments. The body of literature supporting cannabinoids for COP is small and it is not the intent of this scoping review to assess the quality of evidence or to draw conclusions based on the findings of our sources, however, all 8 identified sources concluded that cannabinoid medication was safe and tolerable [27 – 34]. As reported in our summary of sources by results, none of the literature reviewed reported a participant discontinuing treatment due to adverse effects [27 – 34]. 5 out of 8 sources recorded adverse effects [27, 29, 30, 32, 33]. Adverse effects were either wholly not present [27, 30, 32], or relatively minor and tolerable [29, 33]. Two sources listed possible negative consequences of cannabinoid medications not directly related to their pharmacological action; negative stigmatism associated with cannabis use [34], and carcinogenicity of inhaled smoked cannabis [31]. Since the source mentioning negative stigmatism associated with cannabis use was published in 1997, public attitude has shifted toward a more accepting view of cannabinoid and cannabis use [37]. As uncovered in our scoping review, several routes of administration other than smoked cannabis are available which avoid the risks associated with smoke inhalation, however, more research on the risks associated with other routes of administration is required. It must also be mentioned that over representation of recreational/prior marijuana users in a number of our sources may have led to lower rates of adverse effects in the test group compared to the general population because those who suffer adverse effects from cannabinoids would be less likely to use marijuana. None the less, the apparent safety and tolerability of cannabinoid medications make them an appealing option for clinicians and patients looking to reduce suffering caused by COP. The sources in this review, though not free of limitations, support the claim that cannabinoid medication is a safe and tolerable option for COP patients; a survey assessing the knowledge and perceptions of cannabinoid treatment held by those specialists most commonly treating COP would be of benefit in determining if their perceptions aligned with the literature.

Limitations of the methods used in this scoping review exist which may have affected our ability to achieve our primary objective; to find out what evidence is available on using cannabis and cannabinoid medications to treat chronic orofacial pain conditions potentially within the scope of practice of OMFS, OMS, or OPS. Although we searched multiple databases for published and grey literature with the help of a health sciences librarian experienced in dental research, an expanded search of a greater number of databases and key terms may potentially have uncovered additional sources of information. We searched for sources available in English only, which may have left valuable non-English resources undiscovered. The decision to include or not include specific conditions such as migraine or headache within the purview of this review was made after consultation with an oral medicine specialist to keep our search relevant to our objective, yet it may have resulted in exclusion of results relevant to some of our target audience.

In addition to the limitations of the methods used in this scoping review, the general limitations of the literature uncovered prevent any powerful conclusions from being drawn. Generalization of results to larger populations of COP patients is difficult; sampling was not random, and samples often had issues with over representation of specific populations within the target population such as males and current/previous cannabis users. Those who are already cannabis users may have more favourable reactions to the medication or view the medication as more beneficial than non-cannabis users. The placebo effect is generally high in studies reporting treatment for chronic pain, as high as 65 – 70% (8), and there is a public perception that

cannabinoid medications are effective for treating pain [39] which may account for an even higher placebo response rate in non-blinded studies. Therefore, interpreting the results of non-blinded studies is challenging because a large portion of the apparent effect may be due to patient expectations. Only two of our sources used a blinded study design [30, 32] and only one of which concluded that their treatment was effective [32]. Determining the actual clinical utility of any drug requires an understanding of its therapeutic window [40]. If the dose given is below the ideal therapeutic level, the intended effect may be understated, if the dose given is above the ideal therapeutic level, the adverse effects may be overstated. None of our 8 sources cited an evidence-based reason for their chosen dose. One study listed uncertainty of dose as a limitation [30]. All 3 sources which allowed patients to manage their own dosage reported positive results for cannabinoids reducing COP [28, 31, 34].

Not surprisingly there is need for more research into all aspects of cannabinoid use for the management of COP. Larger, randomized, and blinded trials with more comparable designs and homogenous data collection methods are needed before conclusions can be drawn regarding the overall effectiveness and safety of cannabinoids for COP. Research is needed to begin establishing protocols that would enable clinicians and researchers to select the appropriate dose, compound, and route of administration for their patients. Cannabis and cannabinoid medications are becoming increasingly available to patients and clinicians [41]. Investigations into the attitudes, knowledge, and perceptions of cannabinoid medications held by specialists who most often treat COP would help guide educational offerings for students and licensed clinicians. Increasing the knowledge and comfort of clinicians regarding cannabinoid medications would facilitate the safest, most accurate and comprehensive patient education and treatment with these medications.

## CONCLUSION

This scoping review uncovered and assembled a small and diverse body of literature with conclusions generally supporting their respective hypotheses, that cannabinoid medications are of some therapeutic benefit for COP patients [27 – 34]. As uncovered by our sources, the benefits of cannabinoid medications were not limited to pain reduction and included several functional, physical, and psychosocial outcome measures, presenting an appealing therapeutic option for treating COP patients from a biopsychosocial approach. Cannabinoids are being studied as a treatment option for COP conditions refractory to other treatment modalities and show some effectiveness in such cases. In all cases, the respective cannabinoids studied were found to be safe and tolerable. No participants from any source discontinued treatment because of adverse effects, if adverse effects were recorded, they were generally mild. The apparent safety, potential effectiveness for refractory cases, and benefits beyond pain reduction are encouraging, though the studies are few, small scale, and have significant limitations which prevent and definitive conclusions being drawn. Comparison of results between sources is difficult or impossible since sources studied different cannabinoid medications, different COP conditions, and used a variety of study designs and outcome measures. As cannabinoids are becoming increasingly accessible to clinicians and COP patients, it is important to understand current attitudes of clinicians regarding cannabinoid medications with respect to knowledge, confidence, beliefs on efficacy, potential barriers, and willingness to prescribe.

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*Conflict of interest*

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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TABLES

Table 1:

| **Terms used during search process. Strategy informed by Health Sciences Librarian and Oral Medicine specialist** | |
|---|---|
| **Terms used to return sources on COP** | **Terms used to return sources on cannabinoid medication** |
| Anesthesia dolorosa | Cannabidiol |
| Burning Mouth | Cannabis |
| Complex Regional Pain Syndrome | Cannabinoid |
| Facial neuralgia | CBD |
| Glossopharyngeal | Marijuana |
| Mucositis | Pot |
| Occlusal dysesthesia/malocclusion | Tetrahydrocannabinol |
| Pain*Dental | THC |
| Pain*Dentistry | Weed |
| Pain*Face | |
| Pain*Facial | |
| Pain*Head | |
| Pain*Neck | |
| Pain*Orofacial | |
| Postherpetic | |
| Stomatognathic disease | |
| Superior Laryngeal | |
| Temporomandibular | |
| Trigeminal | |

Table 2 a – e: Tables outlining how key terms identified in table 2 were used to search for sources in each database

