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The use of cannabidiol (CBD) in pain reduction and opioid use after shoulder arthroscopy. A Double-Blind, Randomized Control Study

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The use of cannabidiol (CBD) in pain reduction and opioid use after shoulder arthroscopy. A Double-Blind, Randomized Control Study

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I. PURPOSE OF THE STUDY AND BACKGROUND

Purpose

To evaluate the effects of administering CBD to control post-operative pain in patients undergoing shoulder arthroscopy. Secondly, the purpose will be to evaluate the effectiveness of CBD in comparison with opioid therapy for post-operative pain.

Rationale

Shoulder arthroscopy is one of the commonly performed orthopaedic procedures to treat a variety of conditions, with over 500,000 procedures performed every year. Additionally, new techniques are allowing for more pathologies to be treated arthroscopically. However, post-operative pain is a common complaint, and due to the increasing rise in opioid addiction among orthopaedic patients, management strategies have become increasingly important. As a result of the increasing volume of shoulder arthroscopy performed as an outpatient, alternative pain management solutions to opioid therapy have become of increased importance.

The Endocannabinoid System (ECS) is a neuromodulatory system that has recently emerged as a promising new therapeutic target with many potential applications. The ECS is comprised of the CB1 and CB2 cannabinoid receptors, endogenous cannabinoid ligands known as Endocannabinoids, and the enzymes responsible for the synthesis and degradation of cannabinoids. The ECS is involved in regulating the inflammatory response to injury, as well as modulating pain and thus is a pharmacological target in pain management.

Cannabidiol (CBD) has become a subject of growing interest since Congress passed the 2018 Farm Bill, which legalized Industrial Hemp (Cannabis Sativa plants containing <0.3% THC content) and its derivative cannabinoids, including CBD. CBD is a non-psychotropic cannabinoid that has been reported to exhibit a range of therapeutic properties. It is well tolerated in humans with a low risk of side effects, and has not been shown to interact with, nor potentiate the effects of opioid analgesics. This makes it an attractive target for managing post-operative pain.

However, CBD suffers from poor oral bioavailability (6-11%) due to extensive first pass metabolism via CYP3A4. To mitigate this issue, CBD will be administered in a proprietary Orally Disintegrating Tablet (ODT) provided by Concours Pharmaceuticals®. This formulation allows for transmucosal absorption of CBD via the buccal mucosa in the oral cavity. This delivery method reduces the effective dose of CBD needed to achieve relevant plasma concentrations.

Given the potential risks treating postoperative pain with prolonged opioid use, we are proposing a study to evaluate the effects of CBD as an adjunct to opioid analgesics. Therefore, the purpose of the proposed study is to evaluate the analgesic effects of CBD administered via this ODT to patients that have undergone shoulder arthroscopy, with the goals of reducing post-operative pain and lessening the need for prolonged opioid therapy. Our hypothesis is that CBD will reduce postoperative pain, opioid use and associated side effects like nausea.

Study Design

This will be a multi-center, double-blinded randomized controlled study. The study is comparing postoperative pain, patient satisfaction, and opioid use in two cohorts: patients undergoing

shoulder arthroscopy who receive post-operative CBD and a placebo group. Patients will be asked on postoperative Day 1, 2, 7, and 14 to rate their pain according to the VAS scale. Additionally, opioid consumption, CBD consumption, as well as patient satisfaction will be measured. Patients will be asked in the post-trial period to fill out a questionnaire pertaining to 1-year outcomes. The questionnaire will be in the form of a single online survey including ASES score, VAS score, KJOC Shoulder score, and SANE score.

Rationale for multi-center study:
The second site is essential for this project, for both recruitment and logistical purposes. While NYULOH does have high-volume, a large proportion of these patients will be ineligible due to the exclusion criteria and will not want to participate given that this is a randomized, controlled, double blinded study. Additionally, the second site PI was absolutely instrumental in the conceptualization and the design of this study, as well as securing the necessary funding for it happen. This study would not be feasible without their collaboration. Additionally, the second site PI has an academic appointment here at NYU Langone, and is instrumental in the education of the trainees here at our institution

Primary Objective
The primary objective of the study is to determine if there are any differences in post-operative pain between patients receiving CBD after shoulder arthroscopy compared to patients who do not receive it.

