THE IMPACT OF CANNABIS USE ON PROCEDURAL SEDATION AND ANALGESIA FOR THIRD MOLAR SURGERY.

by

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Submitted in partial fulfilment of the requirements
for the degree of Master of Science

at

Dalhousie University
Halifax, Nova Scotia
December 2022

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Abstract

Oral and maxillofacial surgeons are providers of procedural sedation and anaesthesia (PSA) for minor outpatient procedures. The impact of cannabis use on intraoperative (depth of sedation, amount of sedative used, and operator satisfaction) and post-operative outcomes (pain, recall, and patient satisfaction) during PSA are poorly studied. A prospective observational study was designed to investigate the impact of cannabis use on quantity of sedative medication used and quality of procedural sedation for both patients and surgeons. Using a validated questionnaire, the study population of cannabis users was stratified on a continuum according to frequency and quantity of use. Additional variables measured for study and control groups included state and trait anxiety, age, gender, education level, and use of alcohol and other recreational drugs. This study was unable to demonstrate any significant differences in amount of sedative medication administered, post-operative pain, surgeon satisfaction and patient satisfaction between cannabis users and non-cannabis users undergoing extraction of 3rd molar teeth with procedural sedation using midazolam, fentanyl and ketamine.

List of abbreviations

(in alphabetical order)

ANOVA – Analysis of Variance

ASA – American Society of Anesthesiologists

CBD - cannabidiol

DFAQ-CU - Daily Sessions, Frequency, Age of Onset and Quantity of Cannabis Use

GAD7 – General anxiety disorder seven scale

IV – intravenous

LA – local anaesthesia

MDAS – modified dental anxiety scale

OMFS – oral and maxillofacial surgery

PSA – procedural sedation and analgesia

SD – standard deviation

THC - delta-9-tetrahydrocannabinol

TLFB – timeline follow back

VAS- visual analogue scale

Acknowledgments

I would like to thank my thesis advisor Dr. James Brady for his input and guidance on this project. I would also like to thank the other members of my thesis committee – Dr. Ben Davis, Dr. Curtis Gregoire, and Dr. Ben Schelew for providing valuable feedback on the manuscript. Many thanks also to Dr. Sam Baldwin for guidance with statistical analysis, to the RMU for help with the initial project set up, to the staff surgeons, residents and clinic nurses for their help with recruitment, and to my summer research students (Josh Worthen, Ainsley MacIntyre, and Mo Alabdoulsalam) for their efforts in data collection.

Finally, my sincere gratitude to my family, and to my fiancée Matthew for their love, support and encouragement throughout this process.

CHAPTER 1: INTRODUCTION

1.1 Procedural Sedation Anaesthesia

Oral and maxillofacial surgeons perform a variety of procedures ranging from complex facial reconstruction to simple extraction of teeth. Anaesthesia techniques vary from local anaesthesia (LA) only, or a combination of LA and intravenous (IV) procedural sedation, or even general anaesthesia (GA) depending on the extent and complexity of the procedure, as well as the patients' medical comorbidities.

Procedural sedation is often chosen for minor outpatient diagnostic and therapeutic procedures due to its convenience, safety and efficacy. It is defined as a technique for administering short acting sedative or dissociative agents, with or without analgesics, to reduce discomfort, apprehension and unpleasant memories while minimizing cardiorespiratory depression of patients during diagnostic and therapeutic procedures (Dobson et al. 2018). Advantages of procedural sedation and anaesthesia (PSA) include reduced pain, reduced anxiety and amnesia related to memories of discomfort from the surgical procedure. Multiple variables are known to influence the depth of sedation and a patient's response to sedatives including extremes of age, liver function, body mass index, medical comorbidities, and over the counter or prescription medications.

In the oral and maxillofacial surgery department at the Victoria General Hospital, extraction of teeth is the most common minor procedure carried out with procedural sedation. To achieve safe and effective PSA, OMF surgeons in our clinic use a combination of intravenous medications include midazolam, fentanyl, ketamine, and rarely propofol. Amounts used vary according to surgeon preference, patient's medical history or comorbidities, and desired depth of sedation. Typically, medications are titrated to achieve a mild to moderate level of conscious sedation and patients are closely monitored during and after the procedure.

In addition to OMFS, procedural sedation is used by a number of different specialities such as cardiology, gastroenterology, plastic surgery and radiology. However, OMFS is somewhat unique as it is one of the few specialities that undergoes significant anaesthesia training, allowing OMF surgeons the privilege of providing their own procedural sedation for minor procedures independently. Multiple studies have demonstrated that outpatient PSA provided by oral maxillofacial surgeons is safe, efficient and with minimal complications (Wiemer et al. 2021; Braidy, Singh, and Ziccardi 2011; Christensen et al. 2019). In a particularly large study carried out at the Mayo Clinic, a retrospective review of 17,634 sedations performed by OMF surgeons on 16,909 subjects over a 15-year time period was reviewed. The primary outcome variable was the presence of anaesthetic related adverse events (defined as medication errors, patient combativeness, seizure or seizure like activity, cardiac dysrhythmia, myocardial infarction or angina, cardiopulmonary depression, airway emergency, emergency department transfer or hospital admission, and mortality). In 17,534 sedations, 16 (0.1%) adverse events were identified – 5 combative patients, 2 medication errors, 7 emergency department visits and 2 hospital admissions within 24 hours of the sedation. There were no procedural or anaesthetic related patient mortalities observed in this study. There was no association between the type of sedation medications administered and the presence of adverse events. Although this study was limited by its retrospective design, the large sample size was adequate to detect a rare rate of adverse events associated with procedural sedation in the oral and maxillofacial surgery setting (Wiemer et al. 2021).

Anecdotally, some OMF surgeons note that procedural sedation on cannabis users can be more difficult than on a non-cannabis user. This has also been reported in the gastroenterology literature. Woo and Andrews note that in their experience cannabis users require higher doses of sedatives and are more likely to experience paradoxical agitation with adjunct anticholinergic medications (Woo and Andrews 2019). Some of these difficulties could be owing to the fact that patients who use cannabis tend to have increased airway reactivity, heightened anxiety/paranoia, tolerance to anaesthetic medications and possible increased pain perception (Alexander and Joshi 2019).

However, it is also possible that this belief may be due to inherent bias, or generalization from a handful of poor sedation experiences.

1.2 A brief history of Cannabis in Canada

Cannabis (also commonly referred to as marijuana) is a psychoactive drug derived from the cannabis plant that is used recreationally and medicinally. Globally cannabis is used by an estimated 192.2 million people or approximately 3.9% of the general population (United Nations 2018). In Canada, cannabis use was initially banned in 1923. However, with reform and further research into cannabis, medicinal use was legalized nationwide on July 30, 2001. Subsequently with the passing of Bill C-25, on October 17, 2018 Canada became the 2nd country in the world to legalize the production, distribution, sale and non-medical use of cannabis for adults meaning that recreational use of cannabis would no longer violate criminal law.

In Canada, the prevalence of cannabis use is relatively high. A 2020 Statistics Canada survey reports that 20% of Canadians over the age of 15 admitting to cannabis use over the past 12 months, and over one third (35.6%) of those aged 18-24 report having consumed cannabis in the past 3 months. In Nova Scotia over one quarter of residents (27.3%) reported having used cannabis in the past 3 months (Rotermann 2021). According to a MacLean's magazine university survey of 18,000 students at 43 universities across Canada, Dalhousie university ranks 3rd highest with 61% of students surveyed reporting cannabis use (Brownell 2019).

Although cannabis is used recreationally by many, there is little research regarding its interaction with medications and its adverse effects. In the past, fear of stigma, retribution, or punishment may have caused patients to underreport use. However, given the changing legal landscape people tend to be more open and honest about cannabis use. According to Statistics Canada, since the legalization of cannabis 34% of users are more willing to disclose information on use (StatisticsCanada 2019).

1.3 Cannabis – physiology

Cannabis contains over 100 cannabinoids including delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) – the two most well-known ones. THC is the most potent psychoactive component (Zou and Kumar 2018). Cannabinoids work primarily by stimulating receptors within the endocannabinoid system. The endocannabinoid system is a large, widespread network of chemical signals and cell receptors throughout the body that play a role in the mediation of pain, memory, appetite, and metabolism amongst other functions (Sheikh and Dua 2022). The primary receptors of the endocannabinoid system are the CB1 and CB2 cannabinoid receptors, with the CB1 receptor being most abundant in the brain. THC and CBD are strong agonists of the CB1 receptor (Ladha et al. 2019). Neurotransmitters involved in mediating awareness and arousal such as acetylcholine, dopamine and noradrenaline are examples of those inhibited from release by activation of the CB1 receptors.

In addition to its effects on the central nervous system (euphoria, sedation, relaxation, altered spatial and temporal perception), cannabis also has physiological effects on the cardiovascular system and respiratory system. In the cardiovascular system, acute cannabis use is known to result in a biphasic response with tachycardia and increased systolic blood pressure, followed by a second phase of bradycardia and hypotension (Ladha et al. 2019; Huson, Granados, and Rasko 2018). However, in chronic users' physiologic effects such as tachycardia may be blunted (Alexander and Joshi 2019; Echeverria-Villalobos et al. 2019). Cannabis use is also associated with ECG changes such as atrial fibrillation, premature ventricular contractions, and AV block (Huson, Granados, and Rasko 2018). In the respiratory system cannabis smoking is associated with symptoms of chronic bronchitis e.g., cough, sputum production, and some studies suggest that cannabis use may be associated with bronchial hyperreactivity (Ladha et al. 2019).

1.4 Cannabis and General anaesthesia

It is well accepted that cannabis use has an effect on general anaesthesia and there is a growing body of literature reporting this. A major mechanism of action shared by general anaesthetics and endocannabinoids is the modulation of GABA so pharmacological interactions should be expected (Echeverria-Villalobos et al. 2019). Cannabinoids are highly lipid soluble and are metabolized by the liver. The plasma half-life ranges from 20 to 30 hours but the tissue half-life can be as long as 30 days depending on frequency and chronicity of use due to fat accumulation (Alexander and Joshi 2019; Huson, Granados, and Rasko 2018). THC is primarily metabolized in the liver by cytochrome P-450 enzymes CYP2C9, CYP3A4, and CYP2B6. Propofol is also metabolized by the CP2B6 and CYP2Y9 enzymes while fentanyl and midazolam are metabolised by CYP3A4 enzymes (King et al. 2021). This likely plays a large role in the "cross-tolerance" experienced in cannabis users and is explained by the pharmacokinetic and pharmacodynamic interactions of cannabis with commonly used anaesthetic drugs. A 2009 study by Flisberg et al. showed that the induction dose of propofol required for laryngeal mask insertion was 20% higher for cannabis users than for non-cannabis users – but note that this study included only male patients and had relatively small sample size with 30 patients per group (Flisberg et al. 2009).

With respect to perioperative complications associated with cannabis use, a 2020 retrospective cohort study by Goel et al. examined 27,206 patients from the United States "nationwide inpatient sample" cohort between 2006 -2015. They compared matched groups of 13,603 patients with and without cannabis use disorder. Cannabis use disorder was identified by the presence of specific International Classification of Diseases diagnostic codes as discharge diagnoses. Patients having a variety of elective procedures under GA (e.g., coronary artery bypass graft, cholecystectomy, colectomy, total hip or knee arthroplasty, hysterectomy, breast lumpectomy or mastectomy, hernial surgery, and elective spine surgery) were chosen to be part of the study sample. The outcomes included clinically relevant peri and post-operative complications –myocardial infarction, stroke, sepsis, deep vein thrombosis/pulmonary embolism, acute kidney injury requiring

dialysis, respiratory failure and in-hospital mortality. This study showed that there was a strong association with a higher incidence of perioperative myocardial infarction. However, there was no significantly increased risk for other perioperative complications in those with a cannabis use disorder (Goel et al. 2020). This is in keeping with Alexander and Joshi's article which explained the physiology of cannabis induced tachycardia and peripheral vasodilation leading to orthostatic hypotension and an increase in cardiac output and myocardial oxygen demand leading to ischemia (Alexander and Joshi 2019).

A challenge in managing cannabis users from an anaesthesia standpoint is determining the level of exposure. Providers have to consider if a given individual is a new user or chronic user, if use is recreational or medicinal, frequency of dosing and time elapsed since last exposure (Echeverria-Villalobos et al. 2019). This is often hard to reliability elicit from patients.

1.5 Cannabis and Procedural Sedation

When compared to the amount of literature on cannabis and general anaesthesia, there is little with regards to the effect of cannabis use on procedural sedation. There is a knowledge gap with many studies being retrospective, having small sample sizes, not accounting for alcohol or other recreational drug use, and examining cannabis use as a purely binary variable with no accounting or documenting frequency, quantity, or mode of consumption.

In 2019 Twardowski et al. investigated if regular cannabis use had any effect on the dose of sedative medication during endoscopic gastrointestinal procedures. This was a retrospective study in which 250 patient records were reviewed. Importantly, this study was carried out in Colorado *after* the legalization of recreational cannabis use. Cannabis use was self-reported. They categorized regular users as those who smoked or ingested cannabis on a daily or weekly basis. Those who did not use cannabis at all or who reported sporadic or topical use were considered nonusers. The primary outcome was the

dose of sedative medication required to complete the endoscopic procedure. A total of 25 cannabis users and 225 non cannabis users were included. They found that cannabis users required a mean of 125.95 mcg of fentanyl, 9.15mg of midazolam and 44.81mg of propofol, compared to non-cannabis users who required a mean does of 109.91 mcg of fentanyl, 7.61mg of midazolam and 13.83 mg of propofol - 14% more fentanyl, 19.6% more midazolam and 220.5% more propofol (Twardowski, Link, and Twardowski 2019). These differences were statistically significant with p-values <0.05. Limitations of this study include its retrospective nature and a relatively small sample size of cannabis users. Additionally, there was heterogeneity of procedures completed and they did not take into consideration duration of procedure (e.g., upper and lower endoscopy, or removal of polyps would require more time), or weight of the patient. Lastly, it can be argued that the mean differences, while statistically significant are clinically insignificant. This study did offer some similarities with the OMFS practitioner, as sedation was endoscopist provided.

In 2021 King et al used a small retrospective, case control study to examine differences in propofol requirements for esophagogastroduodenoscopy (EGD) with the hypothesis that cannabis users would require higher doses of propofol and would be more likely to require adjuncts such as fentanyl and ketamine. They cross matched and compared 23 self-reported cannabis users to non-users. There were no significant differences in the amount of propofol administered, even when adjusted for weight and duration of procedure. Although fentanyl and ketamine were more frequently administered to users than non-users, this difference was not significant ($p = 0.42$ and $p = 0.32$ respectively). In this study, patients were contacted by phone 24 hours post operatively to assess satisfaction and the results were similar between the two groups with non-significant results (King et al. 2021). The limitation of this study includes its retrospective nature, the self-reported and binary nature of cannabis use with no accounting for dose, route or frequency. A strength of this study is the homogeneity of the procedure completed, with only short duration EGDs examined.

In another study by Thakkar et al they noted that in patients undergoing transoesophageal echocardiography, on average cannabis users required more midazolam for conscious sedation than non-users (5.1mg vs 4.1mg, $p = 0.044$). Doses of fentanyl were similar with no significant differences. As is common with this literature, the study was limited by a small sample size of 18 cannabis users compared with 84 nonusers (Thakkar et al. 2017).

The research on cannabis use and how it affects procedural sedation is sparse. The change in regulations and the legal landscape has outpaced scientific research, leading to a dearth of literature. Despite oral and maxillofacial surgeons being forefront providers of procedural sedation, there are no studies in the OMFS literature that relate to cannabis use and procedural sedation.

1.6 Study Purposes, Hypothesis and Aims

There is an absolute lack of studies exploring the impact of cannabis use on procedural sedation and anaesthesia as it relates to the OMFS setting. The purpose of this study is to evaluate the impact that cannabis use has on procedural sedation requirements for extraction of third molar teeth. We hypothesize that cannabis users will require greater amounts of sedative medication to achieve a minimal to moderate depth of sedation. We aim to evaluate this by assessing amounts of sedative medication provided during surgery and patient depth of sedation during surgery. Secondarily, we aim to assess if there is a difference in patient and surgeon satisfaction, as well as post-operative pain levels between cannabis users and non-users. The outcomes will be analysed against a number of variables including age, gender, difficulty of surgery and length of surgery.

CHAPTER 2: MATERIAL AND METHODS

2.1 Study Design

A prospective observational study was designed by the investigators using a population composed of patients requiring extraction of their 3rd molars teeth at the Victoria General Hospital in Halifax, Nova Scotia, Canada. Patients who did not use cannabis and those who used cannabis were included in the study. The study was reviewed and approved by the institutional ethics committee (Nova Scotia Health Authority Research Ethics Board) and all participants signed an informed consent agreement.

