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# Cannabinoids and Orofacial Pain Management: A Review

Review Article

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## Abstract

**Objective:** The purpose of this review was to present general data of cannabinoids, its function related to orofacial pain management, and its adverse effects.
**Methods:** The data was searched through PubMed database and Google Scholars by various keywords without time limits. Hand searching and citation mining were also applied. Unpublished, incomplete, non-English data were excluded.
**Results:** The presence of cannabinoids receptors throughout orofacial tissues has been reported, which could be a therapeutic site of action. Only in neuropathic pain, cannabinoids have been proven to be successful over conventional treatment. More clinical approvals of its analgesic effects are extremely required for pain originating from other tissues. When prescribing cannabis, dentists should be cautious about its adverse effects in many systems.
**Conclusion:** Currently, cannabinoids have not been officially endorsed for analgesic effects in orofacial area. It can be useful for neuropathic orofacial pain especially when the standard treatment was unsuccessful.

**Keywords:** Cannabis; Cannabinoids; Orofacial Pain; Dental Pain; Pain.

## Introduction

Orofacial pain is defined as pain that originates below the orbitomeatal line, above the neck, and anterior to the ears, including the oral cavity [1]. Recent research reveals a high prevalence of orofacial pain at approximately 22-26% in the general population, which means that at least one-fifth of the world population is affected by orofacial pain [2, 3]. Women experience a higher prevalence of symptoms than men, but only half of the patients had visited dental or medical professionals for treatment [3]. Orofacial pain, briefly, can be categorizedas odontogenic and non-odontogenic pain. A vast range of odontogenic pain can originate from pulpal tissue, periodontium, and post-surgical pain. Therefore, dental providers should be vigilant when diagnosing this type of pain according to the complaint's history, characteristics, and findings [4]. Besides tooth-related pain, non-odontogenic pain can arise from different regions and sources such as musculoskeletal, neuropathic, and neurovascular [5].

Initial management of orofacial pain should be conservative and reversible approach, including pharmacological therapy [5]. Commonly used prescriptions are nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids, and selective serotonin-noradrenaline reuptake inhibitors (SNRI; Duloxetine). Although current treatment options have been cleared, they are not optimal for every patient because seriously unwanted side-effects may occur for a long-term planned prescription. For example, long-term use of NSAIDs for mild-moderate pain increases the risk of severe gastrointestinal and cardiovascular events. Acetaminophen may cause hepatotoxicity when overdosed. Opioids, usually prescribed for moderate to severe pain, may cause nausea, constipation, and hazardous cardiorespiratory depression in vulnerable populations. For example, duloxetine, which is effective for neuropathic pain, may cause nausea, constipation, dizziness, headaches, high blood pressure, and heart palpitations [6]. The development of new efficacious analgesic medications with minimal side effects is needed for chronic orofacial pain management.

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Recently, interest in using cannabinoids has gradually increased, particularly forthe patients who have failed conventional treatments. These chemical compounds are extracted from the plant *Cannabis Sativa* which contains several types of cannabinoids such as delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), and their synthetic derivatives [7]. In recent decades, the medical use of cannabis has been legalized in many countries; however, it was recently introduced to Thai people as an alternative treatment. In some countries, it was reported that 40% of the population aged 14 and above had tried the drug [7], and 35% of non-cancer pain patients had used the drug for pain relief without professional consultation [8].

This review will elaborate on endocannabinoid systems, the current findings about cannabinoids related to orofacial area, and the effects of cannabinoids in management ofdifferent types of orofacial pain. There will be a comprehensive discussion about the pathophysiology of cannabinoids in pain modulators. Hopefully, this review will provide essential baseline data, which could be used as a novel and alternative pharmacological approach in orofacial pain management to avoid the inevitable adverse effects induced by the systemic administration of conservative drugs.