Secondary Objective
Secondary objective of the study is to determine if there are any differences in patient satisfaction, the incidence of opioid induced nausea, and the numbers of opioids and CBD/placebo ODTs consumed by the two patient cohorts.

II. CHARACTERISTICS OF THE RESEARCH POPULATION

Number of Subjects
We will aim to enroll a total of 100 subjects (50 per cohort) as determined by the priori sample size calculator.

Gender of Subjects
Men and women will be included in this study.

Age of Subjects
Subjects included study will be aged 18-75 years, inclusive.

Racial and Ethnic Origin
There are no enrollment restrictions based on race or ethnic origin.

Inclusion Criteria
Patients will be screened for eligibility using the following criteria. All study subjects must meet the following inclusion criteria:

- Patients undergoing an arthroscopic shoulder procedure (rotator cuff repair, decompression, labrum repair)
- Patients ages 18-75, inclusive
- Female patients must be currently practicing effective forms of two types of birth control, which are defined as those, alone or in combination, that result in a low failure rate (less than 1% per year) when used consistently and correctly
- Male patients must be using an effective form of contraception

Exclusion Criteria

Patients meeting the following criteria will be excluded from participation in this study:

- Legally incompetent or mentally impaired (e.g., minors, Alzheimer's subjects, dementia, etc.)
- Younger than 18 years of age
- Older than 75 years of age
- Any patient considered a vulnerable subject: pregnant women or fetuses, children, cognitively impaired adults, prisoners
- History of cannabis abuse or dependence
- History of coagulation abnormalities and thromboembolic disease or current abnormal coagulation test values
- History of stroke or acute coronary syndromes within 3 months before surgery
- Abnormal coagulation profile
- Renal failure (serum creatinine > 250 μmol/L [2.83 mg/dL]) or liver cirrhosis
- Patients with a history of hypersensitivity to Percocet
- Patients that have been on pre-operative opioid management for any reason
- Patients meeting the DSM-V for major psychiatric illness, such as bipolar disorder
- Patients diagnosed with major depression, psychosis, or substance abuse disorder
- Patients with current or a history of suicidal ideation
- Breastfeeding females
- Patients with clinically significant illness, including cardiovascular disorders
- Clinically significant lab abnormalities
- Abnormal LFTs
- Patients with major neurological disorders, such as dementia, Parkinson's disease, cognitive impairment, epilepsy, history of traumatic brain/head injury, or seizures
- Patients with moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C).
- Patients taking moderate or strong inhibitors of CYP3A4 and CYP2C19 (listed below) concomitantly
- Patients taking strong CYP3A4 and CYP2C19 inducers (listed below) concomitantly
- Patients taking substrates of UTG1A9, UTGB17, CYP2A1, CYP2B6, CYP2C8, CYP2C9 and CYP2C19 (listed below) concomitantly

CYP3A4 Strong Inhibitors	Clarithromycin, Telithromycin, Nefazodone, Itraconazole, Ketoconazole, Atazanavir, Darunavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir, Saquinavir, Tipranavir.