2.2 Study Sample

All participants in the study were seen in the outpatient OMFS clinic for their consultation and third molar extraction surgery. Third molar surgery with PSA was chosen for its procedural homogeneity. The inclusion criteria consisted of patients over the age of 16, American Society of Anaesthesiologist (ASA) physical status class I or II, and the presence of at least three third molars that required removal. Reasons for removal of third molars include impaction preventing predictable eruption, caries, periodontal disease, or pericoronitis. Patients were excluded from the study if they were younger than 16, had fewer than three third molars, were noted to have pathology (cyst or tumour) associated with the third molar tooth, or had an ASA status of III or above.

Participants were recruited during the consultation phase of their appointment which consisted of a health history review, clinical and radiographic examination and the risks and benefits of the surgical procedure. At this time participants were made aware of the ongoing study and provided with details. If participants accepted the invitation to participate, informed written consent was obtained and they were provided with the intake form.

2.3. Variables and outcome measures

The primary outcome measure was the amount of medication (midazolam, fentanyl, or ketamine) administered corrected for actual body weight. The secondary outcome measure was depth of sedation measured every 5 minutes by an independent observer using the ASA classification for sedation depth (Appendix A).

Tertiary outcomes included post-operative pain, patient satisfaction, and surgeon satisfaction. Post-operative pain was measured on a ten-point visual analogue scale (VAS) with 1 representing “no pain” and 10 representing “worst pain imaginable”. This was measured at 6-hour intervals for 48 hours post operatively. Patient satisfaction was also measured on a 10-point VAS with 1 representing “least satisfied” and 10 representing “most satisfied”. Surgeon satisfaction was measured on a 5-point Likert scale ranging with 1 being “very satisfied” and 5 representing “very unsatisfied”.

Additional variables measured included patient age, gender, general anxiety, dental anxiety, number and type of third molars removed, length of surgery, and the surgeons grading of procedural difficulty on a scale of 1 to 4 with 1 representing “simple extraction, no incision”, 2 representing “simple extraction with incision”, 3 representing “incision + bone removal” and 4 being “incision + bone removal + tooth sectioning” (Appendix B).

2.4 Surgery, Sedation and Monitoring

Prior to surgery, patients were required to fast for a minimum of 8 hours, and they were required to have a responsible individual accompany them to their appointment and to drive them home post operatively. The clinic nurse assessed all patients preoperatively and reviewed their medical history, medications, allergies, recorded baseline vital signs and verified fasting status. All patients received preoperative analgesics (600mg Ibuprofen) and antibiotics (2g Amoxicillin or 600mg Clindamycin if they were penicillin allergic). Following this, the surgeon met with the patient and obtained surgical consent.

Intravenous access was gained via the antecubital fossa or the dorsum of the hand. Ringers Lactate was the intravenous fluid of choice. 2% Lidocaine with 1:100,000 epinephrine was used for local anaesthesia. Prior to administration of sedative medications, the following were applied for patient monitoring: a non-invasive blood pressure cuff, pulse oximeter, nasal cannula with O2 flow at 1-3L/min and capnography, and a 3-lead ECG.

Sedation was administered and monitored by the treating oral and maxillofacial surgeon. Prior to administering sedation, the surgeon was asked to predict how much medication they thought their patient would require for a satisfactory sedation. The patient's depth of sedation was also monitored by a 3rd party (research assistant) every 5 minutes during the procedure. The research assistant began monitoring at the time of local anaesthetic injection and stopped monitoring once the last suture was placed, or the last tooth was extracted – whichever came last. Sedation was monitored and recorded as per the ASA continuum of sedation guidelines which defines minimal sedation (anxiolysis) as normal response to verbal stimulation, moderate sedation/analgesia (conscious sedation) as purposeful response to verbal or tactile stimulation, and deep sedation/analgesia as depression of consciousness where patients cannot be easily roused but respond purposefully following repeated or painful stimulation (Gross 2002). This was simply monitored by assessing the patient's response to verbal or tactile stimulation from the treating surgeon. The patient was scored as "1" (minimal) if their response was normal (e.g., appropriate answer to a question such as "how are you doing?" or a non-verbal response such as a thumbs-up, and "2" (moderate) if it was purposeful (e.g., grunt, slurred word) and easily to elicit with verbal or tactile stimulation.

2.5 Data Collection

On arrival to the clinic for their appointments, following informed consent for participation in the study, participants filled out their intake form (Appendix C) which consisted of three parts:

1. The first part asked participants about their cannabis consumption using a standardized survey tool titled "Psychometric properties of the Daily Sessions, Frequency, Age of Onset and Quantity of Cannabis Use Inventory" (DFAQ-CU). The DFAQ-CU is a 39-item questionnaire designed to measure frequency, age of onset and quantity of cannabis used. The DFAQ-CU has been found to be a psychometrically sound, valid and reliable questionnaire for measuring cannabis use (Cuttler and Spradlin 2017).
2. The second part asked participants about their anxiety levels. In our assessment of patient anxiety, we considered trait anxiety and state anxiety separately.
    a. Trait anxiety which was measured using the General anxiety disorder -7 (GAD7) scale. It is a valid and reliable measure for screening general anxiety disorder and assessing its severity. It consists of 7 questions scaled from 0 to 3. The scores for each question are then added to get a total score. A score of 0- 4 indicates minimal anxiety, 5-9 indicates mild anxiety, 10-14 indicates moderate anxiety, and 15-21 indicates severe anxiety (Spitzer et al. 2006).
    b. State anxiety which was measured using the modified dental anxiety scale (MDAS). The scale asks participants to indicate their anxiety response or level to 5 different dental situations including: anxiety levels the night before an appointment, being in the waiting room, having a scale and polish, drilling of a tooth and administration of local anaesthetic injection. The scale asks participants to answer each question indicating if they were not anxious, slightly anxious, fairly anxious, very anxious or extremely anxious with scores 1 to 5 for each question. Scores ranging from 5-10 indicate low dental anxiety, 11-14 indicates moderate dental anxiety, 15-

18 indicates high dental anxiety and 19-25 indicates severe anxiety with possible phobia (G. M. Humphris et al. 2000).

3. The third part briefly asked participants about alcohol use, cigarette use, and use of other recreational drugs. Alcohol use was measured in units with a visual description of what quantifies a unit of alcohol provided to the patient.

Intraoperative data was collected by a research associate using a custom procedural sedation monitoring form (Appendix D) adapted from a prior study done within our department (Cheung et al. 2019). The research associate began monitoring once the local anaesthesia was administered. Prior to sedating the patient, the surgeon was asked how much sedative medication they anticipated each participant would require and this was recorded. Following this the research associate measured level of sedation every 5 minutes according to the ASA guidelines on depth of procedural sedation. At the end of the procedure, the surgeon was asked to record their overall level of satisfaction regarding the surgery and the sedation, as well as the difficulty level of each tooth extracted on a scale of 1 to 4. Following the procedure, the participant was taken to the recovery room and handover was provided to the recovery room nurse. Once a participant had met nursing criteria for discharge, they were asked a set of questions (Appendix D) to assess their recall and they were provided with a post-operative questionnaire (Appendix E) asking them to rate their pain levels and record the amount of pain medication used over the next 48 hours. To account for the amnestic properties of sedation, all participants were contacted 48 hours post operatively and asked the same set of questions (Appendix D) regarding their recollection of the procedure. In addition to the recall questions, they were also asked for their current pain levels, patient satisfaction on a scale of 1-10, as well as if they had used any cannabis since their procedure and reminded to send in their post-operative questionnaire if they had not already done so.

Study data was collected and managed using REDCap® electronic data capture tools hosted at the Nova Scotia Health Authority. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data

manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources (Harris et al. 2009).

2.6 Data Analysis

Cohen's power primer was used to estimate our sample size. By considering detection of a medium effect size, with alpha set to 0.05, power of 80%, sample size estimation yielded at least 64 participants per group to detect a statistically significant difference (Cohen 1992). Of note there are few prior studies on this topic, and those in the literature have far smaller sample sizes.

Descriptive/Population Statistics

Descriptive statistics for categorical variables (e.g., sex, education level) were reported as numbers and percentages. Continuous variables (e.g., age) were reported as means with standard deviation. For analysis of the demographic variables, the sample size was considered in a binary fashion as cannabis users and non-users. For comparison of the two groups, ratio/interval data (e.g., age) was compared using the independent t-test. Nominal data was compared using Pearson's Chi-square (X^2) test and ordinal data was compared with the Mann Whitney U test.

Primary and secondary outcomes

The amounts of midazolam and fentanyl given, as well as amounts normalized for body weight were compared between cannabis users and non-users using the independent t-test. Additionally, DFAQ-CU- scores to divide cannabis users based on quantity and frequency into non-users, low users, medium users and high users. Analysis was carried out on each of the above drugs, against the cannabis frequency and quantity scores to determine if there was any difference between the groups using a one-way ANOVA.

The predicted amount of midazolam and fentanyl was subtracted from the given amount to give a "difference value" for each drug. A value of "0" indicates that there was no

difference in the predicted vs. given amount. A negative value occurred if the patient was given *less* than predicted, and a positive value occurred if a patient received *more* than predicted. The mean of the "difference values" for midazolam and fentanyl were compared using an independent t-test.

For each patient, depth of sedation was recorded every 5 minutes. Patients were assigned a score of "1" for minimal sedation, "2 "for moderate sedation, and "3" for deep sedation (Appendix A). Using these scores, an average depth of sedation was calculated for each patient. A score of 2.0 indicated that the patient was moderately sedated for the entire duration of the procedure. A score below 2.0 indicated that for a portion of the procedure the patient was lightly sedated, and a score greater than 2.0 meant that for a portion of the procedure the patient was deeply sedated. One-way ANOVA was used to evaluate if there were any differences in depth of sedation between cannabis frequency and quantity groups.

Tertiary Outcomes

The tertiary outcomes were assessed using cannabis as a binary variable. Further analysis dividing the sample into non-users, low, medium and high users based on frequency or quantity was only done if there was a significant difference in the binary analysis.

Post-operative pain: The average of patient scores which were recorded q6h x 48hrs (8 separate time points) was calculated and compared between cannabis users and non-users using an independent t-test. A Kruskal-Wallis H test was further used to analyse pain levels at the 8 time points using cannabis use and sex as independent variables.

Patient satisfaction: Mann Whitney-U test was used to compare the distribution or median of satisfaction scores between the two groups. Further analysis was carried out by running a Kruskal-Wallis H test using cannabis frequency and quantity as grouping variables and patient satisfaction as the test variable.

Patient recall was also considered in overall patient satisfaction. Patients were asked five yes/no recall questions: do you remember a) entering the operating room, b) the events of procedure, c) any unpleasant experiences, d) pain during the procedure and e) anxiety during the procedure - at 30 minutes and 48 hours post operatively. Based on their response, they were categorized into four groups and assigned an ordinal score for each of the following categories– never remembered, remembered then forgot, forgot then remembered, and always remembered. Distribution of the median scores was then assessed between cannabis users and non-users using the Mann Whitney-U test.

Lastly, anxiety levels were also considered as part of patient satisfaction. At 30 mins and 48 hours post operatively, patients were asked to recall how anxious they felt during the procedure. A Mann-Whitney U test was used to compare anxiety levels in the two groups at those time points. Kruskal-Wallis H test was used to determine if there were differences in patient satisfaction between the different GAD7 and MDAS groups.

Surgeon satisfaction: Mann-Whitney U test was used to compare the difference in surgeon satisfaction between cannabis users and non-users. Kruskal-Wallis test was used to assess if there were any differences in surgeon satisfaction across different levels of GAD7 and MDAS scores.

All statistical analysis was performed using SPSS (version 28.0.1.1). Graphical illustration was also performed using the same software. A p-value of <0.05 was considered statistically significant.

CHAPTER 3: RESULTS

3.1 Patient characteristics

A total of 176 patients were recruited into the study. 18 patients being excluded for failure to meet inclusion criteria due to number of teeth being extracted, and incomplete data on Form A resulting in inability to categorize according to cannabis use. Of the 158 patients who completed the study, there was an even split between those who identified as cannabis users and those who were non-users with a total of 79 people per group. For all participants the preoperative and intraoperative forms were complete. 56 participants did not complete the post-operative form. Of those, 54 did not complete the post-operative phone call at 48 hours. Those with missing post-operative data were still included in our assessment as it did not affect evaluation of their primary and secondary outcome measures.

Within the non- cannabis users 39 (49.3%) were male and 40 (50.6%) were female. From the cannabis user group 36 (45.5%) were male and 43 (54.4%) were female. There was no significant difference in sex distribution between the two groups, X^2 (1) = 0.22, p =0.633. The average age of the non-user group was 18.75 while the average age of users was 21.07. This difference was statistically significant ($p < 0.001$). With regards to education levels, the non-user group had a significantly higher number of people at the "some high school" and "high school" level, while the cannabis user group had higher numbers of people at the "undergraduate/college degree" level. While this difference was statistically significant, it is accounted for the significant age gap between the two groups (Table 1).

Table 1: Cannabis Use - Age, Sex and Educdation Level

VARIABLE	NON-CANNABIS USER	CANNABIS USER	TOTAL	P-VALUE
SAMPLE SIZE, N (%)	79 (50%)	79 (50%)	158	
SEX, N (%)				0.633
MALE	39 (49.4%)	36 (45.5%)	75 (47.5%)	
FEMALE	40 (50.6%)	43 (54.4%)	83 (52.5%)	
AGE, MEAN (SD)	18.75 (+/- 2.84)	21.07 (+/- 4.27)		<0.001
EDUCATION LEVEL, N (%)				
SOME HIGH SCHOOL	31 (39.24%)	14 (17.72%)	45 (28.48%)	0.01
HIGH SCHOOL	18 (22.78%)	20 (25.31%)	38 (24.05%)	
SOME COLLEGE/UNIVERSITY	19 (24.05%)	19 (24.05%)	38 (24.05%)	
UNI/COLLEGE DEGREE	5 (6.32%)	18 (22.78%)	23 (14.55%)	
TRADE SCHOOL	3 (3.79%)	2 (2.53%)	5 (3.16%)	
GRADUATE SCHOOL	0 (0%)	1 (1.26%)	1 (0.63%)	
MISSING	3 (3.79%)	5 (6.32%)	8 (5.06%)	

For further assessment of cannabis users, they were divided into low (n= 44), medium (n=22) and high users (n=11) based on the distribution of their frequency scores. Similarly, based on the distribution of quantity scores, they were also divided into low (n = 36), medium (n=23), and high groups (n=17).

A Spearman's correlation was used to assess the validity of the relationship between frequency and quantity scores in categorizing patients as high, medium or low users. There was a monotonic relationship between the two variables. The correlation coefficient (r_s) was 0.633 with a p-value of <0.001 indicating a strong, statistically significant positive relationship between the frequency and quantity scores (Table 2).

Table 2: Spearman's Correlation between cannabis frequency and quantity scores

			Quantity score	Frequency score
Spearman's rho	Quantity score	Correlation Coefficient	1.000	.633**
		Sig. (2-tailed)	.	<.001
		N	76	76
	Frequency score	Correlation Coefficient	.633**	1.000
		Sig. (2-tailed)	<.001	.
		N	76	77

**. Correlation is significant at the 0.01 level (2-tailed).

Anxiety scores – MDAS and GAD7

The mean score on the GAD7 test was statistically significant between non-users n = 77, 5.25 (+/-4.92) and cannabis users, n =75, 7.02 (+/- 5.98), p = 0.048. However, when participants were grouped into categories of minimal, mild, moderate, and severe anxiety there was no difference between the groups (p = 0.131). When considering state anxiety, the mean MDAS score was 11.46 (+/- 4.37) for non-users (n=76) and 12.04 (+/-4.86) for cannabis users (n=74). This difference was not significant. p= 0.41. When participants were categorized into low, moderate, high, and extreme dental anxiety there was no significant differences. Table 3 shows GAD 7 and MDAS scores categorized by cannabis use.