Table 2a: MEDLINE

| **Search Number** | **Keyword or search combination** | **Results** |
|---|---|---|
| 1 | Cannabis | 20,177 |
| 2 | Cannabinoid or Cannabinoids | 21,067 |
| 3 | 1 OR 2 | 37,158 |
| 4 | Pain | 653,834 |
| 5 | 3 AND 4 | 3,221 |
| 6 | Stomatognathic disease(s) | 455,521 |
| 7 | Head OR Neck | 1,143 |
| 8 | trigeminal neuralgia.mp. or Trigeminal Neuralgia/ | 7,945 |
| 9 | Glossopharyngeal Neuralgia.mp. or Glossopharyngeal Nerve Diseases | 690 |
| 10 | Facial Neuralgia/ or Earache/ or Cranial Nerve Diseases/ or Headache/ or Facial Pain/ or Facial Nerve/ or Nervus intermedius Neuralgia.mp. or Herpes Zoster Oticus/ | 50,277 |
| 11 | Laryngeal Nerves/ or Neck Pain/ or Superior Laryngeal Neuralgia.mp. or Cranial Nerve Diseases/ | 14,230 |
| 12 | Neuralgia, Postherpetic/ or Herpes Zoster/ or Post-Herpetic Neuralgia.mp. | 11,372 |
| 13 | Facial Pain/ or Trigeminal Neuralgia/ or Trigeminal Nerve/ | 20,695 |
| 14 | Complex Regional Pain Syndrome.mp. or Complex Regional Pain Syndromes/ | 2,881 |
| 15 | Burning Mouth Syndrome/ or Mouth Diseases/ or burning mouth.mp. | 18,856 |
| 16 | Facial Pain/ or Malocclusion/ or Dental Occlusion/ or Occlusal Dysesthesia.mp. | 39,082 |
| 17 | Mucositis/ or Stomatitis/ | 8,170 |
| 18 | Cancer Pain AND Oral | 1,060 |
| 19 | 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 | 588,016 |
| 20 | 5 AND 19 | 94 |
| | | **94** |

Table 2b: EMBASE

| Search Number | Keyword or search combination | Results |
|---|---|---|
| 1 | Cannabis | 39,987 |
| 2 | Cannabinoid or Cannabinoids | 13,065 |
| 3 | 1 OR 2 | 50,060 |
| 4 | Pain Or Head pain OR neck pain, OR jaw pain OR tooth pain, Or Neuropathic pain OR chronic pain OR gingiva pain OR larynx pain | 487,560 |
| 5 | 3 AND 4 | 3,390 |
| 6 | Trigeminal neuralgia / Trigeminus neuralgia | 12,763 |
| 7 | Glossopharyngeal neuralgia | 720 |
| 8 | Facial neuralgia | 11,817 |
| 9 | Postherpetic neuralgia OR Superior laryngeal neuralgia | 6,054 |
| 10 | Anesthesia dolorosa | 195 |
| 11 | Burning mouth syndrome | 17,41 |
| 12 | Head and Neck Cancer | 66,121 |
| 13 | Occlusal dysesthesia /Malocclusion | 20 |
| 14 | Oral Mucositis / Oral inflammation | 38,907 |
| 15 | Temporomandibular Joint Disorder | 14,855 |
| 16 | 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 | 143,384 |
| 17 | 5 AND 16 | 159 |
| | | **159** |

Table 2c: WEB OF SCIENCE CORE COLLECTIONS

| Keyword or search combination | Results |
|---|---|
| Pain*Cannabis/*Dentistry | 1 |
| Pain*Cannabis*Dental | 3 |
| Pain*Cannabis*Face | 21 |
| Pain*Cannabis*Orofacial | 0 |
| Pain*Cannabis*Facial | 6 |
| Pain*Cannabis*Head | 13 |
| Pain*Cannabis*Neck | 15 |
| Cannabis*Glossopharyngeal | 0 |
| Cannabis*Superior Laryngeal | 0 |
| Cannabis Temporomandibular | 0 |
| Cannabis*Mucositis | 0 |
| Cannabis*Burning Mouth | 3 |
| Cannabis*Postherpetic | 0 |
| Cannabis*Trigeminal | 21 |
| Cannabinoid*Glossopharyngeal | 0 |
| Cannabinoid*Superior Laryngeal | 0 |
| Cannabinoid*Temporomandibular | 8 |
| Cannabinoid*Mucositis | 4 |
| Cannabinoid*Burning Mouth | 2 |
| Cannabinoid*Postherpetic | 2 |
| Cannabinoid*Trigeminal | 111 |
| | **110** |

Table 2d: U.S. NATIONAL INSTITUTES OF HEALTH CLINICAL TRIAL REGISTER

| **Keyword or search combination** | **Categories of results from keyword search potentially relevant to COP selected for screening** | **Results** |
|---|---|---|
| Pain AND (Cannabis OR cannabinoid) – Synonyms enabled | | |
| | Arthralgia | 4 |
| | Arthritis | 14 |
| | Arthritis psoriatic | 2 |
| | Arthritis rheumatoid | 2 |
| | Cancer pain | 12 |
| | Chronic pain | 47 |
| | Craniomandibular disorders | 3 |
| | Jaw diseases | 3 |
| | Mandibular diseases | 3 |
| | Multiple sclerosis | 10 |
| | Myofascial pain syndromes | 11 |
| | Neck pain | 2 |
| | Neuralgia | 29 |
| | Neuralgia, Postherpetic | 3 |
| | Stomatognathic diseases | 4 |
| | Temporomandibular Joint disorders | 3 |
| | Temporomandibular Joint dysfunction syndrome | 3 |
| | Tooth disease | 1 |
| | Toothache | 2 |
| | | **75** |

Table 2e: Summary of keyword or search combination for three electronic databases

| **Electronic Database** | **Keyword or search combination (KSC)** | **Number of Articles per KSC** | **Number of Articles per Database** |
|---|---|---|---|
| Dentistry and Oral Sciences | Pain AND (cannabis or cannabinoid or marijuana or thc or pot or weed or cbd or tetrahydrocannabinol or cannabidiol) | 42 | 42 |
| Database of Abstracts of Reviews of Effects | Pain AND (Cannabis OR Cannabinoids) | 17 | 17 |
| Cochrane Central Register of Controlled Trials | (Cannabis OR Cannabinoids) AND (Pain) AND (Dentistry OR Dental OR Orofacial OR Facial OR Head OR Neck) | 51 | 107 |
| | (Cannabis OR Cannabinoids) AND (Superior laryngeal OR Glossopharyngeal OR Temporomandibular OR Post herpetic neuralgia OR Burning mouth OR Mucositis OR Trigeminal) | 56 | |