## Materials and Methods

This review literature was performed in 2019 - 2021. There will be three main sections in this review: general information about cannabinoids, its relevance to orofacial pain, and its adverse effects. The second section will be outlined according to International Classification of Orofacial Pain [9]. The searching was performed primarily through PubMed database and Google scholars without time limits, until August 2021.Several search terms included cannabis, cannabinoids, endocannabinoids, phytocannabinoids, synthetic cannabinoids, orofacial pain, pulpal pain, pulpitis, dental pain, periodontal pain, postoperative pain, post-surgical pain, oral cancer pain, myofascial pain, muscle pain, temporomandibular joint pain, headache, migraine, neuropathic pain, trigeminal neuralgia, and burning mouth syndrome. Apart from direct keywords searching, hand search and citation mining technique were done to ascertain original source of data and find out more relevant contents. Unpublished, retracted, unreachable, or out-of-scope data were excluded as well as non-English articles.

## Results

### The endocannabinoid system

Endocannabinoid system (ECS) is generally referred to as an endogenous signaling system comprised of cannabinoid receptors (CBR), constitutive ligands, and enzymes for ligand biosynthesis and inactivation. It plays a significant role in the regulation of synaptic transmission within the central and peripheral nervous system. Moreover, by binding to the receptors, the endocannabinoids serve vital physiological functions, including pain control, immunomodulation, inflammation, appetite, and lipid metabolism [10, 11].

### Cannabinoid receptors

The two most identified and studied common types of cannabinoid receptors are cannabinoid 1 and 2 receptors. They are members of the G-protein coupled receptor superfamily, consisting of seven transmembrane spanning domains [10] Additionally, some receptors that also act through this system have been reported, such as GPR55, GPR18, GPR119 [12], and TRPV1 [13].

### Cannabinoid 1 receptor (CB1R)

CB1R is the most commonly expressed receptors in the human brain, such as the hippocampus, basal ganglia, cerebellum, cerebral cortex, and amygdala. Due to the wide distribution of CB1R within the central nervous system (CNS), it has several effects on the body, such as movement, cognition, emotion, and pain perception [14]. Interestingly, they are predominantly distributed through the spinal trigeminal tract and spinal trigeminal nucleus caudalis, so they can directly affect trigeminal neurons [10].

The CB1R, in the peripheral nervous system, is primarily observed in sympathetic nerve terminals [15, 16]. It can be detected in trigeminal ganglions, dorsal root ganglions, and dermic nerve endings of primary sensory neurons, so that it regulates nociception from afferent nerve fibers. Thus, the activation of CB1R can trigger antinociceptive effects in peripheral sites [16].

### Cannabinoid 2 receptor (CB2R)

Predominantly, expression of CB2R is detected in the immune system, including thymus, tonsils, spleen, and immune cells, such as B lymphocytes, T lymphocytes, macrophages, monocytes, natural killer (NK) cells, and polymorphonuclear cells. Besides, CB2R is expressed primarily on the reactive microglia, especially in the dorsal horn of the spinal cord in a patient with neuropathic pain, Alzheimer's disease, HIV, and multiple sclerosis [17]. The role of CB2R on cell-mediated and humoral immunity is to suppress the proliferation of B and T lymphocytes. Influentially, the cannabinoids can affect immune cell recruitment and chemotaxis to sites of infection or injury [18].

Even though the expression of the CB2R in the CNS and PNS is comparatively limited, recent studies discovered the intracellular presence of CB2R in prefrontal cortical pyramidal neurons. Therefore, CB2R could involve in neurological activities, such as nociception, drug addiction, and neuroinflammation [10, 19, 20].

### Other receptors

Several studies have explored non-cannabinoid receptors but act like cannabinoid receptors. Firstly, G-protein receptor 55 (GPR55) is putatively accepted as a cannabinoid 3 receptor [21, 22]. It is highly expressed in CNS, including the hippocampus, putamen, caudate, hypothalamus, thalamus, cerebellum, and pons. Furthermore, it is also expressed inendothelial cells, adrenal glands, and gastrointestinal tract [23, 24]. Secondly, the transient receptor potential vanilloid 1 (TRPV1), also known as the capsaicin receptor, has been reported to mediate cannabinoid activities and has prompted many scientists to call it an ionotropic cannabinoid receptor [13, 19]. It is abundantly shown in nociceptive neurons of PNS; however, it is also expressed in the heart, blood vessels, lungs, and CNS. Because its activation induces the release of the substance P and calcitonin gene-related peptide (CGRP), TRPV1 plays a vital role in pain detection and tissue inflammation [13]. Moreover, other receptors may be related to the cannabinoid system, such as GPR18 and GPR119, but further research

is needed to clarify the role of these receptors in the cannabinoid system [25].