CYP3A4 Moderate inhibitors	Amiodarone, Erythromycin, Fluconazole, Miconazole, Diltiazem, Verapamil, Delavirdine, Amprenavir, Fosamprenavir, Conivaptan
CYP2C19 Strong Inhibitors	Fluconazole
CYP2C19 Moderate Inhibitors	Amiodarone, Fluvoxamine, Miconazole, Oxandrolone,
CYP3A4 Inducers	Carbamazepine, Dexamethasone, Ethosuximide, Glucocorticoids, Griseofulvin, Phenytoin, Primidone, Progesterone, Rifabutin, Rifampin, Nafcillin, Nelfinavir, Nevirapine, Oxcarbazene, Phenobarbital, Phenylbutazone, St Johns Wort, Sulfadimidine, Sulfinpyrazone, Troglitazone
CYP2C19 Inducers	Carbamazepine, Enzalutamide, Rifampin
UTG1A9 Substrates	Regorafenib, Acetaminophen, Canagliflozin, Propacetamol, Sorafenib, Indomethacin, Entacapone, Etodolac, Irinotecan, Propofol, Mycophenolic acid, Sulfamethoxazole, Valproic acid, Haloperidol, Zileuton, Flurbiprofen, Ibuprofen, Lumiracoxib, Valdecoxib, Buprenorphine, Nateglinide, Seratrodast, Gavestinel, Ketobemidone, Ambrisentan, Troglitazone, Mycophenolate mofetil, Ezogabine, Tapentadol, Dabigatran etexilate, Oxazepam, Dapagliflozin, Topiroxostat, Enasidenib, Dolutegravir, Ertugliflozin, Artenimol, Fostamatinib, Glasdegib, Diclofenac, Labetalol, Ataluren, Naproxen, Vadimezan, Dexibuprofen, Gemfibrozil, Fenofibrate, Darolutamide, Phenytoin, Formoterol
UTGB17 Substrates	Formoterol, Losartan, Diclofenac, Etodolac, Flurbiprofen, Ibuprofen, Naproxen, Suprofen, Mitiglinide, Zaltoprofen, Ambrisentan, Troglitazone, Morphine, Indomethacin, Mycophenolate mofetil, Ezetimibe, Mycophenolic acid, Vadimezan, Epirubicin, Tapentadol, Pitavastatin, Silodosin, Zidovudine, Lovastatin, Simvastatin, Oxazepam, Carbamazepine, Codeine, Fluvastatin, Valproic acid, Dapagliflozin, Enasidenib, Nalmefene, Acemetacin, Ertugliflozin, Artenimol, Labetalol, Tamoxifen, Carvedilol, Ketorolac, Dabigatran etexilate, Dexibuprofen, Gemfibrozil, Anastrozole, Loxoprofen, Cenobamate
CYP1A2 Substrates	Acetominaphen, Amitriptyline, Clomipramine, Clozapine, Cyclobenzaprine, Doxepin, Duloxetine, estradiol, Fluvoxamine, Halperidol, Imipramine n-deme, mexiletine, nabumentone, Napqi, Naproxen, Olanzapine, Ondansetron, Phenacetin, Perfenidone, Propranolol, Riluzole, Ropivacaine, Rucaparib, Tacrine, Theophylline, Tizanidine, Triamterene, Verapamil, Warfarin, Zileuton
CYP2B6 Substrates	Artemisinin, Buproprion, Cyclophosphamide, Efavirenz, Ifosphamide, Ketamine, Meperidine, Methadone, Nevirapine, Propafol, Selegine, Sorafenib, Tramadol, Velpatasvir
CYP2C8 Substrates	Amodiaquine, Cerivastatin, Paclitaxel, Repaglinide, Selexipag, Sorafenib, Torsemide
CYP2C9 Substrates	Amitriptyline, Capecitabine, Celecoxib, Clopidogrel, Diclofenac, Doxepin, Fluoxetine, Fluoxetine, Fluvastatin, Glibenclamide, Glimepiride, Glipizide, Glyburide, Ibuprofen, Irbesartan, Lesinurad, Lornoxicam, Meloxicam, Nateglinide, Phenytoin-4-oh2, Piroxicam, Rosiglitazone, S-naproxen-nor, S-warfarin1, Suprofen, Tamoxifen, Tolbutamide, Tolbutamide1, Torsemide, Valproic Acid, Venlafaxine, Voriconazole, Zakirlukast
CYP2C19 Substrates	Amitriptyline, Atomoxetine, Brivaracetam, Carisoprodol, Chloramphenicol, Citaprolam, Clomipramine, Clopidogrel, Cyclophosphamide, Diazepam-nor, Doxepin, Escritolapram, Esomeprazole, Flibanserin, Hexobarbital, Imipramine-n-deme, Indomethacin, Labetalol, Lansoprazole, Moclobemide, Nelfinavir, Nilutamide, Omeprazole, Pantoprazole, Phenobarbitone, Phenytoin(o), Primidone, Progesterone, Proguanil, Propranolol, r-Methobarbital, r-Warfarin, s-Mephytoin, Suvorexant, Teniposide, Venlafaxine, Vorconizole

Vulnerable Subjects
We do not intend to enroll vulnerable subjects.

Subject withdrawal criteria.
Patients are free to withdraw of their own volition at any time from the study before or after surgery.

A subject may be withdrawn from the study at any time if the Investigator determines that an illness, injury, complication or adverse event requires immediate study removal, whether or not considered by the Investigator to be related to the study drug.

Subjects found to have elevated liver transaminase and/or bilirubin levels on Day 2, or Day 7 will be removed from the study.

