Review Article

Marijuana and cannabinoid use in clinical oral and maxillofacial surgery: a scoping review

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Background: Despite increased use of recreational and medical marijuana over the past decade, little is known about its effect on oral and maxillofacial surgery (OMFS). The goal of this study was to map the current state of marijuana and cannabinoid research within OMFS and review the findings. The investigators hypothesized that the number of studies evaluating the use and effects of marijuana and cannabinoids in OMFS would be limited.

Methods: The investigators implemented a scoping review study design. Studies were identified and collated by a team of 2 researchers who then independently evaluated each study for eligibility. The final cohort of studies were composed of interventional studies written in English available through ClinicalTrials.gov, PubMed, and Web of Science from inception to 11/01/2021 pertaining to the use of marijuana or cannabinoids within the clinical setting of OMFS. Studies were included that assessed the effects of marijuana on patients undergoing oral surgical procedures and/or conscious sedation. Studies were excluded if they lacked an intervention group, were conducted with animal models, or involved procedures not performed by oral surgeons (e.g., dental fillings). The primary outcome was the number of studies, and secondary outcomes included study topics and study conclusions.

Results: A total of 11 studies were identified with sample sizes ranged from 10 to 151 patients. Four studies were observational and 7 studies were prospective, including 4 clinical trials. Topics addressed by these studies included the effects of marijuana and cannabinoids on acute post-extraction pain, temporomandibular joint pain and myofascial pain, extraction socket wound healing, intravenous sedation anesthetic requirements, and intravenous sedation physiologic responses including the cardiovascular response. Two of these studies found that cannabinoids may improve pain, two studies failed to demonstrate improved pain control with cannabinoids, 3 studies reported that cannabinoids had adverse effects on vital signs, 1 study reported increased anesthetic requirements for cannabinoid users, 1 study reported no difference in post-operative healing after dental extractions for cannabinoid and non-cannabinoid users, and 1 study is ongoing.

Conclusions: The effect of marijuana and cannabinoids on the OMFS should be considered. However, there is a paucity of literature available. This study was designed to identify knowledge gaps for guiding future research efforts. The lack of clinically-based interventional studies for post-procedural pain control and anesthetic requirements for cannabinoid users indicates an opportunity for growing the field of OMFS.

Keywords: Marijuana; cannabis; cannabinoids; cannabidiol (CBD); Δ-9-tetrahydrocannabinol (THC); AZD1940; GW842166; oral and maxillofacial surgery (OMFS)

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Introduction

Marijuana has been consumed for thousands of years with the first evidence of its medicinal use occurring around 400 AD (1). Consumption of marijuana was unregulated in the United States until the first federal restriction on cannabis was enacted by the Marihuana Tax Act of 1937. Since then, legislation has remained a strong regulator of marijuana use for recreational or medical purposes. The Controlled Substances Act of 1970 created the first drug scheduling system listing Marijuana as a schedule 1 substance along with heroin. However, due to legislative changes over the past decade, marijuana is now legalized for medical use in 35 states and Washington DC for adults over age 21 (2-4) (*Table 1*). Of the remaining 15 states, 7 of these (i.e., Georgia, Indiana, Iowa, Kentucky, Texas, Virginia, and Wisconsin) have legalized low-Δ-9-tetrahydrocannabinol (THC) cannabidiol (CBD) oil (up to 5% THC) for medical use (2). As a result, only 8 states have yet to legalize any form of marijuana or CBD for medical or recreational use, which may decrease by the end of 2021 based on pending legislation (2). Consequently, the increase in legal marijuana use provides an opportunity for researchers to investigate the therapeutic potential of medical marijuana, as well as to better characterize the physiologic effects of recreational marijuana.

Specifically, "marijuana" refers to parts of the *Cannabis sativa* plant from which it is derived, which contain the highest concentrations of the primary psychoactive compound, THC, while the term "cannabis" refers to all parts of the *C. sativa* plant (5,6). Marijuana contains approximately 450 distinct compounds, including 60 cannabinoids (5,6). THC and CBD are two of the main cannabinoids which are most commonly studied. To date, there have been hundreds of clinical trials and studies on medical marijuana and cannabinoids for conditions such as epileptic seizures, Parkinson's disease, ulcerative colitis, cognitive dysfunction, opioid use disorder, acute and chronic pain (7). However, it is unclear how well studied marijuana is in the context of oral and maxillofacial surgery (OMFS), as well as intravenous (IV) sedation, which is an integral part of the OMFS specialty. Our study sought to characterize the literature on marijuana in OMFS, including treatment outcomes and side effects, with the hypothesis that there is likely a paucity of studies available on this topic. We hope this study will serve as a foundation for future research on marijuana in OMFS, especially as legislation around medical marijuana use grows increasingly relaxed throughout the United States (2). We present the following article in accordance with the PRISMA-ScR reporting checklist (available at https://joma.amegroups.com/article/view/10.21037/joma-21-7/rc).