Table 3: Cannabis Use - MDAS and GAD7 scores

VARIABLE	NON-CANNABIS USER	CANNABIS USER	TOTAL	P-VALUE
GAD7 SCORE, N, MEAN (SD)	n = 77, 5.25 (+/- 4.92)	n= 75, 7.02 (+/- 5.98)		0.048
GAD 7 CATEGORY, N (%)				0.131
0 -4 (MINIMAL ANXIETY)	43 (54.43%)	35 (44.30%)	78 (49.36%)	
5-9 (MILD ANXIETY)	20 (25.31%)	14 (17.72%)	34 (21.51%)	
10-14 (MODERATE ANXIETY)	8 (10.12%)	13 (16.45%)	15 (9.49%)	
15-21 (SEVERE ANXIETY)	6 (7.59%)	13 (16.45%)	19 (12.02%)	
MISSING	2 (2.53)	4 (5.06%)	6 (3.79%)	
MDAS SCORE, N, MEAN (SD)	n= 75, 11.46 (+/- 4.37)	n=74, 12.04 (+/- 4.86)		0.418
MDAS CATEGORY N, (%)				0.658
5-10 (LOW DENTAL ANXIETY)	37 (46.83%)	31 (39.24%)	68 (43.03%)	
11- 14 (MODERATE DENTAL ANXIETY)	18 (22.78%)	21 (26.58%)	40 (25.31%)	
15-18 (HIGH DENTAL ANXIETY)	16 (20.25%)	15 (18.98%)	31 (19.62%)	
19- 25 (EXTREME ANXIETY, POSSIBLE PHOBIA)	4 (5.06%)	7 (8.86%)	11 (6.96%)	
MISSING	4 (5.06%)	5 (6.32%)	8 (5.06%)	

When anxiety scores were assessed by sex the GAD7 score for males (n=72) was 4.68 (+/- 4.66), while for females (n=80) it was 7.43 (+/- 5.92). This difference was statistically significant, p= 0.002. When MDAS scores were assessed, females (n=78) had higher MDAS scores than males (n=72) with scores of 12.84 (+/- 4.90) and 10.59 (+/- 3.99) respectively, p = 0.003. Figures 1 and 2 highlight the differences in GAD7 scores and MDAS scores between males and females.

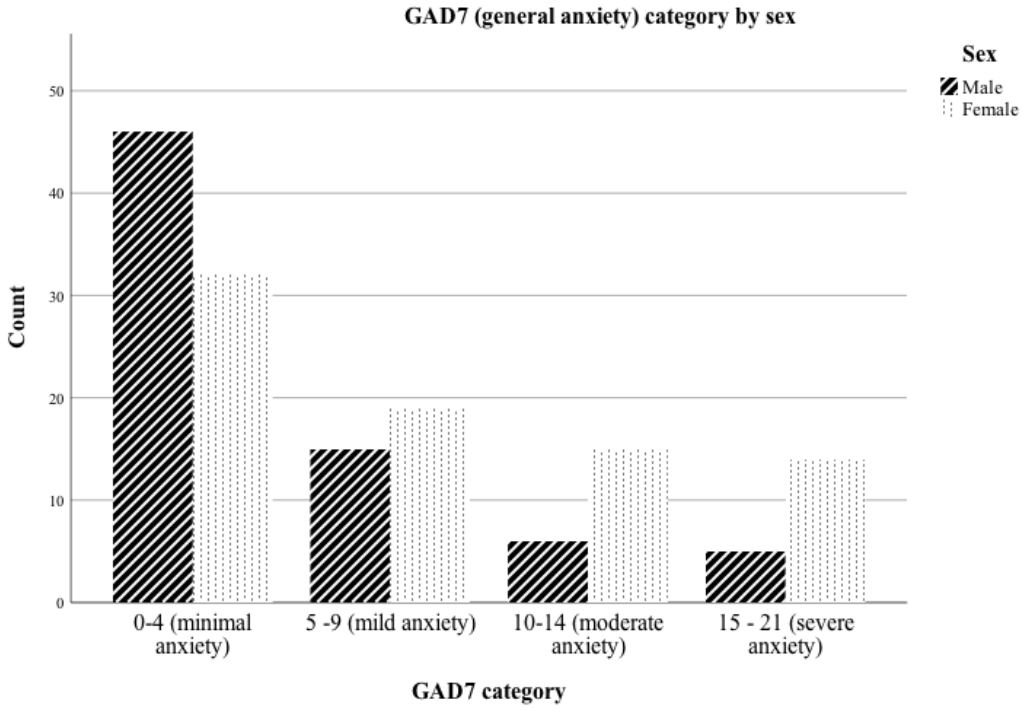


Figure 1: GAD7 category by sex.

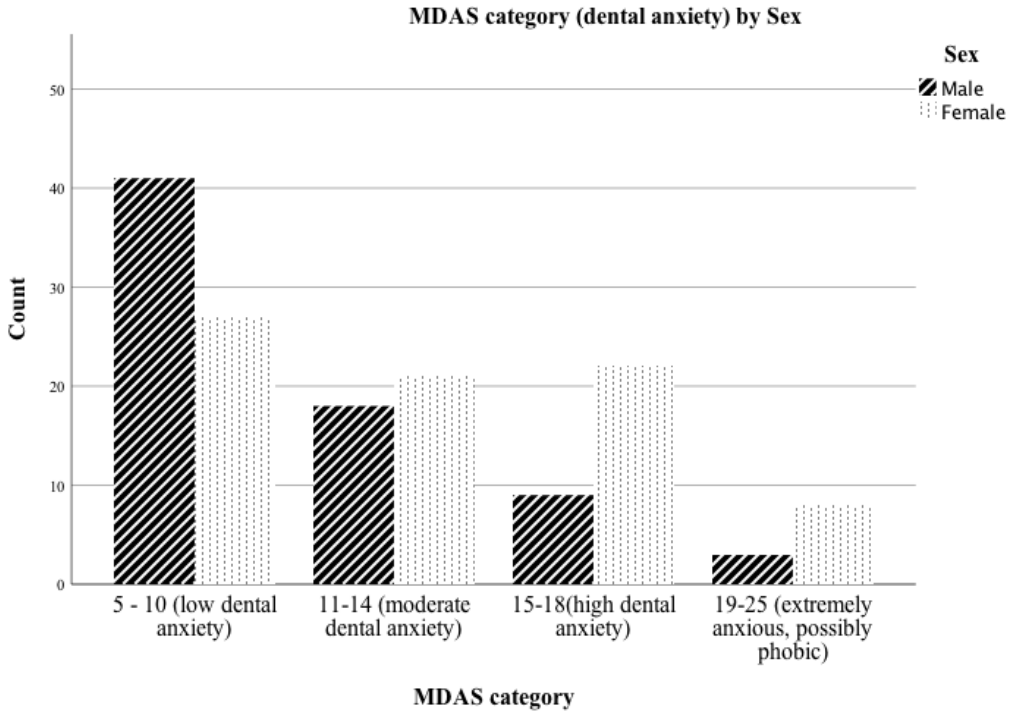


Figure 2: MDAS category by sex.

A Spearman's rank-order correlation used to assess if there was a relationship between MDAS score and GAD7 score. 149 patients were included in the assessment. The relationship was monotonic on visual inspection of a scatter plot. There was a statistically significant, moderate positive correlation between MDAS score and GAD7 score r_s = 0.417, p = <0.001 (Table 4).

Table 4: Spearman's Correlation between MDAS and GAD7 scores

			GAD7 Score	MDAS score
Spearman's rho	GAD7 score	Correlation Coefficient	1.000	.417**
		Sig. (2-tailed)	.	<.001
		N	152	149
	MDAS score	Correlation Coefficient	.417**	1.000
		Sig. (2-tailed)	<.001	.
		N	149	150

**. Correlation is significant at the 0.01 level (2-tailed).

Alcohol, Tobacco and Recreational Drugs

When considering alcohol use, cannabis users were found to utilize more alcohol ($p = <0.001$) and cigarettes ($p = 0.004$) than non-users (Table 5). Again, when accounting for the significant age difference between the two groups this finding is not surprising. Recreational drug use was reported minimally in this study. 4 participants (2.5%) reported cocaine use in varying frequencies. 1 participant reported MDMA use 6 months prior and 1 participant reported use of LSD and mushrooms. 17 (10.75%) participants left the question unanswered.

Table 5: Cannabis use - alcohol and tobacco

VARIABLE	NON-CANNABIS USER	CANNABIS USER	TOTAL	P-VALUE
ALCOHOL USE				<0.001
0 UNITS/WEEK	55 (69.62%)	27 (34.17%)	82 (51.89%)	
1-5 UNITS/WEEK	18 (22.78%)	28 (35.44%)	46 (29.11%)	
6-14 UNITS/WEEK	3 (3.79%)	17 (21.51%)	20 (12.65%)	
>15 UNITS/WEEK	1 (1.26%)	2 (2.53%)	3 (1.89%)	
MISSING	2 (2.53%)	5 (6.32%)	7 (4.43%)	
CIGARETTE USE				0.004
0 CIGARETTES/DAY	76 (96.20%)	63 (79.74%)	139 (87.97%)	
1-5 CIGARETTES/DAY	0 (0%)	8 (10.12%)	8 (5.06%)	
6-10 CIGARETTES/DAY	0 (0%)	3 (3.79%)	3 (1.89%)	
10-20 CIGARETTES/DAY	0 (0%)	1 (1.26%)	1 (0.63%)	
>20 CIGARETTES/DAY	0 (0%)	0 (0%)	0 (0%)	
MISSING	3 (3.80%)	4 (5.06%)	7 (4.43%)	

Surgery

Length of surgery was similar between both groups with an average of 20.72 mins for non-cannabis users and 20.87 minutes for cannabis users. This difference was not significant, p = 0.89. There was no significant difference in the distribution of cannabis users and non-cannabis users amongst surgeons, p = 0.28. Tooth difficulty was measured on a scale of 1 through 4, with increasing levels of difficulty/extent of surgery. Each patient's score for all teeth was averaged to generate a "total tooth difficulty". The maximum score any patient could receive was 16. The difference between the average scores was non-significant with a score of 10.2 for non-user and 9.93 for cannabis users, p=0.49 (Table 6)

Table 6: Cannabis use - length of surgery, surgeon, and surgical difficulty

VARIABLE	NON-CANNABIS USER	CANNABIS USER	TOTAL	P-VALUE
LENGTH OF SURGERY (MEAN, SD)	20.72 (+/- 7.59)	20.87 (+/- 7.40)		0.89
DIFFICULTY				
TOTAL TOOTH DIFFICULTY (MEAN, SD)	10.2 (+/- 2.3)	9.93 (+/-2.4)		0.49
SURGEON				0.28
JB	18 (22.78%)	15 (18.98%)	33 (20.88%)	
CG	14 (17.72%)	9 (11.39%)	23 (14.55%)	
CR	18 (22.78%)	22 (27.84%)	40 (25.31%)	
RG	4 (5.06%)	9 (11.39%)	13 (8.22%)	
BD	11 (13.92%)	7 (8.86%)	18 (11.39%)	
JCD	9 (11.39%)	15 (18.98%)	24 (15.18%)	
RES	5 (6.32%)	2 (2.53%)	7 (4.43%)	

3.2 Primary outcome drug dosage

Midazolam

When predicted and given amounts were compared, there were no significant differences between cannabis users and non-users. Table 7 shows the predicted amounts and given amounts of midazolam.

Table 7: Midazolam - predicted vs. given amount

	NON-USERS	CANNABIS USERS	P-VALUE
MIDAZOLAM, MG (MEAN, SD)			
PREDICTED	5.48 (+/- 1.24)	5.56 (+/- 1.20)	0.38
GIVEN	6.07 (+/- 1.83)	6.59 (+/- 1.94)	0.08
MEAN DIFFERENCE	0.58 (+/- 1.41)	0.93 (+/- 1.70)	0.16

Figure 3 shows the frequency of differences in midazolam dosing. Overall, a majority of patients in both arms received the predicted dose. When the predicted dose was deviated from, more often than not patients in both arms received more than predicted.

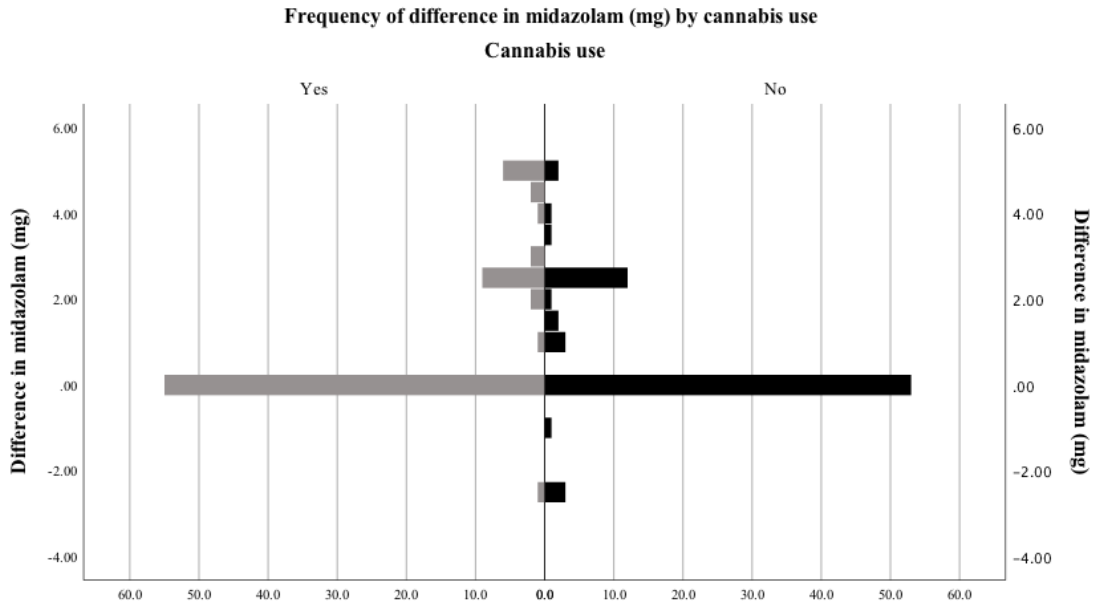


Figure 3: Frequency of differences in predicted vs. given midazolam dose by cannabis use.

When corrected for body weight, the average amount of midazolam received by non-cannabis users was 0.087 mg/kg (+/- 0.03), while cannabis users received an average of 0.089mg/kg (+/- 0.03). This difference was not significant, p = 0.683. With patients divided into nonusers, low, medium, and high users based on cannabis quantity, a one-way ANOVA was carried out to assess if there was any difference in midazolam use between the groups. Non-users (n=82), low users (n=36), medium users (n=23) and high users (n=17) received similar amounts of midazolam - 0.087mg/kg (+/- 0.03), 0.091 mg/kg (+/- 0.02), 0.090mg/kg (+/- 0.03) and 0.083mg/kg (+/- 0.03) respectively. Homogeneity of variances was confirmed via Levene's test (p = 0.55). There were no statistically significant differences in midazolam dose between the different groups (p = 0.82). Similarly, with patients grouped according to cannabis frequency (non-users, low, medium and high), showed no significant differences between groups (p = 0.94) as detailed in Table 8.

Table 8: One-way ANOVA - Midazolam vs. Cannabis frequency and quantity

	ONE-WAY ANOVA - CANNABIS QUANTITY				
	Non-User (n=82)	*Low User (n= 36)*	*Medium User (n=23)*	*High User (n=17)*	p-value
MIDAZOLAM (MG/KG)	0.087 (+/- 0.03)	0.091 (+/- 0.02)	0.09 (+/- 0.03)	0.083 (+/- 0.03)	0.82
	ONE-WAY ANOVA - CANNABIS FREQUENCY				
	Non-User (n= 81)	*Low User (n= 44)*	*Medium User (n=22)*	*High User (n=11)*	p-value
MIDAZOLAM (MG/KG)	0.087 (+/- 0.03)	0.087 (+/- 0.03)	0.090 (+/-0.03)	0.092 (+/- 0.04)	0.94

Fentanyl

When predicted and given amounts were compared, there were no significant differences between cannabis users and non-users. The mean predicted and given amounts of fentanyl are shown in Table 9.

Table 9: Fentanyl - predicted vs. given amount

	NON -USERS	CANNABIS USERS	P-VALUE
FENTANYL, MCG (MEAN, SD)			
PREDICTED	73.10 (+/- 21.4)	79.11 (+/- 20.18)	0.07
GIVEN	73.79 (+/- 24.4)	80.31 (+/- 21.82)	0.07
MEAN DIFFERENCE	0.69 (+/- 10.27)	1.20 (+/-10.83)	0.76

Overall, a majority of patients in both groups received the predicted fentanyl dose. There are similar incidences of deviation from the predicted dose in both groups (Figure 4).