III. METHODS AND PROCEDURES

Methods and Procedures
Patients indicated and scheduled for a shoulder arthroscopy will be identified from faculty surgeon case logs at the NYU Langone Health, Langone Orthopedic Hospital Sports Medicine Division. After informed consent is obtained, a chart review of patients' medications and past medical histories will be performed based on their electronic medical records to identify any current pain medications or exclusion criteria. In order to maintain the blind, another surgeon not involved in the procedure will randomize the patient to one of two cohorts using REDCap. Both surgeons are members of the study team. The randomization will be block randomization, via a computer generator on RedCap.

- Cohort 1: CBD ODTs to be administered with routine post-operative pain management regimen
- Cohort 2: Will not receive CBD; but a visually indistinguishable placebo ODT instead.

The resident physician, physician assistant, anesthesiologist, surgeon and study team members will remain blinded. Additionally, all patients will receive a traditional upper extremity interscalene block as per routine.

Immediate post-operative management will not be affected by this study. All patients will receive a standardized regimen of Percocet for pain management, which is standard of care post-operative treatment. Patients will receive a standard dose of 5/325mg and be discharged with 30 tabs and will be instructed to take 1-2 tablets, as needed, every 4-6 hours.

Additionally, patients will be randomized into one of two cohorts. The first cohort will receive a 25mg CBD ODT, every 4-6 hours as needed, with instructions to take two CBD ODTs if they weigh more than 80 kg (total maximum of 50mg per dose every 4-6 hours as needed). Cohort 2 will receive the same instructions, but with the placebo ODT instead. The dose of 25mg for subjects weighing >/= 80kg and 50mg for subjects weighing more than 80kg was selected based on recommendations from the FDA.

All subjects will be required to refrain from use of THC, or other cannabis-related products for the duration of the study.

Information to be recorded pre-operatively includes age, sex, height, weight, BMI, and American Society of Anesthesiology (ASA) classification. As well as baseline levels of complete blood count (CBC), chemistry profile, liver enzymes, gamma glutamate transferase (GGT), electrocardiogram, urine analysis, 12-panel urine drug test, and a urine pregnancy test.

Intra-operative information will also be recorded, including operative time, procedure, number of anchors, and complications. Patients will subsequently be stratified in different subgroups based on the procedure performed.

Pain severity scores at rest will be assessed by use of a visual analog scale (VAS; 0 = no pain, 10 = worst pain imaginable) at 6, 24, and 48 hours as well as 7 days and 14 days after surgery. Patients will record their satisfaction with their management, on a 0-10 scale, 24 hours, 2 days and 7 days, and 14 days after surgery.

Additionally, any nausea experienced by the patients will be recorded by use of a VAS (0 = no nausea, 10 = worst nausea imaginable) at 2 days, 7 days and 14 days after surgery.

Percocet consumption will be recorded at 24 hours, 2 days and 7 days, and 14 days after surgery. Additionally, subjects will be asked to record the dates and times of CBD consumption.

Liver function tests, consisting of the standard hepatic panel, and including serum transaminase and bilirubin levels will be administered for study purposes on Day 7 and Day 14 after surgery.

Incidence of CBD-related side effects will be noted. Time to discharge from the post-anesthesia care unit (PACU) and time to discharge from the hospital will be recorded. Patients will be in the study a duration of 14 days and will be asked to fill out one online survey at the 1-year mark to determine the long-term effects that may be associated with using CBD.

In order to maintain the blinding, all data, including pain severity scores, side effects, opioid and CBD consumption, will be collected by the resident physician or physician assistant However, if needed, in the event of an emergency or SAE, the unblinded surgeon responsible for randomization will be able to confirm whether a subject has been assigned to receive CBD or placebo.

Study Time Points	
Day 0 - Day of Surgery	Baseline suicidality assessment (C-SSRS), Record Pain (6hrs and 24 hrs), Record clinical data during surgery and post op including time to discharge from PACU and time to discharge from the hospital, monitor for AEs
Day 1	Record Pain, Opioid consumption, CBD consumption, Satisfaction, monitor for AEs