Table 3:

| **Inclusion Criteria** |
| --- |
| • Pain being treated was chronic in nature<br>• The source contained some outcome measure for cannabis or a cannabinoid compound as treatment for pain<br>• Symptoms and conditions being treated were potentially within the scope of practice of oral medicine specialists or oral and maxillofacial surgeons |
| **Exclusion Criteria** |
| • Focus on animal models<br>• Full Text not available in English |

Table 4: Summary of data extracted from each source

| Article reference, country, and year of publication | COP condition studied | Cannabinoid studied | Methods | Relevant results | Limitations | Relevant conclusions drawn |
|---|---|---|---|---|---|---|
| [27]<br><br>Germany, 2009 | Post herpetic neuralgia (PHN) with facial involvement | N-palmitoyle-thanolamine | Open label (OL) trial without control<br>4 chronic PHN cases<br>4 acute PHN cases<br>Sampling method not recorded<br>Topical cannabinoid application twice daily for 2 – 4 weeks directed by researchers.<br>Dose not specified<br>VAS pain scores recorded at baseline and after therapy concluded | 3 of 4 chronic pain patients had no or minimal response (0–17% pain reduction), 1 had 89% pain reduction.<br>No adverse effects were observed.<br>4 out of 4 acute cases reported improvement in pain after treatment. | No control group<br>OL,<br>Small presumably non-random sample | Topical N-palmitoyle-thanolamine was not effective for significant pain relief from **chronic** PHN, but was effective for acute PHN |
| [28]<br><br>Canada, 2018 | Pain related to head and neck cancer, chemotherapy and or radiotherapy | Cannabis – Strain and route of administration were patients' choice and not monitored | OL prospective case match controlled observational study<br>74 HNC patients identified as marijuana users and were matched with 74 non-using patients based on clinical and personal characteristics<br>4 year recruitment period at a single tertiary care center<br>Patients self-administered marijuana<br>When diagnosed with HNC, patients completed the Edmonton Symptom Assessment System (ESAS) and the EuroQOL-5D (EQ5D) | Patients in marijuana user group reported statistically significantly lower mean ratings for pain, discomfort, anxiety, and depression than their case matched controls.<br>Adverse effects not recorded in this study | OL<br>Over representation of male patients<br>Over representation of previous/recreational marijuana users<br>No monitoring or control of cannabis type, route of administration, dose, or frequency<br>Adverse effects not recorded | HNC patients who self-identify as marijuana users report statistically significantly better scores for pain, discomfort, anxiety, and depression when compared to HNC patients who do not use marijuana |
| [29]<br><br>Italy , 2020 | Burning mouth syndrome (primary) | Cannabis sativa (oil)<br>1g cannabis extract: 10g olive oil.<br>Cannabis extract obtained from cannabis sativa as per means of Romano-Hazekamp extraction<br>6.3% THC ; 8% CBD | OL trial without control<br>All patients from a single care center diagnosed with primary burning mouth syndrome by a single trained specialist who consented and met inclusion/exclusion criteria were included in study n=17<br>Titration from 5 drops BID to 20 drops BID<br>4 week regiment directed by researchers<br>24 week follow up<br>Used questionnaires: McGill Pain Questionnaire (MGP), the Present Pain Intensity (PPI) scale, the Oral Health Impact Profile questionnaires (OHIP-14 and OHIP-49), the DN4 (Douleur Neuropathique en 4 Questions), the Hospital Anxiety and Depression Scale | Median pain scores were significantly reduced after 4 week course of oral cannabis extract oil compared to baseline.<br>Pain scores remained reduced at 3 and 6 month follow up despite cessation of treatment.<br>Depression and Anxiety scores were not significantly lower after 4 week treatment, though they were lower at 3 and 6 month follow up.<br>No patient stopped treatment due to adverse effects AE though 1/3 of patients reported at least one adverse effect. | OL<br>No control group<br>Small sample size<br>Sample drawn of apparent convenience | Titrating a variable dose of cannabis extract oil may be an effective and safe method of treating primary burning mouth syndrome.<br>The effects may last beyond cessation of treatment |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | (HADS,) and the Geriatric Depression Scale (GDS). | Dizziness and headache were most reported. | | |
| [30]<br><br>Canada, 2016 | Pain related to head and neck cancer, chemotherapy and or radiotherapy | Nabilone; (synthetic THC analog) | Randomized double blind placebo controlled trial<br>Sample of HNC patients from single tertiary care center n = 28 treatment, n = 28 placebo<br>Dose titrated from 0.5mg/day to 1.0mg BID for 9 – 11 weeks directed by researchers<br>Data collected at baseline, each week for 7 weeks, and 4 weeks following final cancer treatment (11 week total) using a VAS for pain and The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 with specific head and neck module, the EORTC QLQ H&N35<br>Time from baseline until 20% worsening in pain and QOL was primary interest | No significant difference in pain scores or time for 20% worsening in pain scores between test and control groups.<br>No significant difference in QOL, sleep, mood, nausea, appetite, or weight was recorded between test and control groups.<br>No difference in occurrences of adverse effects between test and control group were recorded | Test and control group not case matched.<br>Variance in disease severity and cancer treatment modality between groups could have large influence on recorded effects and or dropout rates.<br>High dropout rate: 19/28 and 13/28 participants completed study in test and control groups respectively.<br>Low dosage cap may have limited recorded effect | At the dosage used in this study there is no evidence that Nabilone prolongs the time for worsening of pain during HNC treatment.<br>There is no evidence to support the claim that Nabilone reduces pain, |
| [31]<br><br>USA, 2016 | Pain related to head and neck cancer, chemotherapy and or radiotherapy | Cannabis – Strain not specified or monitored<br><br>Route of administration was the patients' choice but was recorded by researchers | Retrospective chart review and cross-sectional study<br>Sample of HNC patients from single tertiary care center, all identified as current marijuana users. N = 15.<br>Patients self-administered medical marijuana at their own discretion.<br>Dose/strain/route of administration etc. were not limited but were recorded.<br>Data collection through the EORTC QLQ-C30 (Version 3.0), EORTC QLQ-HN35, QOL-RTI/HN, and one non validated questionnaire of the researcher's design: the medical marijuana quality of life questionnaire (QOL-HN/MM) | 67% patients reported benefits of reduced pain<br>Most patients also reported MM helped manage symptoms of depression, weight, dysphagia, altered sense, and for appetite stimulation<br>Adverse effects not recorded in this study | OL<br>No control<br>Small sample size<br>Apparent convenience sampling<br>Over representation of male patients<br>Over representation of previous/recreational marijuana users<br>No data on dose or strain recorded | HNC patients may find that medical marijuana helps with pain reduction, and may provide benefits in some functional and emotional consequences of HNC and HNC treatment |
| [32]<br><br>Poland, 2019 | Temporo-mandibular Joint Dysfunction | Topical CBD ointment<br>7.3% CBD extract in olive oil, cholesterol as vehicle, 4:1 CBD extract oil: ointment<br>Final composition 1.46% CBD | Randomized double blinded placebo controlled trial<br>Sample selected from TMD patients at single tertiary care center, n = 60.<br>Patients then randomized to test group n = 30 or placebo group n = 30.<br>Topical application of CBD ointment to masseter muscles bilaterally BID x 14 days directed by researchers<br>sEMG of masseter muscle activity and VAS for pain taken at baseline and after 2 week treatment | Patients in test group showed statistically significant reductions in masseter muscle activity and pain associated with masseter region, myofascial pain, and, TMD from baseline to conclusion of 14 day treatment.<br>Placebo group showed no significant changes in | Sample seemingly not randomly selected<br>Short duration study with no follow up cannot indicate whether effect was transient or not<br>Rigid exclusion criteria may make generalizing results of this study to a clinical population of TMD patients difficult | In otherwise healthy patients with myofascial pain in the masseter region and signs and symptoms of TMD, topical CBD application may be beneficial in reducing pain and reducing masseter muscle tension. |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | muscle activity or reported pain.<br>No adverse effects were observed. | | |
| [33]<br><br>Italy, 2016 | Trigeminal neuralgia (MS related) | Nabiximols 1:1 THC:CBD Oromucosal spray | Case study of a male patient diagnosed with secondary progressive MS<br>Patient was treated with Nabiximols for MS related muscle spasticity and found profound relief from MS related trigeminal neuralgia.<br>5 sprays per day directed by researching physician<br>Follow up at 1, 6, and 12 months<br>Pain levels recorded using numeric (0 – 10) rating scale.<br>History of disease progression, past and current medical and pharmacologic interventions, and effect of Nabiximols on trigeminal neuralgia, spasticity, and other MS related symptoms were recorded and reported | 54 year old male patient found profound improvement in MS related trigeminal neuralgia symptoms from the use of Nabiximols.<br>Improvements were stable with continued use of Nabiximols at 12 month follow up.<br>Patient reported adverse effects of fatigue and gait unsteadiness, but they were not severe enough to stop treatment | Case study | Cannabinoid medications may provide benefits for MS patients beyond muscle spasticity including relief of MS related trigeminal neuralgia like symptoms. |
| [34]<br><br>Europe (International publication), 1997 | Trigeminal neuralgia (MS related)<br><br>Non-specific MS related face pain | Cannabis – Strain not specified or monitored<br><br>Route of administration was the patients' choice but was monitored | Cross-sectional observational study,<br>Known medical marijuana users in the USA and UK were sent a questionnaire package, no other sampling methodology reported. N = 53 UK and 59 USA<br>Patients self-administered medical marijuana at their own discretion.<br>Route of administration was smoking.<br>Frequency of smoking was recorded.<br>A self-designed anonymous questionnaire was used to collect demographic data, as well as data on patterns and purposes for use of marijuana. | 73.3% of patients who reported pain in face as a distinct symptom also reported that using cannabis made their face pain either a little better (40%) or a lot better (33.3%).<br>Adverse effects not recorded in this study | OL<br>Over representation of previous/recreational marijuana users<br>No information on dose/strain recorded | More than 2 of out 3 patients with MS related face pain who self-medicate with cannabis find that it helps relieve this symptom. |