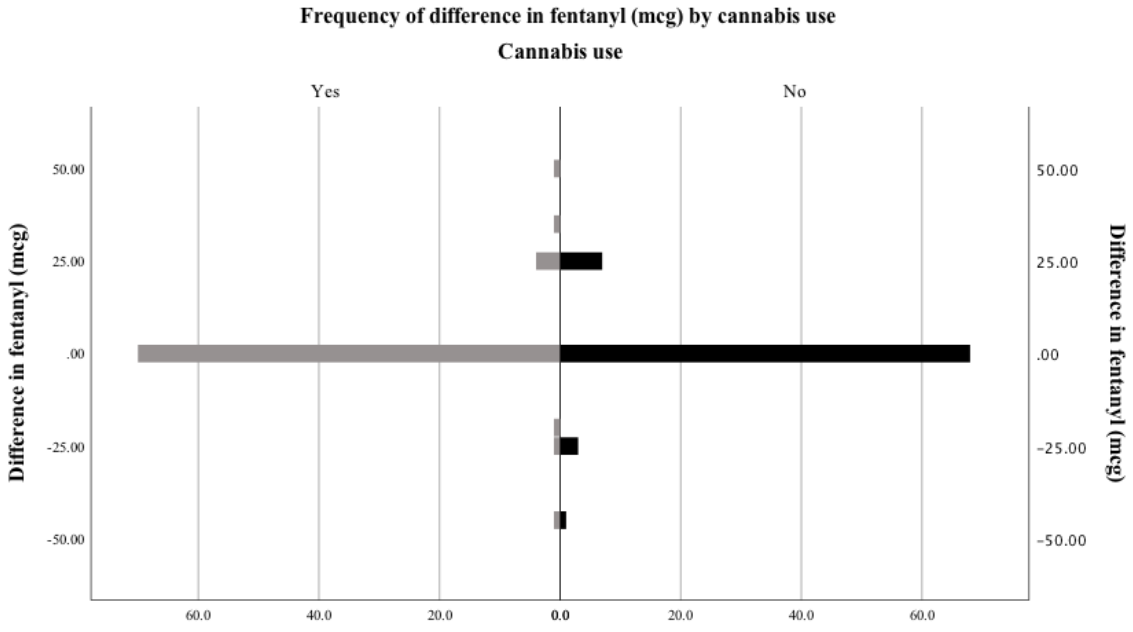


Figure 4: Frequency of differences in predicted vs. given fentanyl dose by cannabis use

When normalized for body weight, the average amount of fentanyl received by non-cannabis users was 1.07mcg/kg (+/- 0.41) while cannabis users received 1.11mcg/kg (+/- 0.38). This difference was not statistically significant, p = 0.462. With patients divided into nonusers, low, medium, and high users based on cannabis quantity, a one-way ANOVA was carried out to assess if there was any difference in fentanyl use between the groups. Homogeneity of variances was assessed with Levene's test (p = 0.80). There were no significant differences in the amount of fentanyl used (p= 0.70). Again, when patients were grouped according to cannabis frequency, the amount of fentanyl used was not statistically significant between groups, however the p-value was approaching statistical significance at 0.06 (Table 10).

Table 10: One-way ANOVA - fentanyl vs. cannabis frequency and quantity

	ONE-WAY ANOVA - CANNABIS QUANTITY				
	Non-User (n=82)	*Low User (n= 36)*	*Medium User (n=23)*	*High User (n=17)*	p-value
FENTANYL DOSE (MCG/KG)	1.06 (+/- 0.40)	1.16 (+/- 0.35)	1.10 (+/- 0.41)	1.08 (+/- 0.40)	0.7
	ONE-WAY ANOVA - CANNABIS FREQUENCY				
	Non-User (n= 81)	*Low User (n= 44)*	*Medium User (n=22)*	*High User (n=11)*	p-value
FENTANYL DOSE (MCG/KG)	1.07 (+/- 0.40)	1.15 (+/-0.34)	0.96 (+/- 0.42)	1.3 (+/- 0.36)	0.06

Ketamine

Given that so few patients received ketamine, assessing the predicted and given amounts did not produce statistically sound or clinically relevant results. Of 158 patients, only 29 (18.35%) received ketamine for their sedation. Of this group, 18 (62.0%) were non-cannabis users and 11(38 %) were cannabis users (Table 11).

Table 11: Crosstabulation ketamine administration vs cannabis use

	CANNABIS USE		
	No	**Yes**	**Total**
NO KETAMINE	61 (77.2%)	68 (86%)	129 (81.6%)
USED KETAMINE	18 (22.8%)	11 (14%)	29 (18.3%)
	79	79	158

A contingency co-efficient test was used to determine if there was a relationship between ketamine administration and cannabis use. The coefficient value was 0.114 ($p = 0.15$) indicating no relationship between the two variables. When accounting for differences in surgeon preference (Figure 5), 18/18 patients of surgeon BD received ketamine with a contingency coefficient value of 0.61 ($p < 0.01$) indicating a strong, statistically significant association between ketamine use and BD.

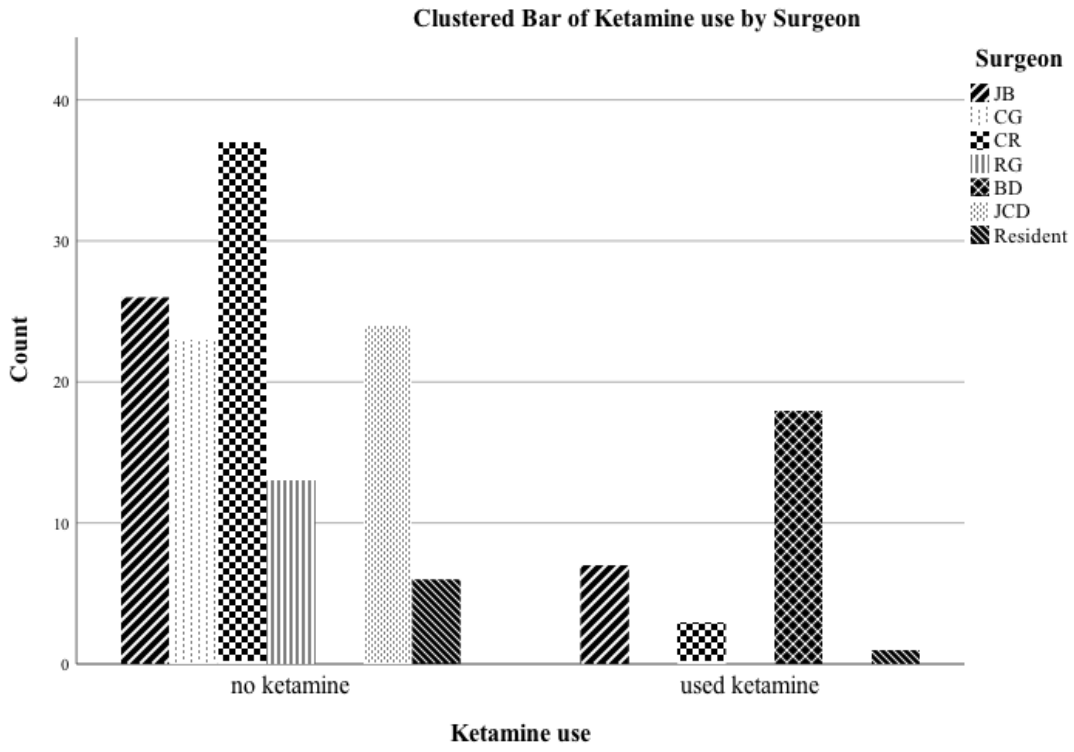


Figure 5: Frequency of ketamine use by surgeon

Was there a difference in drug dose based on patient anxiety?

GAD7 groups were assessed against given doses of midazolam (mg/kg) and fentanyl (mcg/kg). Distribution of midazolam and fentanyl was similar for all groups on visual inspection of a boxplot. A Kruskal-Wallis H test was run to determine if there were differences in midazolam and fentanyl administered across the different levels of GAD7 anxiety. With both midazolam and fentanyl, the median amount given was similar across all groups, and there were no significant differences in drug dosing. Midazolam: $X^2(3) = 4.791$, $p = 0.18$. Fentanyl: $X^2(3) = 6.143$, $p = 0.10$ (Table 12)

Table 12: Drug dose by GAD7 category

GAD7 GROUP	MEDIAN MIDAZOLAM (MG/KG)	MEDIAN FENTANYL (MCG/KG)
MINIMAL ANXIETY	0.08	0.97
MILD ANXIETY	0.089	1.22
MODERATE ANXIETY	0.09	1.18
SEVERE ANXIETY	0.08	1.13
P-VALUE	0.18	0.10

The same test was used to assess if there were any differences in midazolam and fentanyl doses in the different dental anxiety (MDAS) groups. Distribution of midazolam and fentanyl was similar for all groups on visual inspection of a boxplot. Interestingly for both drugs, the median amount of drug given was statistically significant with the Kruskal-Wallis H test, Midazolam $X^2(3) = 13.34$, $p = 0.004$ and Fentanyl $X^2(3) = 9.85$, $p = 0.020$. Pairwise comparisons were performed using Dunn's procedure with a Bonferroni correction for multiple comparisons. This post-hoc analysis revealed statistically significant differences in median midazolam (0.076 mg/kg vs 0.088mg/kg) and fentanyl doses (0.98mcg/kg vs 1.19mcg/kg) between the low dental anxiety and the high dental anxiety group for midazolam (p=0.011), and for fentanyl (p=0.016). There were no other statistically significant group combinations (Table 13).

Table 13: Drug dose by MDAS category

MDAS GROUP	MEDIAN MIDAZOLAM (MG/KG)	MEDIAN FENTANYL (MCG/KG)
LOW DENTAL ANXIETY	0.076	0.98
MODERATE DENTAL ANXIETY	0.09	1.22
HIGH DENTAL ANXIETY	0.088	1.19
EXTREME DENTAL ANXIETY	0.09	1.13
P-VALUE	0.004	0.02

When we divided patients into those who received ketamine and those who did not and compared the distribution of GAD7 and MDAS anxiety levels between the two groups using a Kruskal-Wallis H test, the boxplots for both anxiety scores were similar between the groups for both anxiety scales. The median GAD7 score for those who did not receive ketamine (n = 125) and those who received ketamine (n = 27) was 1 which corresponded to the value indicating minimal anxiety, $X^2(1) = 0.15$, $p = 0.69$. Similarly, for the MDAS scale, the median score for those who did not receive ketamine (n =122) was 2 corresponding to moderate dental anxiety. For those who received ketamine (n = 27) the median score was 1. This difference was not statistically significant, $X^2(1) = 0.16$, $p = 0.69$.

3.3 Secondary outcome: depth of sedation

Depth of sedation was measured on a scale from 1 through 3, with "2" representing a moderate depth of sedation. The average depth of sedation was calculated for each patient. The closer the score to 2.0, the more the patient spent time at a moderate depth. With patients divided into nonusers, low, medium, and high users based on cannabis frequency and quantity, a one-way ANOVA was used to determine if there was any difference in the average depth of sedation between groups. There was homogeneity of variances as assessed by Levene's test for equality of variance (p = 0. 40 for frequency, and p = 0.72 for quantity). The average depth of sedation was 1.49 for non-users, 1.40 for low users, 1.48 for medium users and 1.51 for high users. There was no difference in groups when depth of sedation was assessed against cannabis frequency (p =0.72) or quantity (p=0.92). (Table 14)

Table 14: One-way ANOVA - depth of sedation vs. cannabis frequency and quantity

	ONE-WAY ANOVA - CANNABIS QUANTITY				
	Non-User (n=82)	*Low User (n= 36)*	*Medium User (n=23)*	*High User (n=17)*	p-value
DEPTH OF SEDATION (MEAN, SD)	1.49 (+/- 0.48)	1.44 (+/- 0.45)	1.42 (+/- 0.46)	1.46 (+/- 0.45)	0.92
	ONE-WAY ANOVA – CANNABIS FREQUENCY				
	Non-User (n= 81)	*Low User (n= 44)*	*Medium User (n=22)*	*High User (n=11)*	p-value
DEPTH OF SEDATION (MEAN, SD)	1.49 (+/- 0.48)	1.40 (+/- 0.41)	1.48 (+/- 0.52)	1.51 (+/- 0.46)	0.72

3.4a Tertiary outcome: post-operative pain

Each patient recorded pain levels every 6 hours for 48 hours on a 10-point VAS. The average score for each patient was calculated and again at a binary level there was no difference in pain levels with a mean of 3.73 (+/- 1.74) for non-users and a mean of 3.69 (+/- 1.61) for cannabis users, p = 0.90. Mann-Whitney U test was used to assess pain levels at the 8 time points post operatively based on cannabis use. There were no significant differences in median post-operative pain scores between cannabis users and non-cannabis users (Table 15).

Table 15: Median VAS scores vs. Cannabis use

MEDIAN VAS SCORE				
	Cannabis Use			
TIME (HRS)	**Non-users**	**Users**	**Test Statistic**	**p-value**
6	3	3	1199.5	0.572
12	4	4	1109.0	0.388
18	3.5	4	1284.5	0.713
24	3.5	4	1315.5	0.559
30	4	4	1443.5	0.205
36	3	5	1412.0	0.139
42	3	3	1076.0	0.742
48	3	3	1086.0	0.917

However, when we tested pain scores at each time point against sex there were significant differences at 24 hours, 30 hours, 36, hours and 48 hours with women having significantly higher median pain scores than men at the aforementioned time points (Table 16).

Table 16: Median VAS scores vs. Sex

MEDIAN VAS SCORE

	Sex			
TIME (HRS)	**Male**	**Female**	**Test Statistic**	**p-value**
6	3	4	1468.5	0.242
12	3	4	1402.0	0.263
18	3	4	1488.0	0.086
24	3	4	1609.0	**0.010**
30	4	4	1623.5	**0.015**
36	3	4	1500.0	**0.045**
42	3	4	1300.5	0.246
48	3	4	1406.0	**0.019**

3.4b Tertiary outcomes: patient satisfaction

Patients were asked to record satisfaction levels on a 10-point VAS at 48 hours post operatively. The mean score was 8.16 (+/- 1.51) for non-cannabis users (n=55) and 8.22 (+/- 1.69) for cannabis users (n=49) (Figure 6).

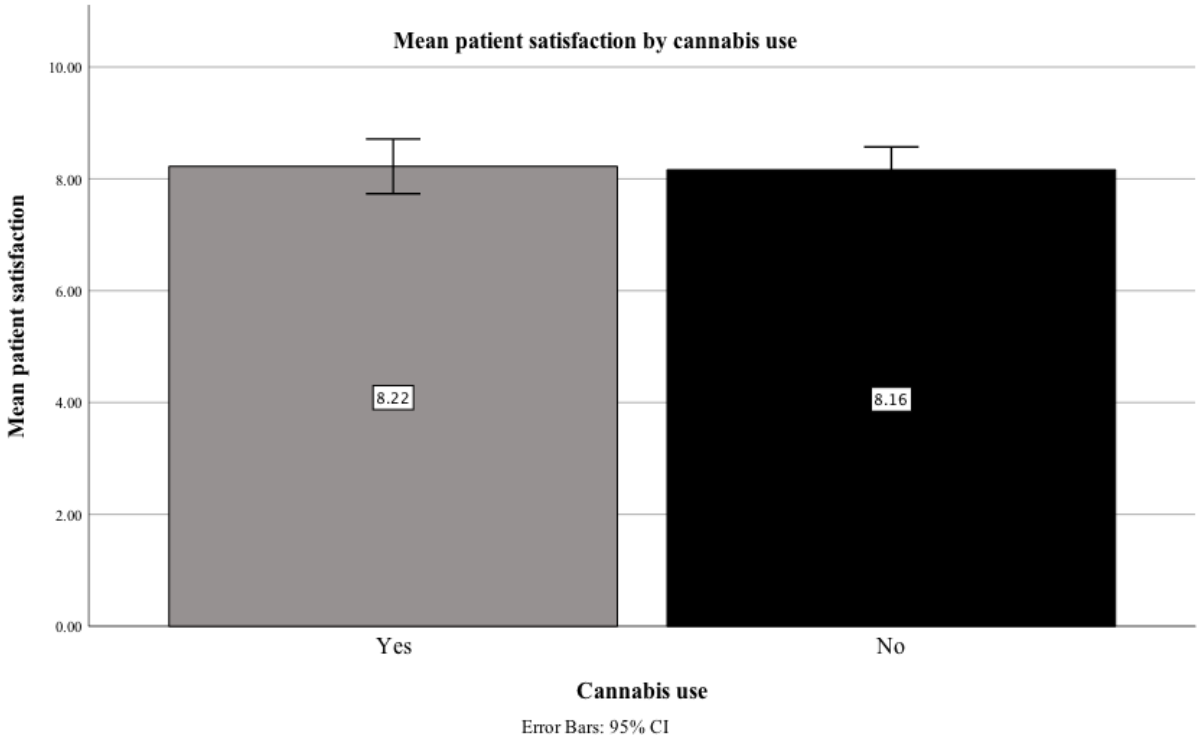


Figure 6: Mean patient satisfaction by cannabis use status

A Mann-Whitney U test was carried out using cannabis as a binary grouping variable and patient satisfaction as a test variable to see if there were any differences in patient satisfaction. Distribution of patient satisfaction scores for cannabis users and non-cannabis users was similar as assessed by visual inspection of the bar charts. Median patient satisfaction was not statistically significant between cannabis users (9.0) and non-users (8.0), $U = 1416.0$, $z = 0.45$, p = *0.647.*

To further assess patient satisfaction, a Kruskal-Wallis H test was run using cannabis frequency as a grouping variable (nonuser, low, medium and high frequency) and patient satisfaction as the test variable. Distribution of patient satisfaction scores was somewhat similar for all groups, apart from the high user group as assessed by visual inspection of a boxplot. Median patient satisfaction scores were not statistically different between groups, X^2 (3) = 6.06, p = 0.108. The same test was applied using cannabis quantity as a grouping variable (nonusers, low, medium and high quantity). Again, distribution of patient satisfaction scores was similar for both groups. Median patient satisfaction scores were not statistically significant between groups based on cannabis quantity, X^2 (3) = 3.77, p = 0.287 (Table 17).