**Endocannabinoids**

Endocannabinoids, the endogenous agonists, are naturally produced from precursor phospholipids within the body, such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG). They are synthesized on-demand only when they receive the signal from the postsynaptic neuron cell membrane. These endocannabinoids are produced by different biosynthetic pathways; 2-AG is synthesized from diacylglycerol (DAG) by diacylglycerol lipase (DAGL), while the synthesis of AEA from the phosphatidylethanolamine is activated by the action of N-acyltransferase and phospholipase D. Then, they are immediately released into the neural synaptic space, inducing retrograde signaling by activating presynaptic neuron receptors such as CB1R, CB2R, and TRPV1 ion channels expressed on primary afferent nociceptors. This phenomenon was termed depolarization-induced suppression of inhibition or excitation (DSI/DSE) [10, 26]. After that, they are eliminated rapidly by degradative hydrolyzed enzymes. Mainly, 2-AG is metabolized by monoacylglycerol lipase (MAGL), whereas AEA is primarily degraded by fatty acid amide hydrolase (FAAH) [10, 11, 16].

In the CNS, endocannabinoids serve as a negative feedback mechanism and inhibit the excessive synaptic release of various neurotransmitters. For example, excessive glutamate release in the dorsal horn of the spinal cord due to painful stimuli indirectly induces 2-AG by calcium influx. Retrograde signaling by 2-AG activates CB1R, located on the presynaptic neuron, closes the calcium channel, which subsequently halts glutamate vesicle release [27]. Moreover, AEA is beneficial for pain regulation through CB1R by inhibiting the release of calcitonin gene-related peptide (CGRP) from primary afferent fibers upon trigeminal neuron, which reduces nociceptive behavior [28].

Mentioning CB2R in white blood cells, AEA and 2-AG act as immunomodulators in cell-mediated immunity where they suppress the production of T-helper1 (Th1), cytokines such as interleukin-2 (IL-2) and interferon-gamma (INFγ), as well as tumor necrosis factor-alpha (TNFα). Conversely, in humoral immunity, they increase the secretion of T-helper2 (Th2) and some cytokines such as IL-4, IL-5, and IL-10. Moreover, B lymphocytes and natural killer cells require ECS and CB2R to function correctly. On the ground of CB2R activation, it leads to anti-inflammatory phenotype [18].

**Phytocannabinoids**

Phytocannabinoids, plant-derived cannabinoids, are the C21/22 terpenophenolic compounds extracted from the plant Cannabis sativa. To date, approximately 120 cannabinoids substances and more than 400 non-cannabinoids substances have been extracted from the plant [29]. The two most commonly studied phytocannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Physiologically, they can mimic endocannabinoid ligands which usually activate cannabinoid receptors [30].

Delta-9-tetrahydrocannabinol (THC) is used therapeutically as an analgesic, muscle relaxant, antiemetic, appetite stimulant, and many more [31, 32]. It acts primarily on the CB1Rand CB2R accordingly. In contrast, it has unavoidable psychoactive effects, which can cause euphoria, relaxation, tachycardia, and heightened sensory perception [31, 33]. Pharmacokinetically, the functions of THC can be varied depending on the route of administration. Inhalation, typically, causes a maximum plasma concentration within a few minutes as well as its psychotropic effects. These effects reach a maximum after 15 to 30 minutes of consumption and taper off within two to three hours. Following oral ingestion, psychotropic effects manifest within 30 to 90 minutes with maximum effect after two to three hours and last for about four to 12 hours, depending on the dose [31].