Table 5: The primary list of topics found in our body of literature grouped into themes and the number of sources discussing each topic.

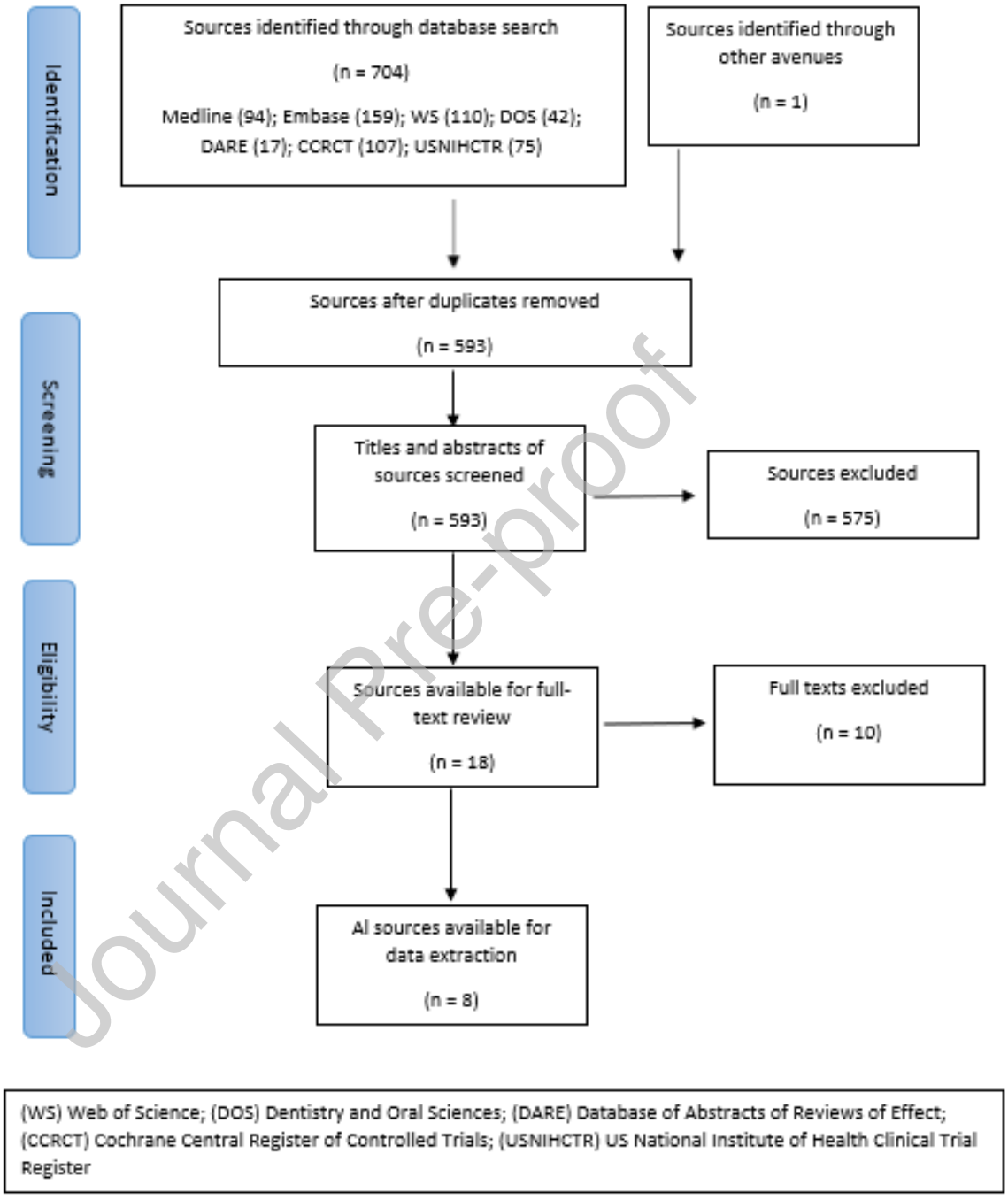
| 1. First Line or adjunctive therapies used | | 2. Study Design/ Type of Study | | 3. Adverse effects/ Acceptability recorded | |
|---|---|---|---|---|---|
| Alpha lipoic acid | 1 | Baseline pain recorded | 4 | Acceptability | 6 |
| Hormone replacement | 1 | Limitations addressed | 6 | Constipation (AE) | 2 |
| Injection | 2 | Participant follow up recordings | 4 | Irritation (AE) | 3 |
| Potassium channel blocker | 1 | Perceived conflict of interest | 2 | Xerostomia/salivary issues (AE) | 1 |
| Steroids | 2 | Declared conflict of interest | 1 | Shortness of breath | 2 |
| Saliva analogues | 1 | Dropout/completion rate | 4 | Psychotropic / psychoactive | 4 |
| Opioids | 5 | Validated questionnaire | 5 | Fatigue (AE) | 1 |
| Sedation | 1 | Prospective cohort study | 1 | Memory loss | 1 |
| NSAIDS | 2 | Case match-control | 1 | Headache (AE) | 2 |
| Stereotactic γ-knife Surgery | 1 | Case study | 1 | Gait unsteadiness (as AE) | 2 |
| Lidocaine / Local anesthesia | 1 | Visual analogue scale | 5 | Glaucoma (AE) | 1 |
| Muscle relaxants | 2 | Numeric rating scale (for pain) | 1 | Dizziness (AE) | 1 |
| Deep massage | 1 | Blinding used | 2 | Contact dermatitis | 2 |
| Needling | 1 | Control / placebo used | 3 | Cramps | 2 |
| Capsaicin | 2 | No control | 5 | | |
| Antiemetics | 3 | Open label | 2 | | |
| Antifungals | 1 | Double blind RCT | 2 | | |
| Botox | 1 | Prospective OL single arm pilot study | 1 | | |
| Analgesics | 7 | | | | |
| Anticonvulsants | 3 | | | | |
| Antidepressants | 1 | | | | |
| **4. Medication and its Administration** | | **5. Functional outcome measures** | | **6. Diagnosis /Cause of COP** | |
| Endocannabinoid | 1 | Mobility | 5 | TMD | 2 |
| Natural cannabinoid tested | 6 | Nausea | 5 | Post-herpetic neuralgia | 1 |
| Synthetic cannabinoid tested | 1 | Vomiting | 4 | Burning mouth syndrome (primary) | 1 |
| Dose / regiment / duration recorded | 5 | Urinary urgency | 2 | Head and neck cancer | 5 |
| Self-medicating patients | 3 | Sleep/ insomnia/ hyper somnolence | 2 | Radio mucositis | 1 |
| Cannabis Oil / extract | 3 | Drowsiness/fatigue/malaise/drowsiness | 5 | Radiotherapy | 4 |
| Ingested | 6 | Self-care | 2 | Chemotherapy | 4 |
| Smoked/loose leaf administration | 5 | Quality of Life | 4 | Multiple sclerosis (associated trigeminal neuralgia) | 3 |
| Vapourization | 2 | Dysphagia | 2 | | |
| Topical application/ transdermal | 2 | Appetite | 5 | | |
| Aerosol / oromucosal spray | 1 | | | | |
| **7. Emotional/ Psychosocial/ Mental/ Cognitive outcome measures** | | **8. Physical outcome measures** | | **9. Pain outcome measures** | |
| Mood | 3 | Dry mouth/salivary issues | 1 | Acute pain | 2 |
| Well-being (general sense of) | 3 | Myofascial pain / trigger points | 3 | Chronic pain | 8 |
| Stress | 2 | Muscle spasm/spasticity | 4 | Odynophagia | 2 |
| Relaxation | 2 | Weight | 5 | Mean Pain Reduction | 1 |
| Psychophysical | 1 | Tremor | 1 | Discomfort | 1 |