Table 17: Patient satisfaction, cannabis frequency and cannabis quantity

PATIENT SATISFACTION VS. CANNABIS FREQUENCY

FREQUENCY	**n**	**median score**	**Test Statistic**	**p-value**
NON-USER	65	8	6.06	0.108
LOW FREQUENCY	32	8.5		
MEDIUM FREQUENCY	11	8		
HIGH FREQUENCY	5	10		

PATIENT SATISFACTION VS. CANNABIS QUANTITY

QUANTITY	**n**	**median score**	**Test Statistic**	**p-value**
NON- USER	57	8	3.77	0.287
LOW QUANTITY	26	8		
MEDIUM QUANTITY	12	8.5		
HIGH QUANTITY	9	9		

Patient recall was also considered in overall patient satisfaction. Patients were asked 5 yes/no recall questions at 30 minutes and 48 hours post operatively. Based on their response, they were categorized into four groups and assigned an ordinal score– never remembered (score A), remembered then forgot (score B), forgot then remembered (score C) and always remembered (score D). Distribution of the median score was then assessed between cannabis users and non-users with the Mann-Whitney U test. Table 18 shows the median score in each group and the associated p -value. On all five recall questions there was no significant differences between the two groups.

Table 18: Cannabis use and patient recall

	CANNABIS USE			
DO YOU REMEMBER…	**No**	**Yes**	**Test Statistic**	**P-Value**
...ENTERING THE OR?	2 (n = 64)	2 (n = 59)	1936.5	0.633
...THE EVENTS OF THE PROCEDURE?	1 (n= 64)	2 (n =58)	1888.5	0.858
...ANY UNPLEASANT EXPERIENCES DURING THE PROCEDURE?	0 (n =64)	0 (n=58)	1954.5	0.358
...ANY PAIN DURING THE PROCEDURE?	0 (n=64)	0 (n=58)	1824.0	0.79
...HAVING ANY ANXIETY DURING THE PROCEDURE?	0 (n=59)	0 (n=58)	1677.0	0.811

Lastly, anxiety was also considered in overall patient satisfaction. Patients were asked about their anxiety during the procedure 30 mins post operatively and asked to recall how anxious they felt 48 hours later. A Mann-Whitney U test was used to compare anxiety levels in the two groups at those time points. At both time points distribution of the scores was similar between the two groups on visual inspection of bar charts. There were no significant differences in anxiety scores between the two groups. The median score at 30 minutes for non-cannabis users (n=77) and cannabis users (n = 79) was 0, $U = 3110$, $z = 0.285$, $p = 0.776$. At 48 hours, cannabis users (n=59) and non-users (n =65) both had median scores of 1, $U = 1880.5$, $z = -0.194$, $p = 0.846$.

Does state and trait anxiety affect patient satisfaction?

A Kruskal-Wallis H test was conducted to determine if there were differences in patient satisfaction scores between GAD 7 groups: minimal (n =56), mild (n= 27), moderate (n = 13), severe (n=8). Median scores were 8.5, 9.0, 7.0 and 7.5 for each group respectively. Distribution was somewhat similar for all groups on visual inspection of the boxplots for both anxiety scores. There was a statistically significant different in median satisfaction scores between GAD7 groups, X^2 (3) = 11.27, p = 0.010. Pairwise comparisons were performed using Dunn's procedure with a Bonferroni correction for multiple comparisons. This post hoc analysis revealed statistically significant differences in median patient satisfaction scores between the mild anxiety (9.0) group and the moderate anxiety group (7.0), p = 0.009. There were no other significant comparisons (Figure 7)

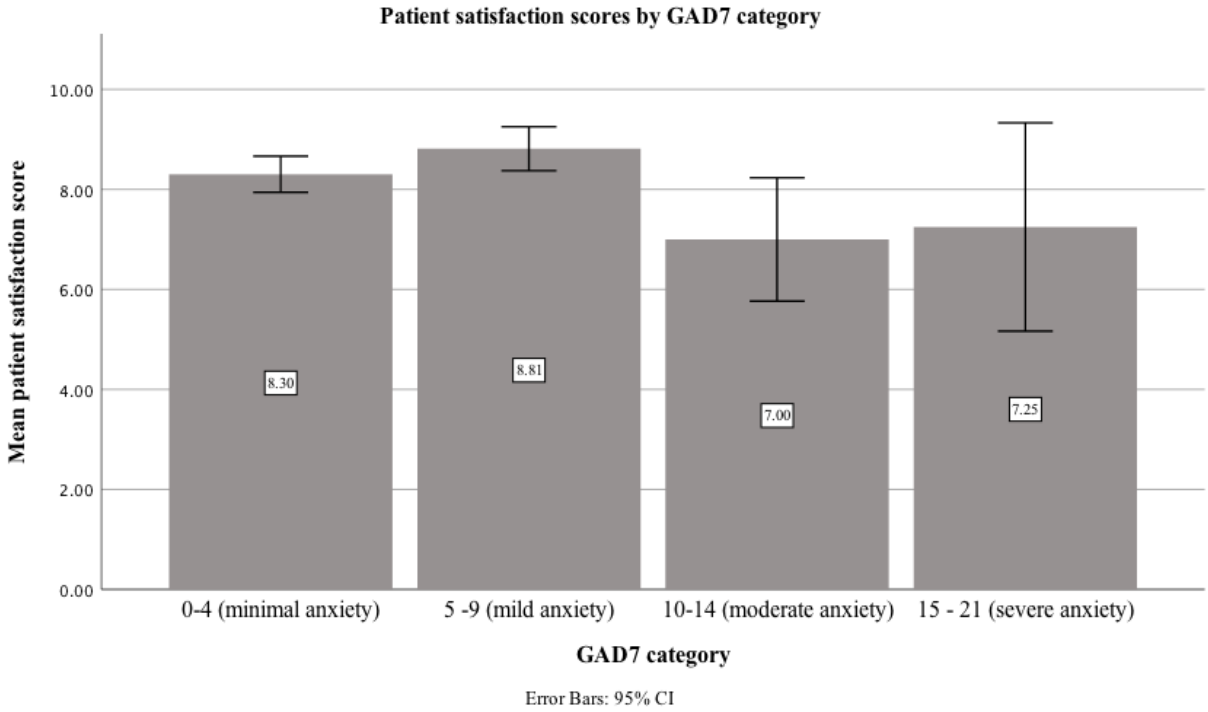


Figure 7: Patient satisfaction by GAD7 category. Mean scores are presented as they are similar to the medians.

Similarly, the Kruskal-Wallis H test was used to see if there were any differences in patient satisfaction scores between MDAS groups (Figure 8): low anxiety (n = 51), moderate anxiety (n = 30), high anxiety (n = 15) and extreme dental anxiety (n = 7). Median satisfaction scores were 9.0, 8.0, 8.0, and 8.0 for the respective groups. There were no significant differences between the groups, X^2 (3) = 2.66, p = 0.446.

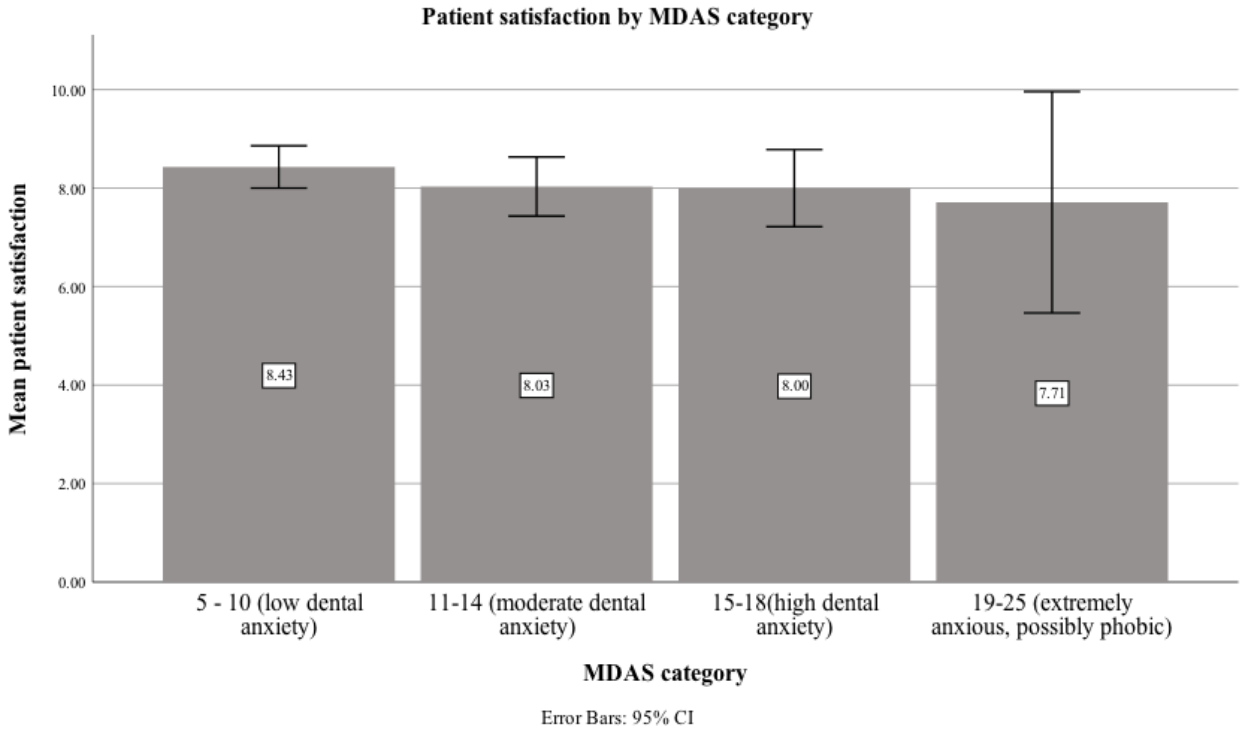


Figure 8: Patient satisfaction by MDAS category. Mean scores are presented as they are similar to the medians.

3.4c Tertiary outcomes: surgeon satisfaction

Surgeons were asked to record their overall satisfaction with the procedure and the sedation immediately post-operatively on a 5-point Likert scale ranging from most satisfied to least satisfied. 65.8% (n= 104) of surgeons were “very satisfied”, 24.1% (n=38) were “satisfied”, 5.2% (n=10) were “neutral”, 3.2% (n=5) were “unsatisfied” and 0.6% (n=1) was “very unsatisfied”.

With cannabis use as a binary variable and surgeon satisfaction as the test variable, a Mann-Whitney U test was used to compare the difference in surgeon satisfaction between cannabis users and non-users. The median score in both groups was 1 “very satisfied”. There was no difference between the two groups $U = 3312$, $z = 0.796$, $p = 0.426$ (Figure 9).

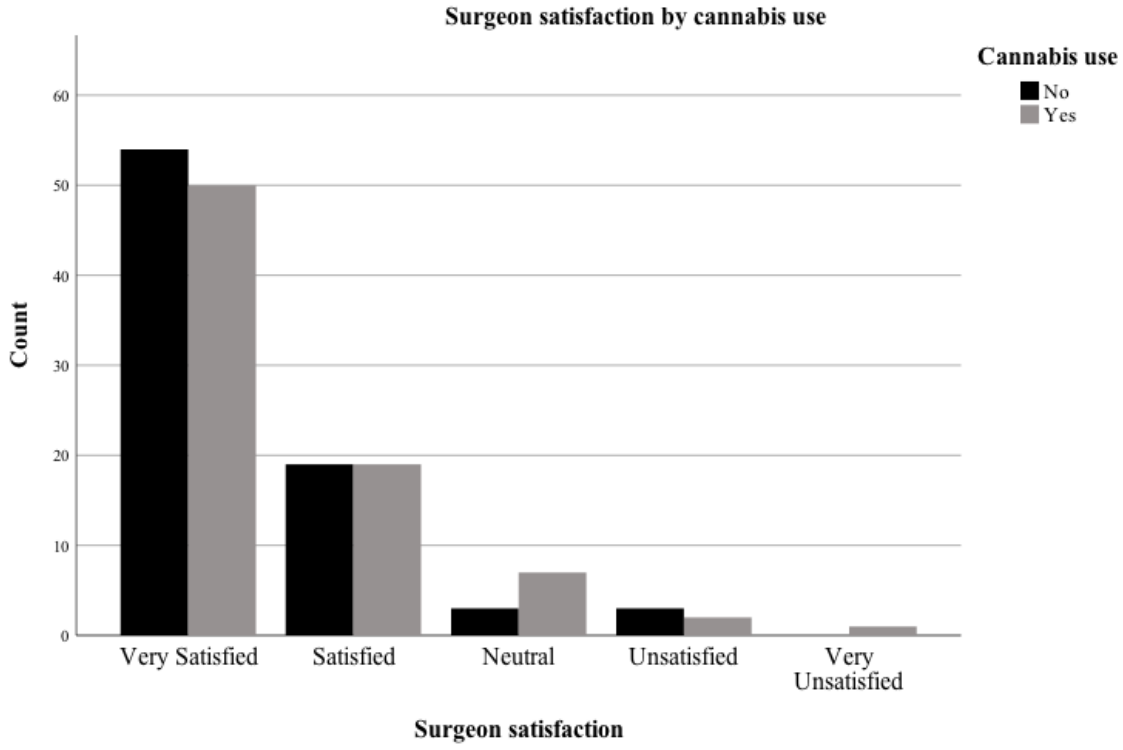


Figure 9: Clustered bar graph of surgeon satisfaction by cannabis use.

Does surgeon satisfaction differ with varying levels of GAD7 and MDAS?

Kruskal-Wallis H test was used to see if there were any differences in surgeon satisfaction across the different levels of GAD7 anxiety: minimal (n = 78), mild (n = 34), moderate (n=21) and severe (n=19). Median surgeon satisfaction is 1.0, 1.0, 1.0 and 2.0 for each group respectively. Box plots were dissimilar across groups, so the mean ranks are presented instead – 80.5, 66.3, 61.7, and 94.3 for each GAD7 group respectively. There is a statistically significant difference in the distribution of surgeon satisfaction scores across the groups. X^2 (3) = 11.45, p = 0.010. Pairwise comparison using Dunn's procedure with a Bonferroni correction were carried out and this post hoc analysis shows significant differences in mean ranks between the moderate and severe anxiety group (p = 0.031), and the mild anxiety and severe anxiety groups (p = 0.046). There were no other significant group combinations (Figure 10).