Materials and methods

We conducted a scoping review of the literature relating marijuana or cannabinoids to clinical OMFS. This review complied with the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Reviews (PRISMA-ScR) reporting checklist.

Our search of relevant studies included ClinicalTrials.gov, PubMed, and Web of Science databases dating from inception until 11/1/2021. Various key words were utilized for the search including oral surg*, TMJ, temporomandibular, dentoalveolar, orthognathic surgery, dental extraction, dental, dentistry AND cannabi*, tetrahydroxy*, marijuana. MeSH terms were also used where available. Studies that assessed the relationship of cannabinoids or marijuana with oral surgery procedures were considered for inclusion (see *Figure 1*). We excluded papers not written in English, those involving animal models, and those without interventional arms. Titles and abstracts were screened by two independent researchers (LY Tang and AR Emery) from 1/10/2021 to 11/10/2021 with disagreements reviewed and decided upon by author (J Wang). Although the aforementioned protocol was designed a priori, no formal protocol registration was performed.

The outcome variables for the clinical trials included the clinical trial number, title of the study, principal investigator (PI) name/author names, PI specialty, study topic, study type, sample size, study start date, study end date, study sponsor, primary outcome, and results reported on ClinicalTrials.gov. The outcome variables for the non-clinical trials included study name, authors, study topic, study type, sample size, date of accepted publication, intervention, primary outcome, and results. No studies meeting the inclusion criteria were excluded. The data

Table 1 Marijuana legalization status in the U.S. by state

Marijuana legalization status	States
Full legal	Alaska, Arizona, California, Colorado, District of Columbia, Illinois, Maine, Massachusetts, Michigan, Montana, Nevada, New Jersey, Oregon, South Dakota, Vermont, Washington
Medical and decriminalized	Connecticut, Delaware, Hawaii, Maryland, Minnesota, Mississippi, Missouri, New Hampshire, New Mexico, New York, North Dakota, Ohio, Rhode Island, Virginia*
Medical	Arkansas, Florida, Georgia*, Indiana*, Iowa*, Kentucky*, Louisiana, Oklahoma, Pennsylvania, Texas*, Utah, West Virginia, Wisconsin*
Fully illegal	Alabama, Idaho, Kansas, Nebraska, North Carolina, South Carolina, Tennessee, Wyoming

*, states that have not legalized medical marijuana but have legalized medical use of low-THC CBD oil. THC, Δ-9-tetrahydrocannabinol; CBD, cannabidiol.