Conversely, cannabidiol (CBD) binds very weakly to CB1R [34] and CB2R [10]. It acts as a non-competitive negative allosteric modulator of these cannabinoid receptors, including GPR55[35]. However, CBD is an agonist of TRPV1 and serotonin 1A (5-HT1A) receptors [35]. In parallel, it inhibits the enzymatic hydrolysis and the uptake of AEA. The increase in AEA levels induced by CBD seems to mediate part of its effects [36]. In addition, CBD differs from THC by its non-psychoactive effect [29, 37, 38]. Therapeutically, CBD has been proposed to possess neuroprotective, antipsychotic, sedative, hypnotic, antianxiety, antinausea, antinociceptive, anti-inflammatory, and antiseizure [30, 39-42]. Interestingly, there was an evidence that CBD may potentially have anticancer effects [43]. Nevertheless, its antidiabetic effect was proved to be worthlessness [44]. It has been approved by the United States Food and Drug Administration (the US FDA) for the treatment of certain forms of epilepsy. Currently, it is being investigated to treat cerebral ischemia and multiple sclerosis [30, 45]. Most commercial cannabinoid formulations contain mainly THC mixing with various CBD ratios to reduce the psychoactive effects of THC. Currently, there appears to be increasing CBD level in the products [46]. For example, one of the medical products is Nabiximols (Sativex®), oromucosal spray containing THC 2.7 mg, and CBD 2.5 mg (THC:CBD = 1:1). It is proven to effectively reduce chronic neuropathic pain [47] and improve spasticity and pain in secondary progressive multiple sclerosis [30, 37, 48]. Pure CBD product for medical use is Epidiolex®, for instance. The US FDA has approved this product to treat severe pediatric epilepsy, Dravet syndrome, and Lennox-Gastaut syndrome, as well as tuberous sclerosis complex [49, 50].

Other than THC and CBD, many phytocannabinoids have also been investigated for therapeutic uses [51-53]. Cannabigerol (CBG) and cannabichromene (CBC), for example, are non-psychoactive agents [29]. CBG was believed to have antiemetic and anti-inflammatory effects [54, 55]. It could be used to treat epilepsy and Huntington's disease, a rare inherited neurodegenerative disorder [56]. CBC is a selective agonist of CB2R with anti-inflammatory and antinociceptive activities [57]. It might be used for dealing with hypomotility seizure, catalepsy, and hypothermia [54]. Cannabinol (CBN), primarily degraded from THC [52], has a mild or less psychoactive effect and higher affinities to CB2R than CB1R [58]. It is believed to be the first phytocannabinoids to be isolated [52]. Tetrahydrocannabivarin (THCV), cannabivarin (CBV), and cannabidivarin (CBDV) are other examples of phytocannabinoids that are in a group of abundant constituents of Cannabis sativa [51]. However, clear evidence of their medical applications is still required.

**Synthetic cannabinoids**

Synthetic cannabinoids are a heterogeneous group of compounds

developed to mimic either endocannabinoids or phytocannabinoids. Pharmacological effects of synthetic cannabinoids are 2-100 times more potent than THC, including analgesic, antiseizure, weight-loss, anti-inflammatory, and anticancer growth effects. Due to the greater intensity, it can adversely induce several toxic events in medical emergencies, including cardiovascular, respiratory, urinary, and especially psychiatric issues [59].

Several compounds are used as cannabis-based medications, other than the previously mentioned Nabiximols and Epidiolex, such as Nabilone, Dronabinol, and Rimonabant. Nabilone (Cesamet®) and Dronabinol (Marinol®), pharmaceutical analog forms of THC, are reported to be successful in chemotherapy-induced nausea and vomiting [32]. Some reported their uses as adjunctive drugs in HIV/AIDS-related and cancer-related weight loss [37, 60]. In one study, Rimonabant, a CB1R antagonist, was found to be effective in a pharmacologically anti-obesity and smoking cessation program [61]. However, the novel generations of CB1R antagonists are being developed in consequence of unwanted neuropsychiatric effects of Rimonabant [62]. Presently, various synthetic cannabinoids are being investigated for their pharmacological effects, clinical applications,and possible adverse events. They include JWH-018, JWH-073, Dimethylheptylpyran, HU-210, HU-331, WIN55,212-2, AM2201, and many more [59].

## Pain

Pain in the orofacial region can be crudely divided into two main groups by its origination, which are odontogenic pain and non-odontogenic pain, or by its site, which can be intraoral pain and extraoral pain. In this review, the sequence of discussion will be assembled according to International Classification of Orofacial Pain by International Headache Society, 2020 [9].