| Psychosocial | 2 | S(EMG) | 1 | Pain progression over time | 1 |

| | | | | | |
|---|---|---|---|---|---|
| Depression | 4 | Myorelaxation | 3 | | |
| Anxiety | 5 | Dermatitis / pruritis | 3 | | |
| **10. Participant Demographics** | | **11. Cannabinoid chemical compounds and strains** | | **12. Cannabis therapeutic potentials cited but not tested** | |
| Age of participants reported | 7 | THC | 7 | Anti-inflammatory | 3 |
| Prior recreational use | 3 | CBD/ cannabidiol | 5 | Antimicrobial | 1 |
| SES recorded | 3 | Cannabis Sativa/marijuana | 7 | Anti-nociceptive | 5 |
| Gender of participants reported | 8 | CBN cannabinol | 1 | Antitumoral effect | 1 |
| Refractory cases | 3 | Cannabis ruderalis | 1 | | |
| **13. Neurogenic symptoms reported** | | **14. Condition severity / Duration** | | **15. History of legality** | |
| Dysesthesia | 4 | Duration of pre-existing condition recorded | 7 | Illicit substances | 2 |
| Neuropathic pain / neuralgia | 6 | | | Legalization | 3 |
| Dysgeusia | 3 | TMN staging | 2 | | |
| Allodynia | 1 | Karnofsky score | 2 | | |
| | | Feeding tube | 2 | | |

Table 6: Coding agreement between reviewers coding topics as present or not present in our body of literature

| Title of article | Number of topics both reviewers coded as present | Number of topics initially coded as present by reviewer 1 only | Number of topics initially coded as present by reviewer 2 only | Number of topics agreed upon as present in article following discussion |
|---|---|---|---|---|
| Adjuvant topical therapy with a cannabinoid receptor agonist in facial postherpetic neuralgia [27] | 27 | 1 | 2 | 30 |
| Association of marijuana use with psychosocial and quality of life outcomes among patients with head and neck cancer [28] | 44 | 1 | 1 | 46 |
| Evaluating the suitability and potential efficiency of cannabis sativa oil for patients with primary burning mouth syndrome: A prospective, open-label, single-arm pilot study [29] | 61 | 4 | 1 | 64 |
| Improving quality of life with Nabilone during radiotherapy treatments for head and neck cancers: A randomized double-blind placebo-controlled trial [30] | 47 | 2 | 2 | 51 |
| Medical marijuana use in head and neck squamous cell carcinoma patients treated with radiotherapy [31] | 46 | 4 | 0 | 50 |
| Myorelaxant effect of transdermal cannabidiol application in patients with TMD: A randomized, double-blind trial [32] | 46 | 3 | 4 | 53 |
| Refractory trigeminal neuralgia responsive to Nabiximols in a patient with multiple sclerosis [33] | 33 | 2 | 2 | 37 |
| The perceived effects of smoked cannabis on patients with multiple sclerosis [34] | 34 | 2 | 0 | 36 |

FIGURES
Figure 1:




(WS) Web of Science; (DOS) Dentistry and Oral Sciences; (DARE) Database of Abstracts of Reviews of Effect; (CCRCT) Cochrane Central Register of Controlled Trials; (USNIHCTR) US National Institute of Health Clinical Trial Register

Figure 2: A theme was determined to have been discussed in a source if a topic belonging within that theme was coded as present in that source. Figure 2 displays how many sources out of 8 total sources discussed each theme.