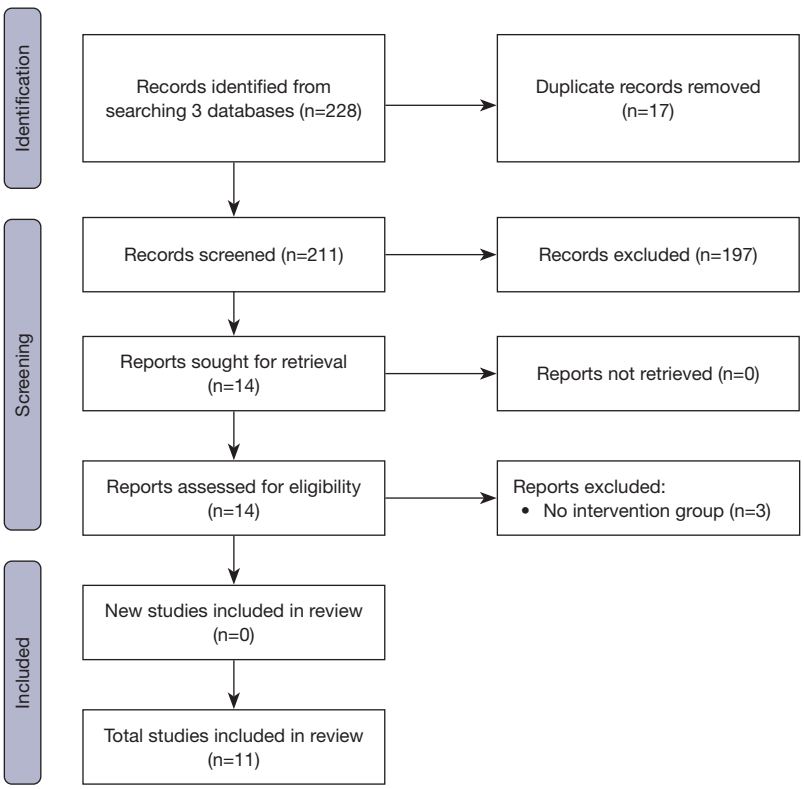

Figure 1 Flow diagram of included articles.

presented in this study is publicly available and thus did not require institutional review board approval.

Results

Eleven studies were identified that met the inclusion criteria, with 2 studies described within a single publication (8). There were 7 prospective studies including 4 clinical trials (*Table 2*) and 3 randomized control trials (RCTs) not registered as clinical trials. There were also 4 observational studies (i.e., retrospective cohorts) identified (*Table 3*). The topics covered by these studies included acute post-dental extraction pain, temporomandibular joint (TMJ) pain and myofascial pain, extraction socket wound healing, IV sedation anesthetic requirements, IV sedation physiologic responses and observations, including cardiovascular responses. The sample

Table 2 Clinical trials of cannabinoids in oral and maxillofacial surgery (OMFS)

Clinical trial No.	Title	PI name/ authors	PI specialty	Study topic	Study type	Subjects (n)	Initiation date	Year of closure (if applicable)	Sponsor	Intervention	Primary outcome	Results posted
NCT04298554	Comparison of Cannabinoids to Placebo in Management of TMJ Pain and Myofascial Pain in the TMJ Region	Gwendolyn Reeve	OMFS	Pain control	Interventional, randomized, parallel assignment, single blinded	Expected 71	3/6/2020	Recruiting	Weill Medical College of Cornell University	Experimental arm: CBD oil Control arm: placebo (hemp oil)	Change in baseline pain based on Visual Analog Scale (VAS) at baseline, 3, 7, and 11 weeks	No
NCT03994640	Myorelaxant Effect of Cannabis Cream Topical Skin Application in Patients With Temporomandibular Disorders: a Randomized, Double-blind Study	Aleksandra Nitecka-Buchta	Dentistry	Pain control	Interventional, randomized, parallel assignment, double blinded, placebo-controlled study	60	6/21/2019	1/1/2019	Medical University of Silesia	Experimental arm: topical, bilateral skin application of cannabis cream with self-massage of masseter muscles twice daily for 14 days	Masseter muscle activity (using surface electromyography) and pain intensity (using visual analog scale)	Yes
										Control arm: same as experimental arm but with placebo cream		Cannabis cream significantly reduced masseter muscle activity and pain compared to placebo
NCT00659490	Evaluation of the analgesic efficacy of AZD1940, a novel cannabinoid agonist, on post-operative pain after lower third molar surgical removal	Jarkko Kalliomäki, Märta Segerdahl, Lynn Webster, Annika Reimfelt, Karin Huizar, Peter Annas, Rolf Karlsten, Hans Quiding	Anesthesiology	Pain control	Interventional, randomized, parallel assignment, double blinded, placebo-controlled study	151	4/16/2008	6/11/2012	AstraZeneca	Experimental arm: 800 µg AZD1940 1.5 hours before surgery Control arm: 500 mg naproxen or placebo 1.5 hours before surgery	Post-operative pain at rest and with jaw movement were evaluated using a visual analog scale (VAS, 0–100 mm) from 0 to 8 hours postop. Subjective cannabinoid effects were assessed by the visual analog mood scale (VAMS)	Yes AZD1940 did not result in reduced post-operative pain after lower third molar surgical extraction
NCT04271917	Surgery With Alternative Pain Management (SWAP): Analgesic Effects of Cannabidiol for Simple Tooth Extractions in Dental Patients	Karen Derefinko	Preventative medicine	Pain control	Interventional, randomized, parallel assignment, double blinded, placebo-controlled study	120	2/24/2020	07/2022 (estimated)	University of Tennessee	Treatment-as-usual (TAU): acetaminophen 500 mg and ibuprofen 200 mg. Take 1 tablet of each medication at the same time every 4–6 hours as needed for pain. 5-day supply	Worst self-reported pain during first following surgery using Wong Baker Faces pain scale	Study ongoing