Day 2	Record Pain, Opioid consumption, CBD consumption, Satisfaction, Nausea, monitor for AEs
Day 7 - Standard of Care Visit 1	Record Pain, Opioid consumption, CBD consumption, Satisfaction, Nausea Liver Function Tests - Non-standard of care, C-SSRS, Drug accountability, monitor for AEs
Day 14 - Standard of Care Visit 2	Record Pain, Opioid consumption, CBD consumption, Satisfaction, Nausea, monitor for AEs
Month 12 – Post-Trial Survey	Liver Function Tests - Non-standard of care, C-SSRS, Drug accountability and review of completed subject diary, monitor for AEs Record Pain; Complete ASES, KJOC Shoulder, and SANE assessment

Data Analysis and Statistical Plan

Our power analysis was based on the literature of post-operative pain control following shoulder arthroscopy. Under the assumption of a VAS of 3 and 1.8 for the control and CBD respectively, with a SD of 2: Group sample sizes of 45 in each group would achieve 80% power to reject the null hypothesis of equal means when the population mean difference between Control and CBD is $\mu 1 - \mu 2 = 3.0 - 1.8 = 1.2$ with a standard deviation for both groups of 2.0 at a significance level (alpha) of 0.05 using a two-sided two-sample equal-variance t-test. Thus, to allow for a 5% drop-out at 14-day follow-up, 100 patients would be required to enroll.

For descriptive statistics, categorical values will be described by percentages, and continuous variables will be described by means with standard deviations. To compare primary and secondary outcomes, a T-Test will be performed, with a p-value of 0.05 set to determine statistical significance. Testing will be performed to determine whether sample distribution is normal; if not, non-parametric testing will be performed.

Analysis of the Primary Efficacy Endpoint(s)

To compare primary outcomes (VAS score), a T-Test test will be performed, with a p-value of 0.05 set to determine statistical significance. Testing will be performed to determine whether sample distribution is normal; if not, non-parametric testing will be performed. Patients who do not complete at least 80% of follow-up visits will be considered lost to follow-up and will not be included in the analysis.

Analysis of the Secondary Endpoint(s)

To compare secondary outcomes (opioid use, satisfaction), complication rates), a T-Test will be performed, with a p-value of 0.05 set to determine statistical significance. For categorical variables, a Fisher's exact test will be performed. Testing will be performed to determine whether sample distribution is normal; if not, non-parametric testing will be performed. Patients who do not complete at least 80% of follow-up visits will be considered lost to follow-up and will not be included in the analysis.

Data and Safety Monitoring Plan

Data monitoring will be done by Dr. Alaia, the principal investigator will oversee the conduct of the study. He will review enrollment, accumulated study data, including pain VAS scores, Percocet consumption VAS scores, liver function test results, adverse events, protocol deviations, study compliance and data accuracy quarterly.

He will monitor whether or not:

1. Collection and storage of patient data was performed in a sensitive and secure manner, as defined in the informed consent form and protocol, ensuring information is stored on REDCap.
2. All study activities were conducted with primary emphasis on patient care and wellbeing, ensuring the patients are not in discomfort and have an abnormally high VAS following the surgery.
3. If there were any adverse events, and if so were addressed appropriately and per protocol
4. The risk/benefit to patients has remained the same throughout the course of the study.

The study will be stopped if there are unexpected severe adverse events in more than one patient. Adverse Events (AEs) will be defined as negative reactions to the CBD treatment. We will submit summaries of data and safety monitoring to the IRB annually. De-identified primary and secondary outcome data will be shared by the participating site PI quarterly, and they will notify the host site PI (MJA) upon each enrolled patient.

The participating site PI will be responsible for verifying data accuracy and compliance at their site, and notifying the host site PI (MJA) of any protocol deviations. The plan for data safety monitoring in the second site will be for the PI there to perform a similar quarterly review of safety (including any adverse response to CBD, LFTs, and C-SSRS), and provide both the raw cumulative data and a summary of the adverse events and outcomes of the safety monitoring to Dr. Alaia. Additionally, there will be a quarterly teleconference between the site PIs to discuss and the affiliate site will be monitored by the IRB at their hospital as well, with NYU being the lead institution.

Data Storage and Confidentiality

Data recorded from this study will be organized in REDCap. Participant medical information will only be available to the principal investigator and research staff as necessary for data analysis. All patient health information will be de-identified and assigned a code. Information linking participants' names, social security numbers and medical record numbers will be stored in a secure location separate from the medical information. No data will be shared to anyone outside of the study team.