### 1. Orofacial pain attributed to disorders of dentoalveolar and anatomically related structures

• **Pulpal pain:** In order to prove that cannabinoids could be used to relieve pulpal pain, studies have demonstrated the expression of cannabinoid receptorin the dental pulp. Regarding the dental pulp of rats, CB1R has been histologically observed both in coronal pulp and radicular pulp. It formed a plexus in the subodontoblastic layer and the cell-rich zone [63]. These findings were similar to the study in human dental pulp in the UK except the detection of receptors in the pulpal subodontoblastic layer, which might be explained by different fixation procedures [64]. Moreover, CB1R, as well as TRPV1, were also present in the human odontoblastic process [65, 66]. According to studies in rats, there were detections of TRPV1 in dental pulp fibroblasts [67] and neurons [68]. However, when comparing the quantity of displayed CB1R area in human dental pulp, there were no significant differences between painful and non-painful samples [64]. According to a recent study in rats, CB1R in the midbrain might be associated in pain signals modulation from dental pulp [69]. As mentioned above, although cannabinoid substances have been histologically demonstrated in dental pulp, the mechanisms of action must be proven in clinical situations as an effective pharmacological treatment for pulpal pain.

• **Periodontal pain:** Many studies attempted to focus on detecting cannabinoids receptors in periodontal tissue. Both CB1R and CB2R, according to the studies in rats [70] and humans [71], were discovered in gingival connective tissue, such as gingival fibroblasts, endothelial cells, and macrophage-like cells. Markedly, the presence of these receptors appeared to be significantly related to gingival inflammation, including pain. Higher expressions in gingivitis and periodontitis patients were reported compared to the control group [71]. In periodontitis patients, AEA was found in gingival crevicular fluid and more at the wound sites after periodontal surgery. Then, the increased level can be attenuated by some selective antagonists of CB1R and CB2R [70]. Moreover, there were CB2R expressions in human periodontal ligament fibroblasts, and many pro-inflammatory cytokines were inhibited by endocannabinoids and synthetic cannabinoids in this in vitro study [72]. Activation of CB2R enhances differentiation of human periodontal ligament cells to be osteoblasts to induce alveolar bone mineralization [73]. These findings concluded that cannabinoids might be a new target forperiodontal therapy [70, 74, 75], however the clinical evidence of these interactions should be clarified. Admittedly, recreational cannabis users may confront more chances of having severe periodontitis, as a deeper periodontal pocket and higher clinical attachment loss were significantly reported [76].

Regarding postoperative pain, many cannabis-based substances had been introduced for postoperative analgesic efficacy following third molar surgery, such as GW842166 (CB2R agonist) [77] and AZD1940 (CB1R and CB2R agonist) [78]. However, both artificial cannabinoids show no statistical differences in the Visual Analog Scale (VAS) compared to placebos, whereas NSAIDs were used as positive controls. Unfortunately, some adverse events occurred, such as being high, nausea, headache, dizziness, and hypotension [77, 78]. Interestingly, a recent systematic review about all types of surgeries, including dental and medical, disagreed with the routine prescription of cannabinoids to reduce acute postoperative pain [79].

• **Oral mucosal pain attributed to malignant lesion:** Squamous cell carcinoma accounted for almost all of oral cancer detected nowadays, followed by salivary gland tumors. The prevalence ranges from 1% to 25% according to inclusion criteria, risk factors, and different countries [80]. CB1R and CB2R were discovered in human oral cancer cells [81]. Systemic administration of cannabinoids receptor agonists could reduce cancer pain with the equal efficacy of opioids. In this study, the authors chose WIN55,212-2 as a non-selective agonist, ACEA as a CB1R agonist, and AM1241 as a CB2R agonist. Furthermore, CB2R agonist was not only able to decrease pain, but it could also inhibit oral cancer cell proliferation [81]. On the contrary, it is unavoidable that there has been a strong association between cannabis users and increased risk of head and neck cancer [82, 83]. Therefore, cannabinoids should not be the initial therapy for pain attributed to oral malignant lesion.