Table 3 Additional studies of marijuana and cannabinoids in oral and maxillofacial surgery (OMFS)

Study name	Authors	Study topic	Study type	Subjects (n)	Date accepted for publication	Intervention	Primary outcome	Results
AAOMS 2019, Poster 4: Effects of Tetrahydrocannabinol (THC) Use on Vital Signs during Intravenous Sedation	D. Lillian: University of Rochester Medical Center/ EIOH, J. Vorrasi, A. Kolokythas	Anesthetic requirement	Retrospective cohort study from July 2018 to July 2019	18	9/2019	Experimental arm: patients with urine toxicology screen positive for THC metabolites undergoing OMS procedure under IV sedation	Changes in baseline MAP%, HR%, RR% at 5 minutes (T5) and 10 minutes (T10) after IV drug administration (i.e., versed and fentanyl)	No statistically significant difference in MAP%, HR%, and RR% at T5 and T10 between the two groups
						Control arm: patients with urine toxicology screen negative for THC metabolites undergoing OMS procedure under IV sedation		Ten minutes after IV administration of THC, significantly higher MAP% (P=0.0429) and significantly lower HR% (P=0.0044) was observed compared to the THC-group
AAOMS 2019, Poster 5: Marijuana Use and Propofol Dose for Intravenous General Anesthesia for Dental Extractions	M. Pace: Loma Linda University Department of Oral and Maxillofacial Surgery	Anesthetic requirement	Retrospective cohort study of a single site over a 2-year period	60	9/2019	Experimental arm: 30 most recent dental extraction cases under intravenous general anesthesia where patients endorsed marijuana use	Propofol use in mg/min between the two groups	Patients that endorsed marijuana use had higher per minute propofol use on average compared to those who denied marijuana use
						Control arm: 30 most recent dental extraction cases under intravenous general anesthesia where patients endorsed no marijuana use		
Postoperative Healing Assessment Using Cannabinoids in Oral Surgery	Algirdas Puisys, Viktorija Auzbikaviciute, Ricardas Kubilius, Rokas Linkevicius, Dainius Razukevicius and Tomas Linkevicius	Wound healing	Interventional, randomized, controlled trial	60	2/2019	Experimental arm: use of phytocannabinoid-cannabidiol gel applied intra- and extra-orally and daily 0.12% chlorhexidine rinse twice daily for 7 days after mandibular third molar tooth extraction	Pain, swelling intensity, alveolar osteitis, tolerance of post-operative healing, and overall assessment of satisfaction	No difference in post-operative healing during the first 7 days after dental extraction between patients treated with oral antibiotics and chlorhexidine rinse versus patients treated with phytocannabinoid gel and chlorhexidine rinse
						Control arm: oral amoxicillin 500 mg 3×/day and daily 0.12% chlorhexidine rinse twice daily for 7 days after mandibular third molar tooth extraction		

Table 3 (*continued*)

Table 3 (*continued*)

Study name	Authors	Study topic	Study type	Subjects (n)	Date accepted for publication	Intervention	Primary outcome	Results
Effects of Cannabis Use on Patients Undergoing office-based Anesthesia: A Brief Literature Review and Case Report of 50 Outpatient Cases of IV Sedation in Marijuana Users	Nicholas Mechas, Paul Deitrick, Allen Fielding	Perioperative observations	Retrospective cohort	50	11/2018	Experimental arm: self-described heavy marijuana users undergoing intravenous sedation at an oral surgery clinic Control arm: none	Differences in impairment (i.e., time from most recent marijuana use) and signing of informed consent, preoperative vitals and physical exam findings, anesthesia drug requirements, sedation course and complications, and post-operative course	1 patient excluded for inverted T waves on ECG prior to surgery and 3 cases were excluded due to inability to sign consent as a result of marijuana consumed within a few hours of surgery 26 cases patients received albuterol for asthma or to maximize airway patency and lung sounds to auscultation 31 cases were given glycopyrrolate to prevent secretions or subsequent complications such as aspiration, bronchospasm, or laryngospasm Diazepam as compared to midazolam resulted in an improved sedation experience and lower intraoperative use of other medications such as fentanyl, propofol, and ketamine
A Randomized, Controlled Study to Investigate the Analgesic Efficacy of Single Doses of the Cannabinoid Receptor-2 Agonist GW842166, Ibuprofen or Placebo in Patients with Acute Pain Following Third Molar Tooth Extraction	Thor Ostenfeld, Jeffrey Price, Massimo Albanese, Jonathan Bullman, Fiona Guillard, Ingo Meyer, Rachel Leeson, Cristina Costantin, Luigi Ziviani, Pier Francesco Nocini, and Stefano Milleri	Pain control	Interventional, randomized, double-blind, placebo-controlled study	123	3/11/2011	Experimental arm: single dose of GW842166 (100 or 800 mg) within 1 hour of surgery Control arm: 800 mg ibuprofen within 1 hour of surgery followed by a second dose of 400 mg four hours after the first dose	Visual analog scale (VAS) and verbal rating scale for scoring pain up to 10 hours after surgery, duration of analgesia, patient global evaluation, proportion of patients requiring rescue medication, and elapsed time to rescue analgesia	Single doses of GW824166 (100 and 800 mg) failed to provide clinically meaningful analgesia for acute dental pain following tooth extraction compared to ibuprofen