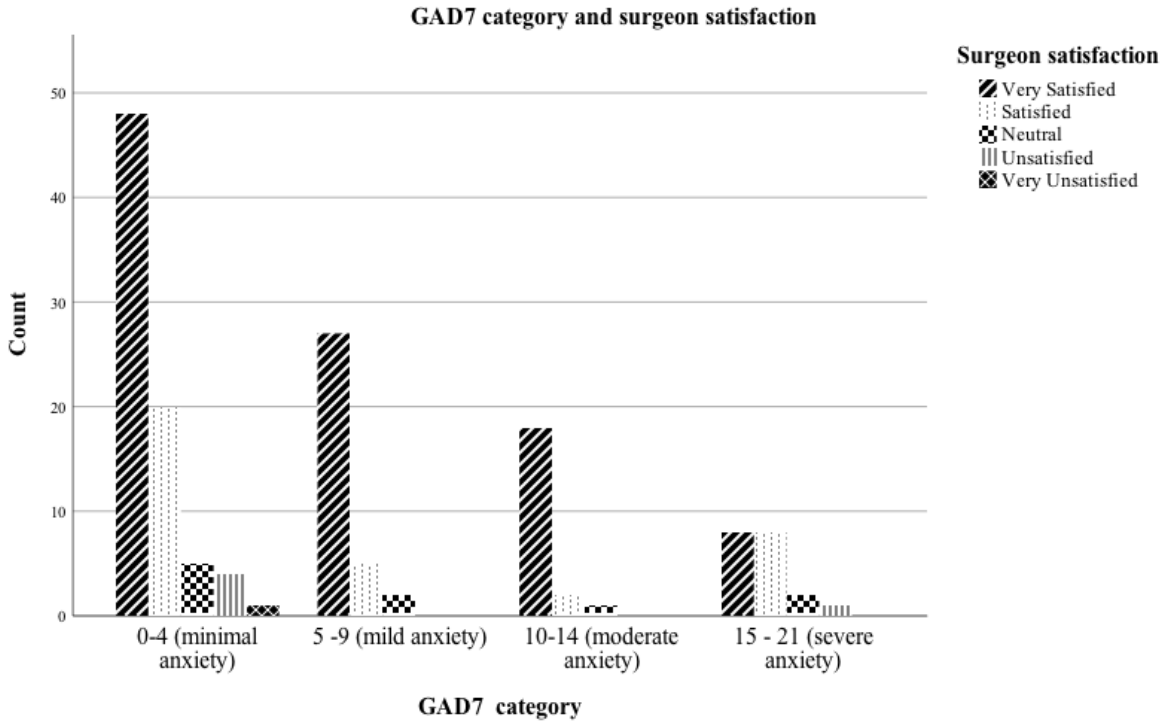


Figure 10: Clustered bar graph of surgeon satisfaction by GAD7 category

The same test was used to see if there were any differences in surgeon satisfaction across the different levels of MDAS anxiety: Low (n = 68), moderate (n= 39), high (n= 31) and extreme anxiety (n= 11). Distribution of surgeon satisfaction was similar on for all groups on visual inspection of a box plot. Median surgeon satisfaction for each group is 1.0, 1.0, 2.0 and 1.0 respectively. There were no significant differences between the groups, X^2 (3) = 6.12, p = 0.10. (Figure 11)

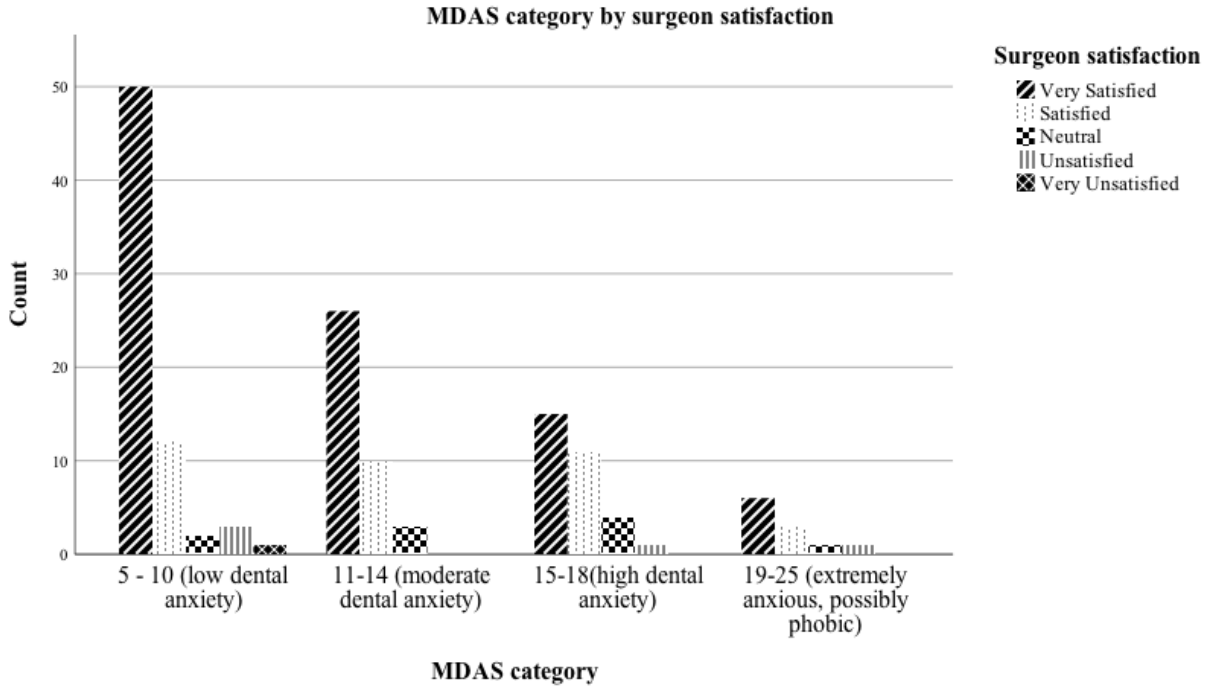


Figure 11: Surgeon satisfaction by MDAS category

3.5 Adverse events

No cardiac, hemodynamic or respiratory complications occurred. In one participant an oxygen saturation below 88% was recorded which was managed by pausing the procedure and providing jaw thrust. There were no procedures where intervention further than a jaw thrust was required. There were no instances where a reversal agent was used. There were no procedures where complication or hemodynamic disturbance required cessation of sedation or the procedure. All procedures were completed as intended

CHAPTER 4: DISCUSSION

When assessing the study demographics, our two study populations were similar in terms of age and gender distribution. The mean age of our population is 19.88 (+/- 3.7) with a range from 16 to 42. This is different from the gastroenterology literature where ages were generally older for patients undergoing colonoscopy and EGD. The average age in the cannabis use group (21.0) was higher than in the non-user group (18.75). A majority of the non-users were under the age of 18. This age difference between the two groups, although statistically significant is not surprising. Similarly, the cannabis user group had higher levels of education and were more likely to be smokers or consume alcohol. Although these variables showed statistical significance, it is not surprising given the higher average age of the cannabis user group.

4.1 Assessing Cannabis Use

Assessing cannabis use is difficult. Although there are a number of different tools available for assessing cannabis addiction and cannabis related problems, there is a lack of psychometrically sound indices for measuring frequency and quantity of cannabis use. This is partly due to the legal landscape surrounding cannabis in many countries. Because of this, outside of psychology and addiction medicine the research on cannabis use and how it affects other areas of medicine is lacking. This is changing as more countries decriminalize cannabis use. That being said, assessment of cannabis use is hampered by recall bias as people often struggle to remember exact amounts consumed over long periods of time. Additionally, there are a variety of methods by which cannabis can be consumed and THC concentration varies among different products. This further limits the ability to confidently estimate the amount ingested. However, government regulation of cannabis production and sales has somewhat regulated and allowed users to better quantify THC content in cannabis products.

In the initial development of this study the Timeline Follow Back method for Marijuana (TLFB) was considered (Robinson et al. 2014). The TLFB method required patients to look at a calendar of the last 30 days and mark all the days that they smoked joints, indicating how many were smoked. The big issue with the TLFB method was that it only accounted for recent cannabis use and would not capture or account for an otherwise frequent cannabis user, whose use had decreased over the last 30 days, or an infrequent heavy cannabis user. Additionally, it is subject to retrospective recall bias – with those who use cannabis regularly having an easier time completing the form more accurately than those who use sporadically. Additionally, the TLFB uses "number of joints smoked" as a measure for quantity of marijuana, and this does not take into account the size of joints, or potency of marijuana used. Although joints are by far the most commonly used method of ingesting cannabis, this does not account for the fact that cannabis is often ingested via other methods for example, bongs, edibles. In our study, 52.6% (n=41) of cannabis users reported that their primary ingestion method was joints. 25.6% (n=20) reported a primary method of bong (water pipe), and 6.4% (n = 5) reported using edibles as a primary ingestion method.

For the reasons mentioned above, we chose to use the DFAQ-CU for assessment of cannabis use. It is a standardized 39-item questionnaire designed to measure frequency, age of onset and quantity of cannabis used. The DFAQ-CU includes photographs of marijuana in joint, bud, and loose-leaf forms to ease identification of the quantity of marijuana typically used. It also asks respondents to indicate the concentration of THC if known. Specific questions are designed to assess frequency and quantity of marijuana used and based on this a score can be developed with higher scores indicate more frequent use, older age of onset and higher quantity of use. The DFAQ-CU has been found to be a psychometrically sound, valid and reliable questionnaire for measuring cannabis use (Cuttler and Spradlin 2017).

4.2 Alcohol, Tobacco and other recreational drugs

Alcohol use is more common among cannabis users (Yurasek, Aston, and Metrik 2017). In our study, we found that 65.9% of cannabis users reported alcohol use, compared to only 30.4% of non-cannabis users. 35.44% of cannabis users consumed 1-5 units per week, compared with 22.7% of non-cannabis users. Only 3.79% of non-cannabis users consumed 6-14 units per week compared with 21.5% of cannabis users. The difference in alcohol use between cannabis users and non-users was statistically significant, with cannabis users consuming more alcohol. However, this is accounted for by the fact that the cannabis use group was older, and more likely to be over the legal drinking age of 19. Similarly, when tobacco use was assessed, a majority of our study population were non-smokers (87.9%). However, the 7.5% of people who were cigarette smokers were all in the cannabis user group. This difference between cannabis users and non-users was significant.

4.3 State Anxiety and Trait Anxiety

Anxiety is a state of apprehension or physical tension combined with the activation of the autonomous nervous system and is a common emotional reaction to fear. High anxiety may preclude a patient to decreased satisfaction, increase the duration of the procedure, the risk of complications and the sedation and analgesic requirements (Gürbulak et al. 2018). The neuroendocrine changes associated with anxiety include reduction of the pain threshold, increase in possibility that non harmful stimulants may be interpreted as painful and the occurrence of hemodynamic changes such as tachycardia, fluctuations in arterial pressure or vasovagal responses (Bovaira et al. 2017).

General anxiety disorder is one of the most common anxiety disorders seen in the general population with an estimated prevalence of 1.6% to 5.0% in the general population (Spitzer et al. 2006). A more recent Canadian survey reported that 2.5% of the population have symptoms consistent with GAD (Pelletier et al. 2017). The average GAD7 score in our study population was 5.25 (+/-4.92) for non-cannabis users and 7.02 (+/- 5.98) for

cannabis users. This difference was statistically significant (p=0.048) and is consistent with literature suggesting a link between cannabis use and higher anxiety levels (Crippa et al. 2009; Kedzior and Laeber 2014; Twomey 2017) - however the literature is lacking consensus about the nature of the association between cannabis and anxiety i.e., did the cannabis use or the anxiety come first? We also found that women have statistically significant higher mean GAD7 scores than men (7.43 compared to 4.68, p = 0.002), this is in keeping with current literature (Watterson et al. 2017).

When considering state anxiety specifically with regards to dental treatment, there are a number of different metrics that can be used. The MDAS was chosen for this study as it is easy to administer, quick, efficient, and has demonstrated reliability and validity across different populations. In this study, the average score was 11.46 (+/- 4.37) in non-users and 12.04 (+/- 4.86) in cannabis users. This difference was not statistically significant. Of note, there was a statistically significant difference (p = 0.03) in mean MDAS scores between men and women, with women having higher dental anxiety than men (12.84 +/- 4.90 vs. 10.59 +/- 3.99). This was found to be consistent with existing literature on the MDAS across different populations (Tunc et al. 2005; Gerry M. Humphris, Dyer, and Robinson 2009).

Anxiolysis is a keynote benefit of procedural sedation. In a prospective study by Gurbulak et al. they investigated the impact of anxiety on sedative medication dosage in 210 consecutive patients undergoing EGD. Patients were evaluated preoperatively by a psychiatrist to assess for baseline anxiety using the Spielberger State-Trait Anxiety Inventory. The endoscopist and anaesthesiologist were blinded to each patient's preoperative anxiety score. In this study patients were sedated with a combination of midazolam and propofol. The decision on if further sedative medication was administered was determined by the anaesthesiologist and endoscopist based on the patient's compliance and the observer's assessment of alertness/sedation scale which was assessed every minute. They found that additional dosing of medication was affected by age, BMI and anxiety scores. Patients who were young, had low BMI and had high anxiety scores required significantly higher doses of sedation medication (Gürbulak et al. 2018). This is

similar to our study findings which showed significant differences in midazolam and fentanyl doses between the low dental anxiety group and the high dental anxiety group, with the higher anxiety group receiving more medication. There were no significant differences in drug dosage when patients were categorized by GAD7 score. In our study, there was no correlation between age and amount of midazolam or fentanyl received. In our study, we also found that there was no difference in ketamine use across different GAD7 and MDAS patient anxiety levels, or between cannabis users and non-users. Ketamine use was found to be more significantly related to surgeon preference.

Patient recall is an important part of anxiety, and desire for amnesia is often a reason that patients request sedation. To assess this, we modified an existing questionnaire (Appendix B, page 2) and used this to assess recall of the operation, perioperative pain and anxiety (Hasen et al. 2003). The questionnaire was modified for our study to exclude questions about nausea and vomiting. Instead, these were noted as an adverse event if they occurred during the procedure or in the immediate post-operative period while the patient remained in the recovery room. This questionnaire was chosen because it had been successfully used in other studies, simple to administer and captured the salient points of patient recall and anxiety surrounding their procedure (for the purposes of our study). In the article by Hasen et al, they found that conscious sedation with midazolam and fentanyl has relatively equivalent patient satisfaction and overall experience as a deep sedation using propofol. In their study all operative and post-operative outcome of pain, anxiety and vomiting were similar in the two groups except for immediate post-operative nausea which was higher in the group that received sedation with a propofol infusion (Hasen et al. 2003). In our study we did not find any significant differences in recall of the procedure between cannabis users and non-cannabis users.

4.5 Monitoring Sedation

There is no gold standard clinical scale or instrument for assessing sedation level. An ideal scale would include multiple easily discriminated levels and be suitable for use with any individual or combination sedative agent. Validated scales which exist for measuring

sedation levels in critical care patients are not suitable or as applicable to procedural sedation in an outpatient setting. Common outcomes typically used include achieved sedation level, use of alternative or additional sedatives (i.e., rescue medications), patient and clinician satisfaction, pain, recall, time to recovery and time to discharge (Williams et al. 2016).

In this study, we monitored sedation according to ASA continuum of depth of sedation. The levels of sedation and corresponding descriptions are approved by the ASA House of Delegates and therefore are assumed to have content validity, however no formal psychometric testing of the continuum is found in the literature (Williams et al. 2016). The ASA guidelines define moderate sedation and analgesia as a state of drug induced depression of consciousness during which the patient responds purposefully to verbal commands, either alone or with light tactile stimulation. Intervention is not required to maintain a patent airway, spontaneous ventilation is adequate, and cardiovascular function is maintained (Gross 2002). For most practitioners, this is an ideal state for a patient during a short duration clinical procedure with PSA. Ideal sedation depth varies between practitioners and is typically dependent on the type of procedure, the patient's physiology and habitus, and surgeon preference. The challenge with sedation is that the degree or depth of sedation induced by a given dose of medication varies among individuals. Additionally, although we ordinally classify and categorize depth of sedation in this study, we acknowledge that sedation depth/level fluctuates on a continuum rather than as distinct categories.

Assessment and evaluation of recall, pain, and satisfaction all help to augment the assessment and overall success of sedation. Although existing research would suggest that cannabis users have greater amounts of post-operative pain (Alexander and Joshi 2019) – this was not found in our study. This may be because the previously cited studies were associated with major procedures done under general anaesthesia while this study focuses on a minor outpatient procedure.

4.6 Assessing patient and surgeon satisfaction

In our study, we did not find any significant differences in patient satisfaction scores when comparing cannabis users and non-users, even when users were grouped based on cannabis frequency and quantity. We see similar results in the study by King et al. where patients were phoned 24 hours following EGD and satisfaction levels were found to be similar between cannabis users and non-users (King et al. 2021). However, in their study patient satisfaction was asked as yes/no questions as opposed to a Likert scale. With regards to surgeon satisfaction, we did not see any significant differences in the distribution of surgeon satisfaction between cannabis users and non-users in our study.

In a prospective study by Boviera et al in 2017 they sought to investigate the influence of preoperative anxiety on patient and surgeon satisfaction in patients undergoing dental implant surgery. They used midazolam (0.05mg/kg), fentanyl (1mcg/kg) and propofol at 0.3 to 0.5mg/kg for sedation. Their sedation was monitored by an anaesthesiologist. There were 180 participants in their study. They found that surgeon satisfaction was adequate in 90% of sedations. Although not statistically significant, the 5% of patients who were “too awake and nervous” had higher preoperative levels of anxiety. In our study there were significant differences in the distribution of surgeon satisfaction between moderate and severe, as well as the mild and severe GAD7 groups, however there were no differences in median satisfaction scores between MDAS groups.

With regard to patient satisfaction, a majority of Boviera’s cohort (61.1%) found the procedure to be comfortable or neutral. 29.4% found it slightly uncomfortable, 7.8% found it unpleasant, and 1.7% (n=3) found it traumatic. They found that the greater the preoperative anxiety, the lower the post-operative satisfaction. Additionally, they found that the longer the surgery, the less satisfied patients were (Bovaira et al. 2017). In our study we found that the median patient satisfaction score was significantly lower in in the moderate GAD7 group compared to the mild GAD7 anxiety group, however not between any other groups. There were no differences across MDAS groups. There were no significant differences in length of surgery between our two groups. We did not find any significant correlation between length of surgery and patient satisfaction in our study.