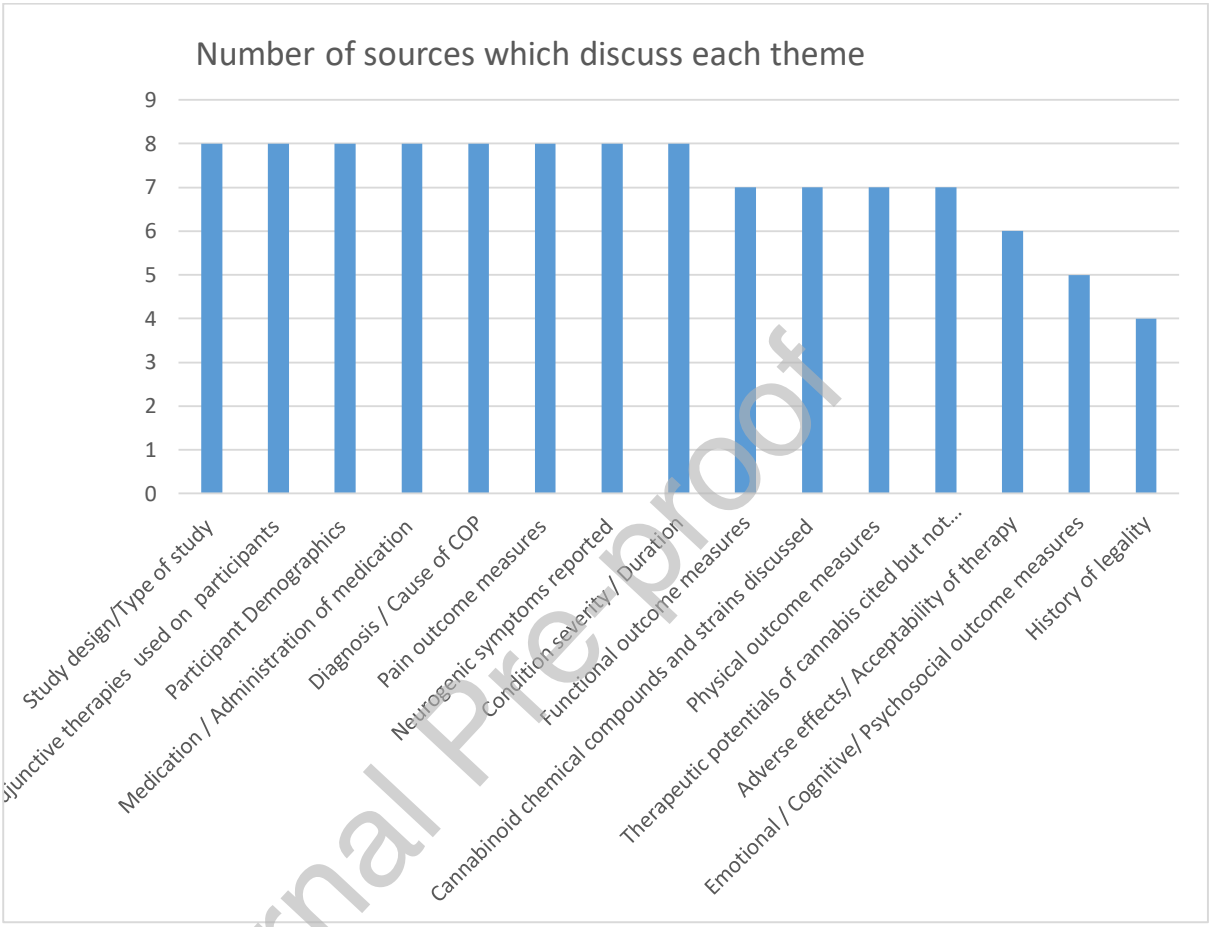


Figure 3: The sum of all topics coded as present in all sources belonging to each theme