Table 3 (*continued*)

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Study name	Authors	Study topic	Study type	Subjects (n)	Date accepted for publication	Intervention	Primary outcome	Results
Randomized split-mouth study on postoperative effects of palmitoylethanolamide for impacted lower third molar surgery	Christian Bacci, Giulia Cassetta, Bruno Emanuele, and Mario Berengo	Pain control	Interventional, randomized, split-mouth, single-blind study	30	3/22/2011	Experimental arm: Normast (palmitoylethanolamide) 300 mg 2×/day for 15 days Control arm: no Normast	Changes in trismus, swelling, pain, NSAID consumption, postoperative complications, drug tolerability, and adverse medication effects after the extraction of an impacted lower third molar	Normast improved post-operative pain and delays the onset of post-operative edema formation
Cardiovascular Effects of Cannabinol During Oral Surgery*	John M. Gregg, Robert L. Campbell, Kenneth J. Levin, Jawahar Ghia, Riley A. Elliot	Cardiovascular effects	Part 1: Interventional, randomized, crossover, double-blinded	Study 1: 10	8/7/1975	Part 1: experimental arm: IV THC (0.044 mg/kg, 0.022 mg/kg); control arm: diazepam (0.157 mg/kg), placebo	Part 1: change in baseline heart rate, blood pressure, ECG, and State-Trait Anxiety Inventory (STAI) anxiety scores	Part 1: THC (0.044 mg/kg) produced a 24.1% higher peak heart rate than placebo, had an average of 8-torr elevation of BP at 25 minutes compared to 9-torr following the smaller dose, and reduced a baseline arrhythmia for 1 hour in a single subject. Transient moderate hypotension of 20–45 torr for systolic and diastolic blood pressures was seen around 4–8 minutes after THC injection and resembled syncopal episodes
			Part 2: retrospective cohort	Study 2: 10		Part 2: experimental arm: patients who endorsed smoking marijuana within 72 hours of surgery; control arm: patients who denied smoking marijuana within 72 hours of surgery	Part 2: changes in baseline blood pressure, heart rate, ECG, and blood gases between preoperative, intraoperative, and postoperative times points	Part 2: Marijuana smokers demonstrated a sustained post-operative tachycardia compared to non-smokers

*, the publication by Gregg et al. contains 2 parts, including part involving an intervention and one part remaining purely observational. OMS, oral and maxillofacial surgery; IV, intravenous; MAP, mean arterial pressure; HR, heart rate; RR, respiratory rate; ECG, electrocardiogram; NSAID, non-steroidal anti-inflammatory drug.

sizes ranged from 10 to 151 patients. In total, two studies found that cannabinoids may improve pain (9,10), while two studies failed to demonstrate improved pain control with cannabinoids (11,12). Additionally, 3 studies reported that cannabinoids had adverse effects on vital signs (8,13,14), with another study noting increased anesthetic requirements for cannabinoid users (15). Lastly, 1 study reported no difference in post-operative healing after dental extractions for cannabinoid and non-cannabinoid users (16).

Discussion

Our study provides an overview of the current marijuana and cannabinoid research in OMFS. As hypothesized for our primary outcome, the number of qualifying studies was small with a total of 11 studies being identified. In the future, studies related to both cannabinoids and oral surgery will likely be more common and will be essential for treating a patient population that now has legal access to cannabinoids. Our secondary outcomes relate to the outcomes of each study which are detailed in *Tables 2*,*3*, and explained in the sections below.