Adverse Event Reporting

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- <u>Related or possibly related to participation in the research</u> (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

The clinician's assessment of an AE's relationship to study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- ***Related*** *– The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.*
- ***Not Related*** *– There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.*

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- ***Definitely Related*** *– There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.*
- ***Probably Related*** *– There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.*
- ***Possibly Related*** *– There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.*
- ***Unlikely to be related*** *– A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).*

Not Related *– The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.*

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a

study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the PI of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The PI should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Information about any breach of confidentiality will be documented in the electronic data collection system and/or on the paper CRFs, as appropriate. It will be the responsibility of the Principal Investigator to report any Serious Adverse Event (SAE) that occurs during the course of the prospective data collection to the Institutional Review Board (IRB) within the timeframe specified by NYU SoM.

Notifying the FDA

The PI (sponsor-investigator) is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND safety reports.

The following describes the IND safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days*** *(via telephone or facsimile report)*
  Any study event that is:
  - associated with the use of the study drug
  - unexpected,
  - fatal or life-threatening

- ***Within 15 calendar days*** *(via written report)*
  Any study event that is:
  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening

    -or-
  - a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

  Any finding from tests in laboratory animals that:
  - suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The following describes the IDE safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 10 working days*** *(via telephone or facsimile report)*
  Any study event that is:
  - associated with the use of the study device, and
  - unanticipated,

  regardless of the seriousness of the event.

- ***Within 5 working days*** *(via written report)*
  - Protocol deviation to protect the life of the subject in emergency
  - Withdrawal of IRB approval
  - Lack of informed consent

Additional reporting requirements
The sponsor-investigator is also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process
Adverse events may be submitted on FDA Form 3500A (MEDWATCH Form) or in a narrative format meeting FDA requirements. The contact information for submitting IND safety reports is noted below: Rigoberto Roca,

Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
5901-B Ammendale Road, Beltsville, MD 20705-1266
Phone: (301) 796-2280
Fax: (301) 796-9723

Notifying participating sites: The study PI will notify the participating sites within 24 hours.

IV. RISK/BENEFIT ASSESSMENT

Risk

This study involves risk of medication side effects as well as a breach of confidentiality. Oral CBD can cause the following side effects:

- Fatigue
- Diarrhea
- Changes in appetite/weight

Rare side effects include:

- Unusual tiredness or weakness
- Hepatic toxicity
- Testicular toxicity was observed in a preclinical study where mice were given CBD, although this has not been observed in clinical studies.

Protection against Risks

Patients will be screened for any contraindication to CBD or Percocet use, including Cannabis dependence. Patients will receive baseline assessments for history and physical, including psychiatric exam, complete blood count (CBC), chemistry profile, liver enzymes, gamma glutamate transferase (GGT), electrocardiogram, urine analysis, 12-panel urine drug test, and urine pregnancy test.

Planned safety monitoring during the duration of the study will include monitoring for liver function, laboratory abnormalities and suicidality assessments throughout the study and for follow-up visits. Liver function tests, including serum transaminase and bilirubin, will be obtained on Day 2, Day 7, and Day 14. Elevated liver transaminase and bilirubin levels will be grounds for immediate removal from the study. C-SSRS will be assessed at baseline, Day 7, and Day 14 by the surgeon. Although CBD does not increase risk of suicidal ideation and behavior, this is being done in accordance with FDA recommendation for clinical trials involving drugs with CNS activity. If subjects are found to pose a risk to themselves, standard institutional procedures will be followed to refer subjects for appropriate care, including emergency care if needed.

The maximum CBD dose given to any subject will be less than 2mg/kg/day, well below levels associated with any hepatic risk (Iffland & Grotenherman, 2017).

CBD was not deemed to increase the severity of Percocet's opioid toxicities, as they act on different pathways. There is a potential for CBD to work in the same C450 cytochrome pathway as the acetaminophen, and thus no additional acetaminophen is to be prescribed outside of this, which is well below the maximum prescribing threshold of 4g per day.

The patients will stay in the recovery unit until cleared for discharge by an anesthesiologist. They will be prohibited from driving or operating a motor vehicle for 2 hours following their first dose of the study drug.

Patients will be educated on the importance of keeping the study drug in a safe place at all times and ensure it is not accessible to anyone other than themselves.

Additionally, all patients will be de-identified and given a code. Information linking the patient codes to the participants' names and medical record numbers will be stored in a secure location separate from the medical information. Access to the information linking the linkage codes with participant identifiers shall be restricted.