### 2. Myofascial orofacial pain

The establishment of CB1R and CB2R expression in human fascia and fascial fibroblasts was discovered. These receptors may play an essential role in diminishing pain, modulating inflammation, and reorganizing microstructure in fascial tissue [84, 85]. There were positive expressions of TRPV1, CB1R, and CB2R by trigeminal ganglions that innervate masseter muscle in rat experimental research. However, only CB1R was shown to be the target receptor in this experiment. Intramuscular injection of THC

could lead to muscle activity reduction. It attenuated nerve growth factor (NGF) that reduces muscle sensitization and increases the mechanical threshold of the masseter muscle's mechanoreceptor. Therefore, through peripheral CB1R, THC injection could relieve pain that arises from masseter muscle [86]. In spite of being less effective than THC, the intramuscular injection of CBD alone (5mg/ml), CBN alone (1mg/ml), and CBD-CBN combination (1:1 mg/ml) might be successful for analgesic relief of myofascial pain syndrome without neurological side effects [87].

Antinociceptive effects of acute pain have successfully been shown through intraperitoneal and intramuscular techniques by plant cannabis which was THC [45], and synthetic cannabis such as WIN55,212-2 (non-selective agonist), ACEA (CB1R agonist), and JWH-015 (CB2R agonist) [88]. Moreover, the double-blind design of CBD transdermal application onto masseter muscle in myofascial pain syndrome patients, compared with the placebo, demonstrated the myorelaxant effect by decreasing muscular activities measured by the electromyography (EMG) and the VAS pain intensity which the final result was 70.2% lower than that prior tothe intervention [89]. In the future, cannabinoids may be a good candidate to treat myofascial pain, but strong confirmations are greatly needed.

### 3. Temporomandibular joint (TMJ) pain

In a study with rats, electroacupuncture treatment was known to possess anti-inflammatory and antinociceptive effects in rat models of TMJ arthritis. The researchers reversed this mechanism by AM251 and AM630, synthetic cannabinoids, which were shown to be positive. Therefore, it was suggested that the anti-inflammatory and antinociceptive effects of TMJ could be activated through cannabinoid receptors [90]. In another study with rats, WIN55,212-2 was administered intraperitoneally to examine nociceptive responses in TMJ and the orofacial area. The positive outcome of antinociception was revealed through CB1R activation [91]. The result was similar to other studies performed by rat intracisternal injection of WIN55,212-2 [15, 92]. Furthermore, similar to morphine, this cannabinoid compound was able to relieve oral inflammatory pain better than indomethacin and ketamine [91]. Presently, the management of osteoarthritis pain still has limited evidence to support. A number of clinical trials should be performed in order to translate the obtained preclinical results to humans [93].

### 4. Orofacial pain attributed to lesion or disease of the cranial nerves

• **Neuropathic orofacial pain:** Neuropathic orofacial pain is a chronic disorder without fully clarified causes of problems, but several peripheral and central mechanisms have been proposed, which requires multidimensional management strategies [94]. Related conditions of neuropathic orofacial pain include, but are not limited to, the following: trigeminal neuralgia, postherpetic neuralgia, and painful trigeminal neuropathy [95].

According to research on trigeminal neuropathic pain, WIN55,212-2 had CB1R preference at the nerve terminal of small-diameter primary afferent fibers. CB1R activation suppresses the primary afferent glutamatergic transmission, leading to an analgesic effect. Moreover, it was observed that C fiber was more sensitive to WIN55,212-2 than A-delta fiber indicating that cannabinoids can reduce dull pain better than sharp pain [96]. Moreover, WIN55,212-2 can dose-dependently attenuate mechanical allodynia and thermal hyperalgesia in a rat's trigeminal nerve through CB1R activation. Therefore, cannabinoids may be a beneficial approach in neuropathic pain management [97]. As current strategies in treating trigeminal neuralgia may have allergic or intolerant limitations, there is growing evidence that cannabinoids may be very promising for addressing these difficulties [98]. Despite the advancement of medical technology, it is still controversial to use cannabinoids in orofacial neuropathic pain. According to the unclear etiology of this type of pain, rational and safe drugs should be prescribed [99]. However, Nabiximols (Sativex®) may be a successful representative worth waiting for [47, 100]. A pilot study in chemotherapy-induced neuropathic pain revealed a success of Nabiximols in pain decrease compared with placebo [101]. Interestingly, according to a systematic review in Cochrane database, it was concluded that cannabis-based medicines provided more benefits than harms in case of chronic neuropathic pain [102].