Routes of cannabinoid administration

Cannabinoids have been formulated for administration by a variety of routes including inhalation, oral, sublingual, IV, intramuscular, and topical use (17,18). However, among the 7 prospective studies included in the present paper (8-12,16,19), oral administration of cannabinoids was the most common mode observed in all except 3 of them with 1 using IV THC (8) and 2 using topical CBD (10,16). One ongoing clinical trial that is currently in the recruiting phase plans to administer CBD and hemp oil under the tongue for 1 minute followed by swallowing (19). The study using IV THC assessed its effects on the cardiovascular system during IV sedation (8). Unlike oral administration of cannabinoids, sublingual and IV administration bypass the liver and thus avoid first-pass metabolism, which otherwise reduces the bioavailability of the active cannabinoid compounds. The 4 observational studies enrolled patients based on positive THC toxicology or self-reported marijuana use, which most likely included inhalational use or edibles, although it was not specified. The route of marijuana administration is important to consider for evaluating drug effect, especially given the variety of administration routes throughout the literature (12). The field of OMFS is especially susceptible to the routes of drug administration given the proximity of oral surgical sites (i.e., sources of pain) to medication taken orally, sublingually, applied topically, or inhaled through the mouth. Future studies may seek to better characterize the how each form of cannabinoid administration can affect OMFS patients and explore which route of administration works best for certain procedures.

Pain

Among the 11 marijuana and cannabinoid-focused studies identified in the OMFS literature, 6 of them assessed pain alleviation. Previous research has shown that cannabinoids likely possess analgesic, anxiolytic, antispasmodic muscle relaxing, anti-inflammatory and anticonvulsant properties (20). The opioid epidemic provided motivation to find alternative pain-relieving modalities, leading many to consider cannabinoids (21). Dental extractions historically represent one of the most common OMFS procedures and sources of patient discomfort requiring prescription pain medications, thus representing a potential role for cannabinoids (22). In 2011, Bacci *et al.* conducted a staged split-mouth study comparing 300 mg of a cannabinoid receptor ligand known as Normast (i.e., palmitoylethanolamide) versus no Normast for patients undergoing third molar extractions (9). They concluded that Normast improved postoperative pain based on visual analog scale (VAS). However, the study's objective assessment of pain was severely limited by participant drop-out rate and heterogeneous post-operative non-steroidal anti-inflammatory drug (NSAID) consumption. The study also identified a delayed onset of edema in the Normast group compared to control suggesting Normast may delay edema formation following extraction. A phase 3 study is currently studying the pain-relieving effects of oral CBD drops at 2 different concentrations versus Tylenol and Ibuprofen versus placebo for patients following dental extraction (23). This study may elucidate whether CBD can serve as a safe adjunct to NSAIDs and Tylenol following tooth extraction, instead of needing to prescribe narcotics. Conducting prospective studies and working to increase study protocol compliance may allow stronger conclusions to be drawn about the potential of cannabinoids to treat post-extraction dental pain.

In 2011, a RCT evaluated the effects of preoperatively administering GW842166 (an experimental cannabinoid and CB2 selective agonist) versus ibuprofen and placebo prior to mandibular third molar surgical extraction. Unfortunately, no clinically meaningful analgesic benefit

of GW842166 was found (12). The authors attributed the lack of observed benefit to subtherapeutic plasma drug concentrations potentially from high protein-binding of the drug that was also previously seen in rat and human studies. Higher drug doses or administration in more bioavailable forms (e.g., intramuscular or IV) could potentially increase drug concentrations within the blood stream to a therapeutic or effective level. The same authors also suggested increasing the exposure time of the drug to its CB2 receptor to elicit an effect response. CB2 selective agonists, like GW842166, which lack the psychotropic effects of CB1 agonists, and thus may be preferred and worth pursuing more. In 2012, another experimental cannabinoid, AZD1940 (CB1 and CB2 agonist), given preoperatively was tested against placebo and Naproxen prior to mandibular third molar tooth extraction (11). The study concluded that AZD1940 did not result in reduced post-operative pain. Despite a lack of convincing evidence of the effects of these experimental cannabinoids, there is still hope for increasing their efficacy through alternative routes of administration and dosing. Also, as additional opioids are discovered, a focus on the receptor selectivity (i.e., CB1 *vs.* CB2) may also alter therapeutic effects, as well as, potential side effects.