4.7 Adverse effects

In this study we considered adverse effects as "cardiac or respiratory event while in the hospital defined by requiring a pause or termination of the procedure (i.e., bag-mask ventilation, artificial airway insertion, cardiopulmonary resuscitation, defibrillation), administration of rescue medication, elevation in level of care, and/or unplanned admission to the hospital" (King et al. 2021). There were no adverse events in this study. This is generally in keeping with multiple other studies that demonstrate the safety of procedural sedation in the OMFS setting (Wiemer et al. 2021; Christensen et al. 2019). It is also of note that all participants in our study were young and healthy with no significant medical comorbidities.

4.8 Study Limitations

While the results of this study are strengthened by a large number of participants and a homogenous group there are some limitations. Cannabis use is self-reported, and this introduces inherent limitations in accuracy of information when relying solely on patient recall. Stigma surrounding cannabis use, and dependence on patient recall limits validity to some extent. There is always a possibility of inaccurate information as some patients (e.g., teenagers brought to appointment by parents/guardians) may not feel comfortable disclosing their use or may fill out the form dishonestly. We also noticed anecdotally during recruitment that a number of patients who seemed to be significantly anxious about the procedure chose not to participate in the study. This could certainly skew some of our results with regards to distribution of anxiety levels. Retention is always an issue with survey-based research. Although post-operative forms were returned conveniently via text message there were still a number of participants who did not return their forms or returned them filled out incompletely. With regards to analysis, we arbitrarily grouped patients in our sample into low, medium and high groups based on reported frequency and quantity of cannabis use. This grouping was based on our population but could certainly vary in a different population sample. Assessing the relationship between

cannabis use and sedation is complex and fraught with confounders. Much of the existing literature is made up of retrospective study designs, with small sample sizes and a purely binary assessment of cannabis use. We attempted to overcome some of these limitations by designing a prospective study, with an appropriate sample size, assessing a homogenous surgical procedure and taking cannabis quantity and frequency into account.

Chapter 5: Conclusion

Cannabis use is common, and its effects on procedural sedation are poorly studied. This study was unable to demonstrate any significant differences when comparing cannabis users and non-cannabis users undergoing extraction of 3rd molar teeth with procedural sedation using midazolam, fentanyl and ketamine. There were no statistically or clinically significant differences found in the amount of sedative medication received or depth of sedation achieved. Cannabis use does not appear to impact whether or not ketamine will be administered. Sedation practices and practitioner preference seems to play a bigger role in the administration of ketamine as an adjunct. There were also no statistically significant differences in surgeon or patient satisfaction when comparing cannabis users with non-cannabis users. However, we did find some minor differences in satisfaction when we grouped patients based on their anxiety levels. Overall, cannabis use did not seem to affect the overall quality or safety of sedation in this cohort of patients. Future studies can examine the effect of cannabis use on different sedation protocols e.g., using propofol. Despite these findings, elucidation of cannabis use history still remains an important aspect of a comprehensive social history and pre-operative assessment.

Appendix A

ASA Continuum of depth of sedation

	MINIMAL SEDATION ANXIOLYSIS	MODERATE SEDATION/ ANALGESIA	DEEP SEDATION/ ANALGESIA	GENERAL ANESTHESIA
RESPONSIVENESS	Normal response to verbal stimulation	Purposeful** response to verbal or tactile stimulation	Purposeful** response following repeated or painful stimulation	Unarousable even with painful stimulus
AIRWAY	Unaffected	No intervention required	Intervention may be required	Intervention often required
SPONTANEOUS VENTILATION	Unaffected	Adequate	May be inadequate	Frequently inadequate
CARDIAC FUNCTION	Unaffected	Usually maintained	Usually maintained	May be impaired

** Reflex withdrawal from painful stimuli is not considered a purposeful response

Appendix B

Tooth Extraction Difficulty Scale

Tooth Difficulty Grade	Procedural description
1	**Simple Extraction, no incision**
2	**Simple extraction, with incision**
3	**Incision + bone removal**
4	**Incision + bone removal + tooth sectioning**

Appendix C

CANNABIS STUDY PRE-OPERATIVE SURVEY

Date of appointment: _____ Patient#: _____

Age: _____ Weight: _____

Education level *(please circle highest completed)*

Some high school High school diploma Some college/university

Trade School Undergraduate/College degree Graduate/Professional degree

Thank you for taking some time to fill out this pre-operative survey for the study titled "***A single center prospective evaluation on the impact of cannabis use on procedural sedation anesthesia for oral and maxillofacial surgery procedures".***

Please note that this form is **ANONYMOUS**. We do NOT collect any identifying information on this form such as your name or date of birth.

It is very important that you fill out the following form as accurately as you can. If you require assistance with completing the form, please ask to speak to a research assistant or your surgeon.

There are 3 sections to this form

1 – Cannabis use
2 – Use of other substances
3 – Anxiety

This form will take you approximately **10 - 15 minutes** to complete.

Part 1: Cannabis Use (DFAQ-CU Inventory)

Instructions: Please read each of the following questions and mark the response alternative that best describes your use of cannabis. *Note that the term cannabis is being used to refer to marijuana, cannabis concentrates, and cannabis-infused edibles.*

1. Have you ever used cannabis?
   0 = No
   1 = Yes

If response* *= 0 (NO),*** *then skip to end of questionnaire*

2. Which of the following best captures when you last used cannabis?

1 = over a year ago
2 = 9 – 12 months ago
3 = 6 – 9 months ago
4 = 3 – 6 months ago
5 = 1 – 3 months ago
6 = less than 1 month ago
7 = last week
8 = this week
9 = yesterday
10 = today*
11 = I am currently high*

**If response = 10 (today) or 11 (I am currently high) then answer 2b below*

2b. How high are you right now?
   0 = I am not at all high
   1 = I am a little bit high
   2 = I am moderately high
   3 = I am very high
   4 = I am extremely high

3. Which of the following best captures the average frequency you currently use cannabis?

0 = I do not use cannabis
1 = less than once a year
2 = once a year
3 = once every 3-6 months (2-4 times/yr))
4 = once every 2 months (6 times/yr)
5 = once a month (12 times/yr)
6 = 2 – 3 times a month
7 = once a week
8 = twice a week
9 = 3 – 4 times a week
10 = 5 – 6 times a week
11 = once a day
12 = more than once a day

4. Which of the following best captures how long you have been using cannabis **at this frequency?**

1 = less than 1 month
2 = 1 – 3 months
3 = 3 – 6 months
4 = 6 – 9 months
5 = 9 – 12 months
6 = 1 – 2 years
7 = 2 – 3 years
8 = 3 – 5 years
9 = 5 – 10 years
10 = 10 – 15 years
11 = 15 – 20 years
12 = more than 20 years

5. Before the period of time you indicated above, how frequently did you use cannabis?

0 = I did not use cannabis
1 = less than once a year
2 = once a year
3 = once every 3-6 months (2-4 times/yr.)
4 = once every 2 months (6 times/yr.)
5 = once a month
6 = 2 – 3 times a month
7 = once a week
8 = twice a week
9 = 3 – 4 times a week
10 = 5 – 6 times a week
11 = once a day
12 = more than once a day

6. How many days of the past week did you use cannabis?

0 = 0 days
1 = 1 day
2 = 2 days
3 = 3 days
4 = 4 days
5 = 5 days
6 = 6 days
7 = 7 days

7. Approximately how many days of the past month did you use cannabis? _____

8. Which of the following best captures the number of times you have used cannabis in your entire life?

1 = 1 – 5 times in my life
2 = 6 – 10 times in my life
3 = 11 – 50 times in my life
4 = 51 –100 times in my life
5 = 101 – 500 times in my life
6 = 501 – 1000 times in my life
7 = 1001 – 2000 times in my life
8 = 2001 – 5000 times in my life
9 = 5001 – 10,000 times in my life
10 = More than 10,000 times in my life

9. Which of the following best captures your pattern of cannabis use throughout the week?

0 = I do not use cannabis at all
1 = I only use cannabis on weekends
2 = I only use cannabis on weekdays
3 = I use cannabis on weekends and weekdays

10. How many hours after waking up do you typically first use cannabis?

0 = I do not use cannabis at all
1 = 12 – 18 hours after waking up
2 = 9 – 12 hours after waking up
3 = 6 – 9 hours after waking up
4 = 3 – 6 hours after waking up
5 = 1 – 3 hours after waking up
6 = within 1 hour of waking up
7 = within ½ hour of waking up
8 = immediately upon waking up

11. How many times a day, on a typical weekday, do you use cannabis? _____

12. How many times a day, on a typical weekend, do you use cannabis? _____

13. What is the primary method you use to ingest cannabis?

0 = I do not use cannabis
1 = Joints
2 = Blunts (cigar sized joints)
3 = Hand pipe
4 = Bong (water pipe)
5 = Hookah

6 = Vaporizer (e.g., Volcano, Vape pen)
7 = Edibles
8 = Other _____

14. Which of the following other methods to ingest cannabis do you use **regularly** (at least 25% of the time use you cannabis)? [Mark all that apply]

0 = None
1 = Joints
2 = Blunts (cigar sized joints)
3 = Hand pipe
4 = Bong (water pipe)
5 = Hookah
6 = Vaporizer (e.g., Volcano, Vape pen)
7 = Edibles
8 = Other _____

15. What is the primary form of cannabis you use?

0 = None****
A = Marijuana***
B = Concentrates (e.g., Oil, Wax, Shatter, Butane Hash Oil, Dabs)**
C = Edibles*
D = Other_____

16. What other forms of cannabis do you use **regularly** (at least 25% of the time you use cannabis)? [Mark all that apply]

0 = None****
A = Marijuana***
B = Concentrates (e.g., Oil, Wax, Shatter, Butane Hash Oil, Dabs)**
C = Edibles*
D = Other_____

*****If response to questions 15 and 16 = 0 (None) then skip to question 29*
****If responses to questions 15 or 16 = A (Marijuana) then answer questions 17-21*
***If responses to question 15 or 16 = B (Concentrates) then answer questions 22-26*
**If responses to question 15 or 16 = C (Edibles) then answer question 27*
Note: If you use more than one form of cannabis then complete all of the associated questions listed above.

****If responses to questions 15 or 16 = A (Marijuana) then answer questions 17-21 below.*

Please use the image below to refer to various quantities of marijuana. The image is not to scale; the dollar bill is included to help provide size perspective.

For questions 17 to 19 below, clearly indicate the number of grams of marijuana you use with a number between 0 – 100. Do NOT include other forms of cannabis you may use (such as concentrates). You may use up to 3 decimals to indicate amounts under 1 gram.

Note: 1/8 of a gram = 0.125 grams, ¼ of a gram = 0.25 grams, ½ of a gram = 0.5 grams, ¾ of a gram = 0.75 grams. 1/8 of a ounce = 3.5 grams, ¼ of an ounce = 7 grams, ½ ounce = 14 grams, 1 ounce = 28 grams

17. In a typical session, how much marijuana do you personally use? _____

18. On a typical day you use marijuana, how much do you personally use? _____

19. In a typical week you use marijuana, how much marijuana do you personally use? _____

20. On a typical day you use marijuana, how many sessions do you have? _____

21. What is the average THC content of the marijuana you typically use? Leave blank if you do not know.

1 = 0 – 4%
2 = 5 – 9%
3 = 10 – 14%
4 = 15 – 19%
5 = 20 – 24%
6 = 25 – 30%
7 = greater than 30%

***If response to questions 15 or 16 = B (Concentrates) then answer questions 22-26 below*

22. In a typical session you use cannabis concentrates, how many hits do you personally take? __

23. On a typical day you use cannabis concentrates, how many hits do you personally take? ____

24. How many hits of cannabis concentrates did you personally take yesterday? _____

25. On a typical day you use cannabis concentrates, how many sessions do you have? _____

26. What is the average THC content of the concentrates you typically use? Leave blank if you do not know.

1 = 0 – 9%
2 = 10 – 19%
3 = 20 – 29%
4 = 30 – 39%
5 = 40 – 49%
6 = 50 – 59%
7 = 60 – 69%
8 = 70 – 79%
9 = 80 – 90%
10 = greater than 90%

***If response to questions 15 or 16 = C (Edibles) then answer question 27 below*

27. When you eat edibles how many milligrams of THC do you personally ingest in a typical session? _____

28. What is your current age? _____

29. How many years in total have you used cannabis? _____

30. How old were you when you FIRST tried cannabis? _____

31. Has there been any time in your life when you used cannabis regularly (2 or more times per month for 6 months or longer)?

0 = No
1 = Yes*

**If response = 1 (Yes) then answer questions 31b and 31c below*

31b. How old were you when you FIRST STARTED using cannabis regularly (2 or more times/month)? _____

31c. Has there been any time in your life when you used cannabis on a daily or near daily basis for 6 months or longer?

0 = No
1 = Yes*

**If response = 1 (Yes) then answer question 31ci below*

31ci. How old were you when you FIRST STARTED using cannabis on a daily or near daily basis? _____

32. Which of the following best captures the average frequency that you used cannabis before the age of 16?

0 = more than once a day
1 = once a day
2 = 5 – 6 times a week
3 = 3 – 4 times a week
4 = twice a week
5 = once a week
6 = 2 – 3 times a month
7 = once a month
8 = once every 2 months (6 times/yr.)
9 = once every 3-6 months (2-4 times/yr.)
10 = once a year
11 = less than once a year
12 = never

33. Do you have a physician's recommendation to use cannabis for medicinal purposes?

0 = No
1 = Yes*
2 = Yes, but I use it for both medicinal and recreational purposes*

**If response = 1 or 2 (Yes) then answer questions 33b and 33c*

33b. Which medical condition(s) do you use cannabis for?

_____

33c. What percentage of the time do you use cannabis for recreational (rather than medicinal) purposes? _____

Part 2: Use of other substances

How much alcohol do you CURRENTLY drink during an average week?

0 unit/week 1- 5 units/week 6-14 units/week >15 units/week

1 unit =

How many cigarettes do you CURRENTLY smoke during an average day?

0 cigarettes/day 1-5/day 6-10/day 10-20/day More than 1 pack/day

Have you used any other recreational substances within the past 6 months? For example: cocaine, heroin, ecstasy, MDMA, methamphetamines etc? *If yes, please name the drug estimate how often you've used over the past 6 months.*

What about recreational use of prescription drugs such as opioids? (e.g., codeine, morphine, hydromorphone) or benzodiazepines (e.g. lorazepam, diazepam)? *If yes, please name the drug estimate how often you've used over the past 6 months.*

Part 3a: GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Add the score for each column	+	+	+	
Total Score *(add your column scores)* =				

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all _____

Somewhat difficult _____

Very difficult _____

Extremely difficult _____

Part 3b: Modified Dental Anxiety Scale

CAN YOU TELL US HOW ANXIOUS YOU GET, IF AT ALL,WITH YOUR DENTAL VISIT?

PLEASE INDICATE BY INSERTING 'X' IN THE APPROPRIATE BOX

1. **If you went to your Dentist for TREATMENT TOMORROW, how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

2. **If you were sitting in the WAITING ROOM (waiting for treatment), how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

3. **If you were about to have a TOOTH DRILLED, how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

4. **If you were about to have your TEETH SCALED AND POLISHED, how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

5. **If you were about to have a LOCAL ANAESTHETIC INJECTION in your gum, above an upper back tooth, how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely* Anxious ☐

Appendix D

CANNABIS STUDY – SURGEON'S POST OP

Date of surgery: _____ Patient#: _____

Age: _____ Weight: _____

How much sedative medication do you predict this patient will require?

Please rate the extent of surgery per tooth:
(Consider also the difficulty of removal, duration of surgery and patient cooperation)

Tooth: 1-8: _____
2-8: _____
3-8: _____
4-8: _____

Extent of surgery scale:
1= Simple (no incision)
2 =Simple (with incision)
3= Incision + Bone removal
4 = Incision + Bone removal + Tooth

Surgery Start time: _____ (measured at time of giving LA)
Surgery End time: _____ (measured at time of last suture/throat pack removal)

Surgeon satisfaction:
(consider the entire procedure experience including sedation, administration of local anaesthesia, and the surgery itself)

Level of Satisfaction *(circle one)*

1. Very satisfied
2. Satisfied
3. Neutral
4. Unsatisfied
5. Very unsatisfied

How much sedative medication did you give this patient?

T 0	t+5	t+10	t+15	t+20	t+25	t+30	t+35	t+40	t+45

Surgeons additional remarks:

CANNABIS STUDY – PATIENT'S POST OP

Modified questionnaire (adapted from Hasen et al.) *to be completed just prior to discharge from the recovery room*

Please answer YES or NO to the following 5 questions:

1. Do you remember entering the operating room?

2. Do you remember the events of the procedure?

3. Do you remember any unpleasant experiences or emotions during the procedure?

4. Do you remember having pain during the procedure?

5. Were you anxious during the procedure?

Please estimate your anxiety **DURING THE PROCEDURE** on a scale of 0 to 10
(0 being no anxiety at all and 10 being extremely anxious)

0	1	2	3	4	5	6	7	8	9	10
None										Worst

Please estimate the severity of pain you have **NOW** on a scale of zero to 10
(0 being "no pain at all" and ten being "worst pain imaginable")

0	1	2	3	4	5	6	7	8	9	10
None										Worst

Appendix E

Patient Take Home Survey (adapted from Cheung et al)

For each time slot below, please indicate the intensity of pain you are experiencing. Please **circle** the most appropriate number.