### 5. Orofacial pains resembling presentations of primary headaches

• **Orofacial migraines:** Much research has reported a reliable connection between endocannabinoid and migraine diseases [103-106]. A study in cerebrospinal fluid revealed a lower level of AEA in chronic migraine patients, which implied reduced function of the endocannabinoids system. This finding may lead to chronic head pain and increased calcitonin gene-related peptide (CGRP) and nitric oxide (NO) production, which are the aggravating factors of migraines [103]. Cannabinoids substances may interrupt many pathways of the pathogenesis of headache disorders, including migraine [107]. Firstly, the overactivation of the trigeminovascular system, one of the causes of headache disorder, can be neutralized by AEA, which inhibits dural blood vessel dilation and the release of CGRP, which induces anti-migraine effects [107, 108]. Secondly, the aura in migraine is considered to be involved with cortical spreading depression (CSD), a wave of electrophysiological hyperactivity followed by inhibition resulting from excessive glutamate signaling. The endocannabinoids can help relieving the aura at this point by suppressing glutamate signaling. Furthermore, serotonin, which is released from aggregating platelets, may play an essential role in migraines. Another effect of cannabinoids that has been proven is platelet stabilization and the prevention of serotonin release [107]. Lastly, AEA in the ventrolateral periaqueductal gray (VPG) has been found to attenuate trigeminovascular afferents from noxious stimulation in the dura mater [108].

THC has been proved to soothe migraine-like pain when administered optimally and immediately after the migraine attack [105]. This mechanism was found to be mediated by CB1R activation [104, 105]. Clinical research in 2017 revealed that THC-CBD combination as prophylaxis might help decreasing migraines. It can be used immediately to treat acute pain attacks in migraine groups and cluster headache groups with a previous migraine history. At the same time, it showed no effects in those without a history of migraines [109]. Prescription of medical marijuana has significantly decreased the frequency of migraine headaches per month. It can prevent migraine attacks when used daily. Interestingly, when acute migraine occurred, the commonly used form was inhalation [110].

• **Trigeminal autonomic orofacial pain:** According to a study about cluster headache in French, cannabis use showed unpredictable effects (51.8%), beneficial effects (25.9%), and, unfortunately, deleterious effects (22.3%)[111]. Furthermore, a study in Dutch cluster headache population, only 15% and 17% of cannabis users reported the decrease in duration and frequency of cluster headache episodes respectively [112]. Due to these results, Cannabis is not recommended for management of cluster headaches.

**6. Idiopathic orofacial pain**

• **Burning mouth syndrome (BMS):** There were significant alterations in the expression of cannabinoid receptors in tongue epithelial cells. These modifications, which were increased TRPV1, decreased CB1R, and increased CB2R, may be potential biomarkers for therapeutic targets [113]. A pilot trial using a cannabis oil recently showed effectiveness in patients with primary BMS [114]. There are many possible mechanisms that may contribute to the future treatment strategies of BMS by its anti-inflammatory effect and neuroprotective characterization [115], as well as favorable alterations in the salivary flow rate and cerebral blood flow [100]. But, conclusively, the verifications of these actions should be clinically tested.

**Adverse effects**

Different cannabinoids play different physiological and psychological effects in various human body systems, creating unwanted side effects. The most reported change involves neurological system which dizziness is the most common side effect, nevertheless it is typically not very serious [116]. Cannabis can cause mood and perceptual changes, which can be stated as "being high" or euphoria. It can also produce dysphoric reactions, including severe anxiety, panic, depression, paranoid, and agitation [116, 117]. Short-term use may cause impaired short-term memory and impaired motor coordination [118]. On the other hand, long-term use of cannabis has been linked to a motivational syndrome, simulating depression with symptoms of apathy, dullness, lethargy, and impaired judgment [117]. Heavy marijuana users also suffer from declined brain development, cognitive impairment, poor educational outcome, and significantly increased risk of schizophrenia and psychotic symptoms [118, 119]. Furthermore, it was reported that cannabis users whose blood THC concentration was more than 5 μg/mL had an increased risk of traffic collisions [120].