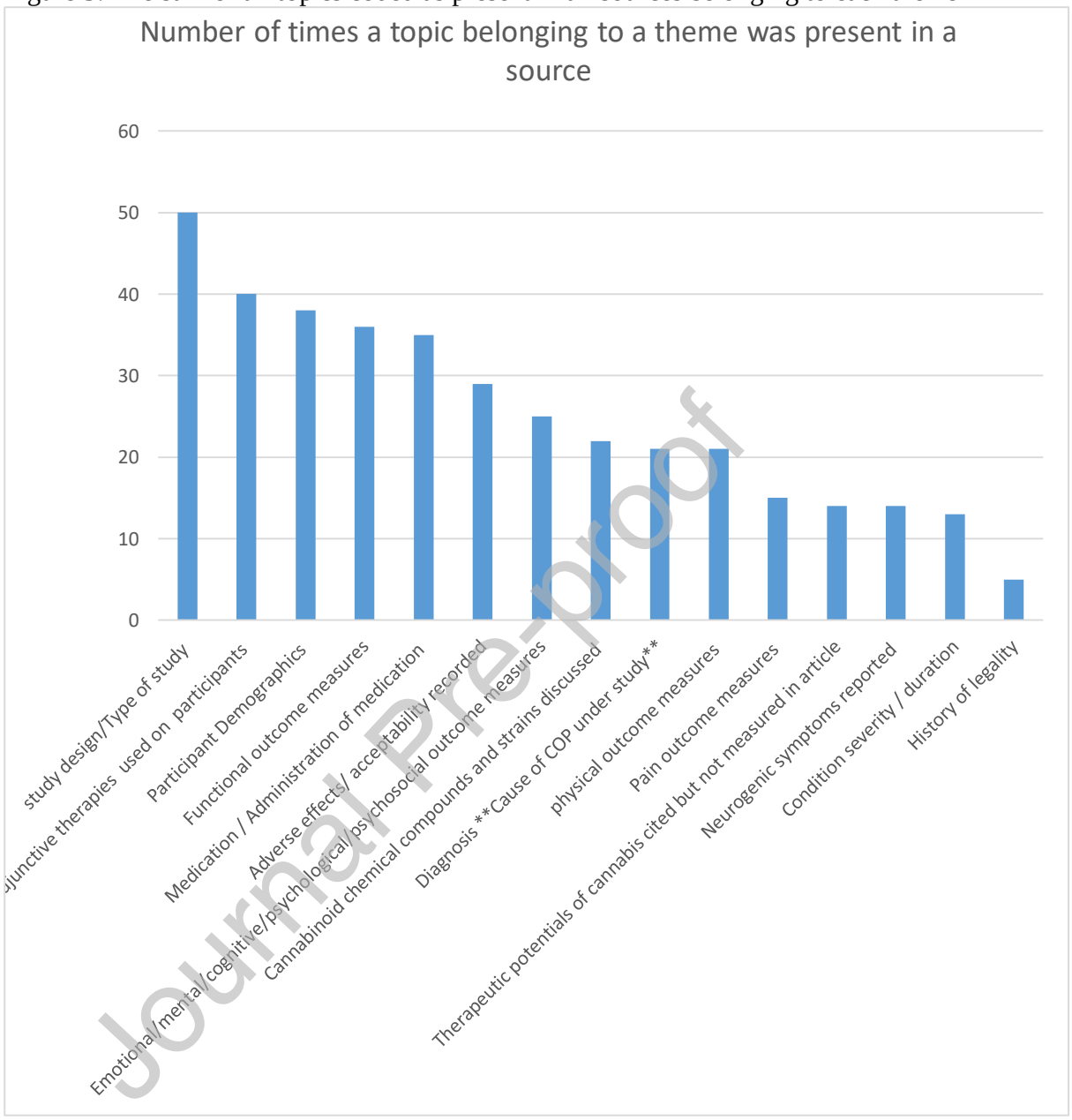


Figure 4: Visual representation of the relative prevalence of all words or common phrases which appeared in the text of titles and abstracts of our 8 sources.




REFERENCES

[1] Malik, N. A. (2020). Revised definition of pain by 'International Association for the Study of Pain': Concepts, challenges and compromises. *Anaesthesia, Pain & Intensive Care*, *24*(5), 481-483. DOI: : 10.35975/apic.v24i5.1352

[2] Treede, R. D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., ... & Giamberardino, M. A., 2019. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). *Pain*, *160*(1), 19-27. DOI: 10.1097/j.pain.0000000000001384

[3] Tait, R. C., Ferguson, M., & Herndon, C. M., 2017. Chronic orofacial pain: burning mouth syndrome and other neuropathic disorders. *Journal of pain management & medicine*, *3*(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5475277/

[4] Madland, G., Newton-John, T., & Feinmann, C. (2001). Chronic idiopathic orofacial pain: I: What is the evidence base?. *British dental journal*, *191*(1), 22-24. Available from: https://www.nature.com/articles/4801081

[5] McDonough, P., McKenna, J. P., McCreary, C., & Downer, E. J. (2014). Neuropathic orofacial pain: cannabinoids as a therapeutic avenue. *The international journal of biochemistry & cell biology*, *55*, 72-78. Available from: https://doi.org/10.1016/j.biocel.2014.08.007
[6] Liang, Y. C., Huang, C. C., & Hsu, K. S. (2004). Therapeutic potential of cannabinoids in trigeminal neuralgia. *Current Drug Targets-CNS & Neurological Disorders*, *3*(6), 507-514. Available from: https://doi.org/10.2174/1568007043336833
[7] Pereira, S. R., Tello Velasquez, J., Duggan, S., Ivanisevic, B., McKenna, J. P., McCreary, C., & Downer, E. J. (2020). Recent advances in the understanding of the aetiology and therapeutic strategies in burning mouth syndrome: Focus on the actions of cannabinoids. *European Journal of Neuroscience*. Available from: https://doi.org/10.1111/ejn.14712
[8] Chaudhary, S., Kumar, D., & Vaghela, D. (2019). The Ayurveda Treatment Protocol in the Management of Anantavata (Trigeminal Neuralgia)- A Case Study. *International Journal of AYUSH Case Reports*, 3(1), 69-72. Available from: http://www.ijacare.in/index.php/ijacare/article/view/69
[9] Sharav. Y., Benoleil. R., Orofacial Pain and Headache. Edinburgh: Mosby Elsevier; 2008.
[10] Vadivelu, N., Vadivelu, A., Kaye, A.E. (2014) Orofacial pain: a clinician's guide. Springer. DOI 10.1007/978-3-319-01875-1
[11] Yaron, H., Avraham Z., PhD, Yoni, E., Valeri, K., Alex, D., Yair, S., Rafael, B., Galit, A. (J2017). The impact of chronic orofacial pain on daily life: the vulnerable patient and disruptive pain. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 123(1), 58-66. Available from: https://doi.org/10.1016/j.oooo.2016.08.016
[12] Durham, J. (2018). Persistent facial pain costs economy£ 3,000 per year. British dental journal, 225(3). Available from: https://www.nature.com/articles/sj.bdj.2018.660.pdf?origin=ppub
[13] Peters, S., Goldthorpe, J., McElroy, C., King, E., Javidi, H., Tickle, M., & Aggarwal, V. R. (2015). Managing chronic orofacial pain: A qualitative study of patients', doctors', and dentists' experiences. *British journal of health psychology*, *20*(4), 777-791. Available from: https://doi.org/10.1111/bjhp.12141
[14] Hoffman, D., & Puig, L. (2014). Complications of TMJ surgery. *Contemporary Management of Temporomandibular Joint Disorders, An Issue of Oral and Maxillofacial Surgery Clinics of North America, E-Book*, *27*(1), 109. Available from: https://doi.org/10.1016/j.coms.2014.09.008
[15] Ganzberg, S. (2010). Pain management part II: pharmacologic management of chronic orofacial pain. *Anesthesia progress*, *57*(3), 114-119. Available fom: https://doi.org/10.2344/0003-3006-57.3.114
[16] Beecroft, E. V., Durham, J., & Thomson, P. (2013). Retrospective examination of the healthcare'journey'of chronic orofacial pain patients referred to oral and maxillofacial surgery. British dental journal, 214(5), E12-E12.
[17] Friedman, D., & Sirven, J. I. (2017). Historical perspective on the medical use of cannabis for epilepsy: ancient times to the 1980s. *Epilepsy & Behavior*, *70*, 298-301. Available from: https://doi.org/10.1016/j.yebeh.2016.11.033
[18] Liu, J., Chen, H., Newmaster, S., Wang, S., & Liu, C. (2021). Global Trends in Cannabis and Cannabidiol Research from the Year 1940 to 2019. *Current pharmaceutical biotechnology*, *22*(5), 579-591. Available from: https://doi.org/10.2174/1389201021666200601152118