Potential Benefits to the Subjects

Patients may experience less pain post-operatively, and may require less narcotics use, which has a steeper side-effect profile. However, these benefits cannot be guaranteed.

Additionally, it is the hope of the research team that results of this study will benefit future patients and their physicians by providing more information regarding the use of CBD after surgery. This will allow for a more open and informed dialogue, and possibly a change standard of care treatment.

Drug Shipment, Storage, Dispensing, Accountability, and Destruction: The CBD and matching placebo ODTs will be shipped to the NYU Langone Health Research Pharmacy in bottles labeled CBD or Placebo 25mg ODT with the subject #, date of dispensing and # of ODTs. Subjects will be dispensed enough 25mg ODTs for a maximum dose of every 4-6 hours for 14 days (subjects weighing over 80kg will be dispensed twice the amount of ODTs to account for 2 ODTs per dose (a total of 50mg CBD or placebo per dose). Subjects will be reminded that they should take the CBD or placebo ODT orally, every 4-6 hours, as needed for 14 days. The dates and times the ODT is taken are to be recorded in the subject's diary. Subjects will need to bring the drug with them (including empty and unused bottles) to the site for their Day 7 and Day 14 visits for accountability. Any remaining drug will be collected at Day 14 and destroyed per NYULH Research Pharmacy SOP.

V. INVESTIGATOR'S QUALIFICATIONS AND EXPERIENCE

The CV, medical license, and human subjects' tutorial completion report are attached for all investigators who are participating in this study. All research personnel have medical research experience and are qualified to participate in this quality study. Most importantly, staff have been properly educated and certified with CITI training to conduct research in a matter that will maintain full patient confidentiality. The research coordinator for this study is trained in GCP

principles and practices and will be responsible for compliance with GCP guidelines for all study investigators and research assistants.

VI. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT/ASSENT

Method of Subject Identification and Recruitment

Appropriate patients, who meet all of the inclusion criteria and none of the exclusion criteria, who require a shoulder arthroscopy, will be identified from the clinical offices of the investigator surgeons.

Process of Consent

Written consent will be obtained from subjects who are eligible candidates for shoulder arthroscopy based upon their medical condition (as determined by their physician). The consent process will take place during the office visit when it is determined necessary to perform the procedure—at which time the investigator has determined subject's voluntary participation has been upheld. Subjects will be informed about the study and the intended purpose. They will be given the opportunity to ask questions and receive thorough explanations. They will be made aware of the possible risks and anticipated benefits. They will also be informed of alternative procedures. Subjects will then be given another opportunity to ask questions and agree or disagree to consent.

Subject Capacity

All subjects enrolled in this study will have capacity to provide informed consent.

Consent Forms

Written consent will be obtained from the patient.

Documentation of Consent

Signed consent forms will be kept in a binder and stored in a locked file cabinet.

Costs to the Subject

Subjects will not incur any additional financial costs as a participant in this study.

Payment for Participation

Subjects will be paid $100 for participating in this study.

VII. References

1. Lu HC, Mackie K. An Introduction to the Endogenous Cannabinoid System. *Biol Psychiatry*. 2016;79(7):516–525. doi:10.1016/j.biopsych.2015.07.028
2. Guindon J, Hohmann AG. The endocannabinoid system and pain. CNS Neurol Disord Drug Targets. 2009;8(6):403–421.
3. Bergamaschi MM, Queiroz RH, Zuardi AW, et al. Safety and side effects of cannabidiol, a Cannabis sativa constituent. Curr Drug Saf. 2011;6:237–249
4. Iffland K, Grotenhermen F (2017) An update on safety and side effects of cannabidiol: a review of clinical data and relevant animal studies, Cannabis and Cannabinoid Research 2:1, 139–154, DOI: 10.1089/can.2016.0034.

5. Zhornitsky S, Potvin S. Cannabidiol in humans-the quest for therapeutic targets. Pharmaceuticals (Basel). 2012;5(5):529–552. Published 2012 May 21. doi:10.3390/ph5050529
6. Parker LA, Rock EM, Limebeer CL. Regulation of nausea and vomiting by cannabinoids. Br J Pharmacol. 2011; 163(7):1411-1422. doi:10.1111/j.1476-5381.2010.01176.x