Other surgical specialties outside of OMFS have also considered cannabinoids for the treatment of acute pain. For example, a 2020 meta-analysis (24) of 8 RCTs and 4 observational studies assessed the utility of cannabinoids for post-surgical pain following various types of surgery (i.e., cardiac, general, neurological, orthopedic, urologic, vascular and 2 RCTs on dental extraction (11,12). They found that the addition of cannabinoids to analgesics did not improve acute post-surgical pain. Similarly, another 2020 meta-analysis of 6 RCTs using cannabinoids for acute post-surgical pain (25), including 2 RCTs on dental extraction (11,12), found a small but significant improvement of subjective pain scores with intramuscular cannabinoid administration and less so with oral administration. The mixed results of these studies regarding the efficacy of cannabinoids for acute post-surgical pain calls for additional high-level studies, such as RCTs, to draw more convincing conclusions. Given the different pain experiences associate with various types of surgery, future studies investigating cannabinoids administration for OMFS procedures would be most informative for OMFS practitioners.

Chronic pain, including both cancer pain and non-cancer pain subtypes, have also been studied (26). A 2015 systematic review of chronic nonmalignant neuropathic pain found that cannabinoids may provide effective analgesia in conditions refractory to other pain modalities (27). A 2019 clinical trial evaluating the use of cannabis cream applied to skin over bilateral masseter muscles found a significant decrease in myofascial pain and in masseter muscle activity measured by surface electromyography (sEMG) compared to placebo (10). One active clinical trial investigating TMJ and myofascial pain will hopefully provide insight into any potential therapeutic cannabinoids may hold for such pain, which is often chronic in nature (19). The current authors are hopeful that a continued interest in cannabinoids will elucidate any analgesic properties that cannabinoids may have for treating TMJ pain and myofascial pain (28), which are difficult to control forms of pain within OMFS.

Anesthetic requirement

The IV anesthetic requirement associated with recreational marijuana users has also been studied. A 2019 retrospective cohort of self-described marijuana users versus non-users undergoing dental extractions under IV sedation found that marijuana users consumed a higher average amount of propofol in milligrams per minute (15). These findings suggest pharmacokinetic variations in OMFS patients based on experience with marijuana. As a result, OMFS providers who quantify marijuana use during pre-sedation evaluations may be able to predict intraoperative sedation requirements for each patient, and even determine if a patient is fit for outpatient sedation.

Vital signs, cardiovascular effects, and perioperative observations

The effects of THC and cannabinoids on normal physiology, especially cardiovascular effects, is also important information for OMFS providers. A 2019 retrospective cohort study of adult patients sought to characterize the effects of THC on vital signs during IV sedation with IV versed (midazolam) and IV Fentanyl. The patients were placed in the experimental arm if they tested positive for urine THC and put in the control group if they tested negative (13). Patients who tested positive had statistically significant higher mean arteriolar pressure percentage change and lower heart rate percentage change at 10 minutes into surgery than the group testing negative for THC. However, there was no significant change in the respiratory rate. These findings suggest that there may be

different physiologic responses to IV sedation for patients who use marijuana compared to those who do not.

Another study by Gregg *et al.* (1976) investigated the cardiovascular effects of cannabinol during oral surgery (8). They compared presurgical administration of IV THC to diazepam and placebo and found that the higher dose of IV THC (i.e., 0.044 mg/kg, compared to 0.022 mg/kg) resulted in higher peak heart rate, syncopal-like episodes of hypotension around 4–8 minutes after administration, and elevated blood pressure at 25 minutes after administration. They also noted that one patient, who received the 0.044 mg/kg dose of THC, had a reduction in their preoperative arrhythmia for 1 hour after administration. By contrast, the preoperative arrhythmias increased for 4 of the patients in the 0.022 mg/kg group. The paper by Gregg *et al.* also conducted a retrospective study of 10 patients undergoing IV general anesthesia for tooth extraction and found that those who endorsed THC use within 72 hours of their procedure demonstrated a sustained post-operative tachycardia for an average of 38 minutes after the end of anesthesia compared to 7 minutes in the control group. These observations are important considerations as marijuana, and cannabinoids, become more available for both recreational and medicinal purposes. Understanding the physiologic effects will help providers counsel patients and also prepare for any perturbations in vital signs attributable to marijuana exposure.