[19] Romero-Sandoval, E. A., Kolano, A. L., & Alvarado-Vázquez, P. A. (2017). Cannabis and cannabinoids for chronic pain. *Current rheumatology reports*, *19*(11), 1-10.
[20] Aggarwal, S. K., Carter, G. T., Sullivan, M. D., ZumBrunnen, C., Morrill, R., & Mayer, J. D. (2009). Characteristics of patients with chronic pain accessing treatment with medical cannabis in Washington State. Journal of Opioid Management, 5(5), 257-286.
[21] Costales, B., van Boemmel-Wegmann, S., Winterstein, A., & Segal, R. (2021). Clinical Conditions and Prescription Drug Utilization among Early Medical Marijuana Registrants in Florida. *Journal of Psychoactive Drugs*, 1-10. Available from: https://doi.org/10.1080/02791072.2020.1864069
[22] Furrer, D., Kröger, E., Marcotte, M., Jauvin, N., Bélanger, R., Ware, M., ... & Dionne, C. E. (2021). Cannabis against chronic musculoskeletal pain: a scoping review on users and their perceptions. *Journal of Cannabis Research*, *3*(1), 1-2
[23] Schiffman, E., Ohrbach, R., Truelove, E., Look, J., Anderson, G., Goulet, J. P., ... & Svensson, P. (2014). Diagnostic criteria for temporomandibular disorders (DC/TMD) for clinical and research applications: recommendations of the International RDC/TMD Consortium Network and Orofacial Pain Special Interest Group. *Journal of oral & facial pain and headache*, *28*(1), 6. DOI: 10.11607/jop.1151
[24] Hussain, T., Jeena, G., Pitakbut, T., Vasilev, N., & Kayser, O. (2021). Cannabis sativa research trends, challenges and new-age perspectives. *iScience*, 103391. Available from: https://doi.org/10.1016/j.isci.2021.103391
[25] Arksey, H., & O'Malley, L. (2005). Scoping studies: towards a methodological framework. *International journal of social research methodology*, *8*(1), 19-32. Available from: https://doi.org/10.1080/1364557032000119616
[26] Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., ... & Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Bmj*, *372*. https://doi.org/10.1016/j.ijsu.2021.105906
[27] Phan, N. Q., Siepmann, D., Gralow, I., & Ständer, S. (2010). Adjuvant topical therapy with a cannabinoid receptor agonist in facial postherpetic neuralgia. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft*, *8*(2), 88-91. Available from: https://doi.org/10.1111/j.1610-0387.2009.07213.x
[28] Zhang, H., Xie, M., Archibald, S. D., Jackson, B. S., & Gupta, M. K. (2018). Association of marijuana use with psychosocial and quality of life outcomes among patients with head and neck cancer. *JAMA Otolaryngology–Head & Neck Surgery*, *144*(11), 1017-1022. DOI: 10.1001/jamaoto.2018.0486
[29] Gambino, A., Cabras, M., Panagiotakos, E., Calvo, F., Macciotta, A., Cafaro, A., ... & Arduino, P. G. (2021). Evaluating the Suitability and Potential Efficiency of Cannabis sativa Oil for Patients with Primary Burning Mouth Syndrome: A Prospective, Open-Label, Single-Arm Pilot Study. *Pain Medicine*, *22*(1), 142-151. Available from: https://doi.org/10.1093/pm/pnaa318
[30] Côté, M., Trudel, M., Wang, C., & Fortin, A. (2016). Improving quality of life with nabilone during radiotherapy treatments for head and neck cancers: a randomized double-blind placebo-controlled trial. *Annals of Otology, Rhinology & Laryngology*, *125*(4), 317-324. Available from: https://doi.org/10.1177/0003489415612801
[31] Elliott, D. A., Nabavizadeh, N., Romer, J. L., Chen, Y., & Holland, J. M. (2016). Medical marijuana use in head and neck squamous cell carcinoma patients treated with radiotherapy. *Supportive Care in Cancer*, *24*(8), 3517-3524.

[32] Nitecka-Buchta, A., Nowak-Wachol, A., Wachol, K., Walczyńska-Dragon, K., Olczyk, P., Batoryna, O., ... & Baron, S. (2019). Myorelaxant effect of transdermal cannabidiol application in patients with TMD: a randomized, double-blind trial. *Journal of clinical medicine*, *8*(11), 1886. Available from: https://doi.org/10.3390/jcm8111886
[33] Gajofatto, A. (2016). Refractory trigeminal neuralgia responsive to nabiximols in a patient with multiple sclerosis. *Multiple sclerosis and related disorders*, *8*, 64-65. Available from: https://doi.org/10.1016/j.msard.2016.05.004
[34] Consroe, P., Musty, R., Rein, J., Tillery, W., & Pertwee, R. (1997). The perceived effects of smoked cannabis on patients with multiple sclerosis. *European neurology*, *38*(1), 44-48. Available from: https://doi.org/10.1159/000112901
[35] Goldenberg, M., Reid, M. W., IsHak, W. W., & Danovitch, I. (2017). The impact of cannabis and cannabinoids for medical conditions on health-related quality of life: A systematic review and meta-analysis. *Drug and Alcohol Dependence*, *174*, 80-90.
[36] Loeser, J. D. (2000). Pain and suffering. *The Clinical journal of pain*, *16*(2 Suppl), S2-6. DOI: 10.1097/00002508-200006001-00002
[37] Peters, J., & Chien, J. (2018). Contemporary routes of cannabis consumption: a primer for clinicians. *Journal of Osteopathic Medicine*, *118*(2), 67-70. Available from: https://doi.org/10.7556/jaoa.2018.020
[38] Mussen, F., Salek, S., & Walker, S. *Benefit-risk appraisal of medicines: A systematic approach to decision-making*. John Wiley & Sons. 2009.
[39] Staton, M., Kaskie, B., & Bobitt, J. (2022). The changing cannabis culture among older Americans: high hopes for chronic pain relief. *Drugs: Education, Prevention and Policy*, 1-11. Available from: https://doi.org/10.1080/09687637.2022.2028728
[40] Naci, H., & Ioannidis, J. P. (2015). How good is "evidence" from clinical studies of drug effects and why might such evidence fail in the prediction of the clinical utility of drugs?. *Annual review of pharmacology and toxicology*, *55*, 169-189. Available from: https://doi.org/10.1146/annurev-pharmtox-010814-124614
[41] Bowles, N. P., Herzig, M. X., & Shea, S. A. (2017). Recent legalization of cannabis use: effects on sleep, health, and workplace safety. *Nature and science of sleep*, *9*, 249. DOI: 10.2147/NSS.S152231