In the cardiovascular system, cannabinoids can adversely cause orthostatic hypotension, raised heart rate, raised blood pressure, increased risk of several cardiovascular events such as atrial fibrillation, ventricular tachycardia, acute myocardial infarction, and ischemic stroke [121, 122]. However, a US study with adults showed no relationship between cardiovascular diseases and cannabis use [123]. In addition, cannabis smokers are associated with an increased risk of chronic bronchitis due to the changes in mucosal epithelial cells and more mucus accumulation in the respiratory tract [118, 124], while the changes in oral mucosa can induce a higher prevalence of leukoedema, candidiasis, and clinical symptoms of xerostomia [125, 126]. Stinging sensation and burning lesions should be warned after use of oromucosal spray [127].

Another adverse effect that chronic cannabis users have encountered is drug dependence [117, 119]. The dependence syndrome has been reported among one in ten users [128]. Furthermore, the presence of cannabis withdrawal syndrome also encourages the users to reverse the cessation. These withdrawal symptoms include irritability, anxiety, increased aggression, restlessness, insomnia, a depressed mood, a low appetite, sweating, headaches, stomach pain, and muscle tremors [129]. In polypharmacy situations, drug interaction should be seriously aware because cytochrome P450 enzymes metabolize both THC and CBD extensively. For example, taking medical THC or smoking marijuana can limit the metabolic rate of warfarin, which results in elevated INR (international normalized ratio) and bleeding complications [130-132]. Theoretically, although cannabinoid substances and other drugs which involve cytochrome P450 may potentially interact, human studies to determine clinical significance should be researched to confirm the mechanisms and declare the precautions [133].

## Discussion

To date, there are many suggestions that medical cannabinoids substances can be prescribed for chemotherapy-induced nausea and vomiting, intractable epilepsy, spasticity in multiple sclerosis, appetite stimulation, and, noticeably, chronic neuropathic pain [134, 135]. Obviously, there will be an increasing number of cannabis users in the near future due to the recent legalization of medical and recreational cannabis use in many countries, such as Thailand. It is unavoidable that well-planned strategies are critically needed before implementation. The strategies include educating both providers and patients, informing public awareness, and standardizing the products [136].

In terms of dental treatment, clear indications with minimal side effects should be developed before regularly prescribing cannabis for coping with pain in the maxillofacial area. In this review, much evidence positively shows the presence of cannabinoid receptors in various oral tissues which may be therapeutic targets for the novel treatment of orofacial pain. Studies also suggested that inhibition of degradative enzymes, FAAH and MAGL, could be therapeutic site in order to keep raised level of endocannabinoids [137, 138]. Future research should focus on the clinical use of cannabis-based medicines in case of pulpal pain, periodontal pain, joint and muscular pain, and migraines. More interestingly, cannabinoids are considerably promising for neuropathic pain if the guidelines from trusted organizations are introduced [139]. However, the standard treatment has proven to be better than cannabinoids for postoperative pain, oral mucosal pain, and cluster headache.

## Conclusion

As a recommendation, cannabis-based medicines should be prescribed only for proven indications and when the available standard treatment was unsuccessful. Currently, cannabinoids have not been officially endorsed for analgesic effects in orofacial area. It can be useful for neuropathic orofacial pain especially when the standard treatment was disappointed. Although cannabinoids receptors are presence in many tissues, future studies should confirm the clinical relevance to pain reduction in pulpal pain, periodontal pain, myofascial pain, TMJ pain, and migraines. Before that, dentists should be primarily concerned about possible adverse effects and drug interactions prior to prescription. Also, the

concerns should be raised when performing dental operations on recreational users. Lastly, dental healthcare providers should continuously follow the updated trends and research in order to use cannabis-based products appropriately and effectively.

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