Other studies have also focused on the perioperative changes seen in patients who consume marijuana. One retrospective cohort by Mechas *et al*. (2018) of 50 IV sedation cases noted that 26 patients required preoperative albuterol for asthma or to improve lung sounds to auscultation (14). They also reported that 31 patients received glycopyrrolate to prevent consequences of secretions including aspiration, bronchospasm, or laryngospasm. Diazepam reduced the intraoperative use of other medications such as propofol, fentanyl, and ketamine. Having excluded 3 patients for marijuana use within a few hours of their planned procedure, the authors of that study advocated for delaying elective procedures 24 hours from the last marijuana consumption to ensure informed consent is possible. They also advocated for more careful cardiovascular and respiratory monitoring during and after surgery. Finally, they report the antiemetic effect of marijuana occurs briefly after consumption, which is unlikely to benefit the patient undergoing surgery at least 24 hours later. Knowing these physiologic trends will equip OMFS practitioners to competently manage such physiologic perturbations among marijuana users to keep patients safe. Future studies may seek to quantify and correlate the amount of marijuana consumed with the amount of physiologic perturbation observed.

Wound healing

Cannabinoids have also been shown to have immunomodulatory effects, including inhibition of interleukin-6 (IL-6), an upregulator of pathways in microglial cells that decrease inflammation (29). A 2019 study by Puisys *et al.* found that post-extraction use of oral amoxicillin and chlorhexidine rinse had no difference in outcomes (i.e., pain, swelling intensity, alveolar osteitis, tolerance of post-operative healing, and overall assessment of satisfaction) compared to those that used phytocannabinoid-CBD gel intraorally and extraorally along with chlorhexidine rinse (16). This study suggests similar effects on post-extraction healing caused by cannabinoids and antibiotics. However, this study may have been confounded by administration of chlorhexidine rinse to both groups that may be responsible for similar outcomes. The proposition of cannabinoids imposing anti-inflammatory effects is intriguing, but calls for more robust head-to-head comparisons of cannabinoids against controls, such as antibiotics, for validation.

Risks of marijuana use

Despite recent legalizations, the medical use of marijuana still remains controversial. According to Volkow *et al.* (2014), short term adverse effects include impaired memory, impaired motor coordination, altered judgement, paranoia and psychosis (30). Long term impacts include altered brain development and cognitive impairment (30). Long-term marijuana use can also lead to dependence with 9% of overall users and 17% of those who begin using marijuana in adolescence becoming addicted (30). Furthermore, the THC content of marijuana has steadily increased from about 3% in the 1980s to 12% in 2012, which may have led to more emergency department visits (17). Also, marijuana can have complex drug interactions with other painkillers or anesthetic drugs, and the precise mechanism of these interactions is still unclear. These potential risks must be considered in the context of alternative treatments, such as opioids, which also carry the risk of addiction. Legalizing marijuana for medical use may potentially lower the rate of opioid prescriptions and mortalities, although this idea calls

for greater investigative efforts for understanding (21).

Limitations of the study

This study is limited by the inclusion of only studies written in English. It is also limited by the quality of the studies with 4 of the 11 being observational studies and the remaining 7 RCTs having relatively small sample sizes (i.e., 10–151). Patient drop out and lack of compliance with preset trial protocols also impaired the success of some studies (9,14).

Conclusions

In conclusion, very few studies have evaluated the role of marijuana and cannabinoids in OMFS and we only identified 11 studies in the English literature. Two of these studies found that cannabinoids may improve pain (9,10), two studies failed to demonstrate improved pain control with cannabinoids (11,12), 3 studies reported that cannabinoids had adverse effects on vital signs (8,13,14), 1 study reported increased anesthetic requirements for cannabinoid users (15), 1 study reported no difference in post-operative healing after dental extractions for cannabinoid and non-cannabinoid users (16), and 1 study is ongoing (23). Given the liberalization of marijuana laws over the past decade leading to an increase in recreational and medical marijuana use, more patients are expected to have tried or actively use cannabinoids prior to interaction with OMFS providers. Future studies will be essential to understanding the effects and potential therapeutic benefits of these substances and medications, particularly their clinical implications. This study will hopefully lay the foundation for guiding future studies aimed at elucidating the role and impact cannabinoids may have within the OMFS scope of practice.

Statement of clinical relevance

The effects of marijuana and cannabinoids in OMFS is vastly understudied, thus necessitating future research to better elucidate its pain-relieving potential, effects on wound healing, and physiologic perturbations, particularly during anesthesia.

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Footnote

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