No Pain **Moderate Pain** **Worst Possible Pain**

Time after surgery:

1) _____ 0 1 2 3 4 5 6 7 8 9 10

2) _____ 0 1 2 3 4 5 6 7 8 9 10

3) _____ 0 1 2 3 4 5 6 7 8 9 10

4) _____ 0 1 2 3 4 5 6 7 8 9 10

5) _____ 0 1 2 3 4 5 6 7 8 9 10

6) _____ 0 1 2 3 4 5 6 7 8 9 10

7) _____ 0 1 2 3 4 5 6 7 8 9 10

8) _____ 0 1 2 3 4 5 6 7 8 9 10

Thank you very much for completing this survey and for your participation in this research study. **Once completed, please do not discard this documen**t. A member of the research team will contact you by phone approximately 72 hours after your surgery to review this document.

Please see reverse side for tracking pain medication use.

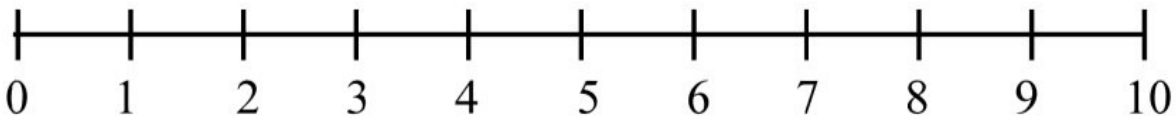
Please indicate what pain medication you used at each time slot, and also indicate the dosage (*in **milligrams** for Ibuprofen and Tylenol (Regular), and in **number of tablets** for Tylenol #3*).
Please check all that apply.

Time after surgery:

1) _____	☐ Ibuprofen Dose: _____	☐ Tylenol (Regular) Dose: _____	☐ Tylenol #3 Tablets: ____	☐ None
2) _____	☐ Ibuprofen Dose: _____	☐ Tylenol (Regular) Dose: _____	☐ Tylenol #3 Tablets: ____	☐ None
3) _____	☐ Ibuprofen Dose: _____	☐ Tylenol (Regular) Dose: _____	☐ Tylenol #3 Tablets: ____	☐ None
4) _____	☐ Ibuprofen Dose: _____	☐ Tylenol (Regular) Dose: _____	☐ Tylenol #3 Tablets: ____	☐ None
5) _____	☐ Ibuprofen Dose: _____	☐ Tylenol (Regular) Dose: _____	☐ Tylenol #3 Tablets: ____	☐ None
6) _____	☐ Ibuprofen Dose: _____	☐ Tylenol (Regular) Dose: _____	☐ Tylenol #3 Tablets: ____	☐ None
7) _____	☐ Ibuprofen Dose: _____	☐ Tylenol (Regular) Dose: _____	☐ Tylenol #3 Tablets: ____	☐ None
8) _____	☐ Ibuprofen Dose: _____	☐ Tylenol (Regular) Dose: _____	☐ Tylenol #3 Tablets: ____	☐ None

Please indicate your overall satisfaction with your surgery (including sedation) and recovery. Please circle the most appropriate number**.**

Not Satisfied **Moderately Satisfied** **Very Satisfied**



This 3rd page will NOT be provided to participants
Phone call on POD#3

- Review pain scores and analgesic medication use

Re-administer modified Hansen post op questionnaire

Please answer YES or NO to the following 5 questions:

6. Do you remember entering the operating room?

7. Do you remember the events of the procedure?

8. Do you remember any unpleasant experiences or emotions during the procedure?

9. Do you remember having pain during the procedure?

10. Were you anxious during the procedure?

Please estimate your anxiety **DURING THE PROCEDURE** on a scale of 0 to 10
(0 being no anxiety at all and 10 being extremely anxious)

0 1 2 3 4 5 6 7 8 9 10
None Worst

Please estimate the severity of pain you have **NOW** on a scale of zero to 10
(0 being "no pain at all" and ten being "worst pain imaginable")

0 1 2 3 4 5 6 7 8 9 10
None Worst

Have you used cannabis since your procedure? YES / NO

Has the amount of cannabis you used:

a) Increased

b) Decreased

c) Stayed the same (no change)

References

1. Alexander, John C., and Girish P. Joshi. 2019. "A Review of the Anesthetic Implications of Marijuana Use." *Baylor University Medical Center Proceedings* 32 (3): 364–71. https://doi.org/10.1080/08998280.2019.1603034.
2. Bovaira, Maite, Alberto Babiloni, María Jovaní, Miguel Peñarrocha-Diago, Sandra González-Lemonnier, and David Peñarrocha-Oltra. 2017. "Preoperative Anxiety and Its Influence on Patient and Surgeon Satisfaction in Patients Receiving Dental Implant Surgeries Performed Under Intravenous Conscious Sedation." *The International Journal of Oral & Maxillofacial Implants* 32 (4): 912–18. https://doi.org/10.11607/jomi.5712.
3. Braidy, Hani F., Prabhjot Singh, and Vincent B. Ziccardi. 2011. "Safety of Deep Sedation in an Urban Oral and Maxillofacial Surgery Training Program." *Journal of Oral and Maxillofacial Surgery* 69 (8): 2112–19. https://doi.org/10.1016/j.joms.2011.04.017.
4. Brownell, Claire. 2019. "Reported Marijuana Use 'higher' at Canadian Universities in 2019: Survey." Maclean's. 2019. https://www.macleans.ca/education/reported-marijuana-use-higher-at-canadian-universities-in-2019-survey/.
5. Cheung, Johnson, Ahmad Alashi, Prosper Koto, James Brady, and Benjamin Davis. 2019. "Does Sub-Anesthetic Ketamine Provide Postoperative Analgesia for Third Molar Surgery?" *Journal of Oral and Maxillofacial Surgery* 77 (12): 2452–64. https://doi.org/10.1016/j.joms.2019.05.009.
6. Christensen, Louis, Lance Svoboda, Joshua Barclay, Brett Springer, Brett Voegele, and Diana Lyu. 2019. "Outcomes With Moderate and Deep Sedation in an Oral and Maxillofacial Surgery Training Program." *Journal of Oral and Maxillofacial Surgery* 77 (12): 2447–51. https://doi.org/10.1016/j.joms.2019.07.007.
7. Cohen, Jacob. 1992. "A Power Primer." *Quantitiave Methods in Psychology* 112 (1): 155–59. https://doi.org/10.1037/0033-2909.112.1.155.

8. Crippa, Jose Alexandre, Antonio Waldo Zuardi, Rocio Martin-Santos, Sagnik Bhattacharyya, Zerrin Atakan, Philip McGuire, and Paolo Fusar-Poli. 2009. “Cannabis and Anxiety: A Critical Review of the Evidence.” *Human Psychopharmacology* 24: 515–23. https://doi.org/10.1002/hup.
9. Cuttler, Carrie, and Alexander Spradlin. 2017. “Measuring Cannabis Consumption: Psychometric Properties of the Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory (DFAQ-CU).” *PLoS ONE* 12 (5): 1–14. https://doi.org/10.1371/journal.pone.0178194.
10. Dobson, Gregory, Matthew A Chong, Lorraine Chow, Alana Flexman, Heather Hurdle, Matthew Kurrek, Claude Laflamme, et al. 2018. “Procedural Sedation: A Position Paper of the Canadian Anesthesiologists’ Society.” *Canadian Journal of Anesthesia/Journal Canadien d’anesthésie* 65 (12): 1372–84. https://doi.org/10.1007/s12630-018-1230-z.
11. Echeverria-Villalobos, Marco, Alexandre B. Todeschini, Nicoleta Stoicea, Juan Fiorda-Diaz, Tristan Weaver, and Sergio D. Bergese. 2019. “Perioperative Care of Cannabis Users: A Comprehensive Review of Pharmacological and Anesthetic Considerations.” *Journal of Clinical Anesthesia* 57 (November 2019): 41–49. https://doi.org/10.1016/j.jclinane.2019.03.011.
12. Flisberg, P., M. J. Paech, T. Shah, T. Ledowski, I. Kurowski, and R. Parsons. 2009. “Induction Dose of Propofol in Patients Using Cannabis.” *European Journal of Anaesthesiology* 26 (3): 192–95. https://doi.org/10.1097/EJA.0b013e328319be59.
13. Goel, Akash, Brandon McGuinness, Naheed K. Jivraj, Duminda N. Wijeysundera, Murray A. Mittleman, Brian T. Bateman, Hance Clarke, Lakshmi P. Kotra, and Karim S. Ladha. 2020. “Cannabis Use Disorder and Perioperative Outcomes in Major Elective Surgeries: A Retrospective Cohort Analysis.” *Anesthesiology* 10: 625–35. https://doi.org/10.1097/ALN.0000000000003067.

14. Gross, Jeffery B. 2002. “Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists.” *Anesthesiology* 96 (4): 1004–17. https://doi.org/10.1097/00000542-200204000-00031.
15. Gürbulak, Bünyamin, Muhammed Zübeyr Üçüncü, Erkan Yardimci, Ebru Kirli, and Filiz Tüzüner. 2018. “Impact of Anxiety on Sedative Medication Dosage in Patients Undergoing Esophagogastroduodenoscopy.” *Wideochirurgia I Inne Techniki Maloinwazyjne* 13 (2): 192–98. https://doi.org/10.5114/wiitm.2018.73594.
16. Harris, Paul A., Robert Taylor, Robert Thielke, Jonathon Payne, Nathaniel Gonzalez, and Jose G. Conde. 2009. “Research Electronic Data Capture (REDCap)-A Metadata-Driven Methodology and Workflow Process for Providing Translational Research Informatics Support.” *Journal of Biomedical Informatics* 42 (2): 377–81. https://doi.org/10.1016/j.jbi.2008.08.010.
17. Hasen, Kent V., Dino Samartzis, Laurie A. Casas, and Thomas A. Mustoe. 2003. “An Outcome Study Comparing Intravenous Sedation with Midazolam/Fentanyl (Conscious Sedation) versus Propofol Infusion (Deep Sedation) for Aesthetic Surgery.” *Plastic and Reconstructive Surgery* 112 (6): 1683–89. https://doi.org/10.1097/01.PRS.0000086363.34535.A4.
18. Humphris, G. M., R. Freeman, J. Campbell, H. Tuutti, and V. D’Souza. 2000. “Further Evidence for the Reliability and Validity of the Modified Dental Anxiety Scale.” *International Dental Journal* 50 (5): 367–70. https://doi.org/10.1111/j.1875-595X.2000.tb00570.x.
19. Humphris, Gerry M., Tom A. Dyer, and Peter G. Robinson. 2009. “The Modified Dental Anxiety Scale: UK General Public Population Norms in 2008 with Further Psychometrics and Effects of Age.” *BMC Oral Health* 9 (1): 1–8. https://doi.org/10.1186/1472-6831-9-20.
20. Huson, Henry B., Tamara Marryshow Granados, and Yvonne Rasko. 2018. “Surgical Considerations of Marijuana Use in Elective Procedures.” *Heliyon* 4 (9): 1–26. https://doi.org/10.1016/j.heliyon.2018.e00779.

21. Kedzior, Karina K., and Lisa T. Laeber. 2014. “A Positive Association between Anxiety Disorders and Cannabis Use or Cannabis Use Disorders in the General Population- a Meta-Analysis of 31 Studies.” *BMC Psychiatry* 14 (1). https://doi.org/10.1186/1471-244X-14-136.
22. King, Daniel D., Scott A. Stewart, Angela Collins-Yoder, Tara Fleckner, and Lori Lyn Price. 2021. “Anesthesia for Patients Who Self-Report Cannabis (Marijuana) Use before Esophagogastroduodenoscopy: A Retrospective Review.” *AANA Journal* 89 (3): 205–12.
23. Ladha, Karim, Varuna Manoo, Ali- Faizan Virji, and Hance Clarke. 2019. “Ladha_2019_The Impact of Perioperative Cannabis Use- A Narrative Scoping Review.Pdf.” *Cananbis and Cannabinoid Research* 4 (4).
24. Pelletier, Louise, Siobhan O’Donnell, Louise McRae, and Jean Grenier. 2017. “The Burden of Generalized Anxiety Disorder in Canada.” *Health Promotion and Chronic Disease Prevention in Canada* 37 (2).
25. Robinson, Sean M., Linda Carter Sobell, Mark B. Sobell, and Gloria I. Leo. 2014. “Reliability of the Timeline Followback for Cocaine, Cannabis, and Cigarette Use.” *Psychology of Addictive Behaviors* 28 (1): 154–62. https://doi.org/10.1037/a0030992.
26. Rotermann, Michelle. 2021. “Looking Back from 2020, How Cannabis Use and Related Behaviours Changed in Canada.” *Health Reports* 32 (4): 1–14. https://doi.org/10.25318/82-003-x202100400001-eng.
27. Sheikh, Nafiz K., and Anterpreet Dua. 2022. *Cannabinoids*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK556062/.
28. Spitzer, Robert L., Kurt Kroenke, Janet B.W. Williams, and Bernd Löwe. 2006. “A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7.” *Archives of Internal Medicine* 166 (10): 1092–97. https://doi.org/10.1001/archinte.166.10.1092.
29. StatisticsCanada. 2019. “Cannabis Stats Hub.” 2019. https://www150.statcan.gc.ca/n1/pub/13-610-x/cannabis-eng.htm.
30. Thakkar, H., A. Mahindajit, D. Taylor, L. Roberts, and J. Cooke. 2017. “Conscious Sedation for Transoesophageal Echocardiography in Cannabis

Users." *Heart, Lung and Circulation* 26: S254. https://doi.org/10.1016/j.hlc.2017.06.484.

31. Tunc, Elif Pak, Deniz Firat, Ozen Dogan Onur, and Vedat Sar. 2005. "Reliability and Validity of the Modified Dental Anxiety Scale (MDAS) in a Turkish Population." *Community Dentistry and Oral Epidemiology* 33 (5): 357–62. https://doi.org/10.1111/j.1600-0528.2005.00229.x.
32. Twardowski, Mark A., Margaret M. Link, and Nicole M. Twardowski. 2019. "Effects of Cannabis Use on Sedation Requirements for Endoscopic Procedures." *Journal of the American Osteopathic Association* 119 (5): 307–11. https://doi.org/10.7556/jaoa.2019.052.
33. Twomey, Conal D. 2017. "Association of Cannabis Use with the Development of Elevated Anxiety Symptoms in the General Population: A Meta-Analysis." *Journal of Epidemiology and Community Health* 71 (8): 811–16. https://doi.org/10.1136/jech-2016-208145.
34. United Nations. 2018. "Global Overview of Drug Demand and Supply." In , 1–60. https://doi.org/10.18356/3a4c2e67-en.
35. Watterson, Rita A., Jeanne V. A. Williams, Dina H. Lavorato, and Scott B. Patten. 2017. "Descriptive Epidemiology of Generalized Anxiety Disorder in Canada." *The Canadian Journal of Psychiatry* 62 (1): 24–29.
36. Wiemer, Steven J., John M. Nathan, Benjamin T. Heggestad, W. Jonathan Fillmore, Christopher F. Viozzi, James M. van Ess, Kevin Arce, and Kyle S. Ettinger. 2021. "Safety of Outpatient Procedural Sedation Administered by Oral and Maxillofacial Surgeons: The Mayo Clinic Experience in 17,634 Sedations (2004 to 2019)." *Journal of Oral and Maxillofacial Surgery* 79 (5): 990–99. https://doi.org/10.1016/j.joms.2020.12.002.
37. Williams, Mark R., Andrew McKeown, Franklin Dexter, James R. Miner, Daniel I. Sessler, John Vargo, Dennis C. Turk, and Robert H. Dworkin. 2016. "Efficacy Outcome Measures for Procedural Sedation Clinical Trials in Adults: An ACTTION Systematic Review." *Anesthesia and Analgesia* 122 (1): 152–70. https://doi.org/10.1213/ANE.0000000000000934.

38. Woo, Matthew, and Christopher N. Andrews. 2019. “Implications of Cannabis Use on Sedation for Endoscopic Procedures.” *Gastrointestinal Endoscopy* 90 (4): 656–58. https://doi.org/10.1016/j.gie.2019.06.005.
39. Yurasek, Ali M., Elizabeth R. Aston, and Jane Metrik. 2017. “Co-Use of Alcohol and Cannabis: A Review.” *Current Addiction Reports* 4 (2): 184–93. https://doi.org/10.1007/s40429-017-0149-8.
40. Zou, Shenglong, and Ujendra Kumar. 2018. “Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System.” *International Journal of Molecular Sciences*. MDPI AG. https://doi.org/10.3390/ijms19030833.