Cover Page

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Protocol Title: The Effect of Dispensed Cannabis on Taxane Induced Peripheral Neuropathy

Principal Investigator: Diana Martinez, MD and Margaret Haney, PhD

Email: dm437@cumc.columbia.edu; mh235@cumc.columbia.edu

Telephone: 646-774-6160

Office: 3626 Cell Phone: 917-771-6572

Lay Summary

This section is intended to provide a basic overview of the study including a description of its purpose, methods, and subject population. The summary should provide a concise overview of the study for non-scientific and scientific members of the IRB. Please avoid medical or technical terminology. In general, the abstract of a grant does not provide a suitable lay summary.

Please also paste of a copy of the Lay Summary into the PRISM PSF Form.

Peripheral neuropathy results from damage or injury to the nerves of the hands and feet. Chemotherapy induced peripheral neuropathy can be particularly distressing to patients. The symptoms consist of numbness and pain, which can progress to weakness and limited function. The taxanes (paclitaxel and docetaxel) are chemotherapeutic drugs often used in breast cancer treatment that are known to cause neuropathy. It's estimated that taxane-induced neuropathy (TIPN) occurs in up to 40% in patients, and a substantial portion of patients are unable to complete chemotherapy as a result.

Studies in mice show that cannabinoids can ameliorate TIPN. Cannabidiol (CBD), a cannabinoid with no subjective effects (no intoxication or mood-altering properties), has been shown to prevent and improve peripheral neuropathy caused by paclitaxel in mice. CBD has not yet been tested for this indication in humans. However, human studies have shown that Δ^9-tetrahydrocannabinol (known as THC) reduces pain secondary to diabetic and HIV associated neuropathy. THC also reduces TIPN in mice.

Our goal is to investigate the effect of high CBD and low THC on taxane-induced neuropathy in volunteers with breast cancer and TIPN. At the Cannabis Research Laboratory in the Department of Psychiatry of CUMC, we have been studying the acute effects of cannabis and its constituents (cannabinoids) in research volunteers for 20 years. For this study, medical cannabis will be provided by Tilray, a GMP-certified medical cannabis producer, that is compliant with FDA regulations. Our goal is to enroll 96 subjects in two groups: 48 subjects in the active group and 48 in a placebo group. The active group will receive high dose cannabidiol (100 mg) plus low dose THC (5 mg) in capsules, up to three a day. Our hypothesis is that THC and CBD will synergistically reduce the pain and numbness of TIPN.

Background, Significance, and Rationale

In this section, provide a brief summary of the status quo of the relevant work field, and how the proposed study will advance knowledge. Specifically, identify the gaps in knowledge that your project is intended to fill. If no gaps exist that are obviously and directly related to your project, explain how your proposed research will contribute to the overall understanding of your field. Describe potential impacts of your project within your field of study and in a broader context. Provide a critical evaluation of existing knowledge. The literature review does not have to be exhaustive.

Taxane-Induced peripheral neuropathy (TIPN) occurs in up to 40% of patients (1), and there is a lack of effective treatments (2). Given the clinical impact of TIPN and the fact that some patients experience dose-limiting symptoms, there is a need for the development of new, effective approaches to treat this disorder.

Phytocannabinoids are select compounds derived from the cannabis plant. Δ^9-tetrahydrocannabinol (THC), the primary psychoactive phytocannabinoid, mimics the effects of the endogenous cannabinoids by activating the cannabinoid receptors (CB1 and CB2) (3). Intoxication results from THC binding to the CB1 receptor (4). Another phytocannabinoid, cannabidiol (CBD), has a varied and complex pharmacology (5-7). However, CBD does not bind CB1 or CB2 receptors with high affinity and, consequently, produces no intoxication (8).

Both THC and CBD can ameliorate paclitaxel-induced neuropathic pain in mice (9-11). Two studies showed that pretreatment with CBD (2.5, 5 mg/kg), prior to injections of paclitaxel, prevented the development of mechanical sensitivity, while producing no evidence of abuse liability or cognitive deficits (9, 10). A subsequent study showed that either CBD (1 mg/kg) or THC (2.5 mg/kg) alone attenuated mechanical allodynia in paclitaxel-induced neuropathic pain (11). Furthermore, the combination of CBD and THC were synergistic: low, ineffective doses of CBD (0.16 mg/kg) and THC (0.16 mg/kg) were effective when combined (11). Despite these promising results, the effect of cannabinoids on TIPN have not been well characterized in humans. Cannabis and a synthetic analog of THC (nabilone) have been shown to improve diabetic and HIV-induced neuropathy (12-14).

Previous research demonstrates that CBD does not interfere with the efficacy of chemotherapeutic agents, and in fact, may even inhibit tumor growth (9, 15-17). CBD inhibits aggressive, hormone-independent breast cancer cells and up-regulates pro-differentiation factors (15, 16). CBD has also been shown to inhibit breast cancer metastasis in xenograft models (17). More recently, a study investigating the combined effects of CBD with paclitaxel showed a synergistic effect on the inhibition of breast cancer cell viability in human and mouse cell lines (9). Although these studies were performed in cells or rodents, they indicate that CBD is unlikely to have an adverse effect on response to chemotherapy and may even be beneficial. The FDA has granted CBD Orphan Drug Status for another cancer, glioblastoma, due to its favorable safety profile in humans and its potential to serve as an adjunct treatment for this disease. Synthetic THC (dronabinol) and a THC analogue (nabilone) are FDA approved for nausea and vomiting in cancer patients receiving chemotherapy.

The current clinical management of TIPN largely includes dose reduction, treatment delays, or even discontinuation of chemotherapy. Furthermore, among breast cancer patients who experience TIPN, up to 80% still report symptoms up to 2 years later (18). Previous clinical studies of TIPN have investigated treatments that include acetyl-l-carnitine, gabapentin, lamotrigine, nortriptyline, amitriptyline, duloxetine, electro-acupuncture, and topical agents (for review see (19)). To our knowledge, only one of these studies, that of Smith et al (20), showed a positive treatment effect for CIPN (20). This study was a randomized clinical trial of duloxetine compared to placebo and included subjects with any type of cancer who had been treated with

paclitaxel, docetaxel, oxalipatin, nab-paclitaxel, or cisplatin. The results showed that the duloxetine group experienced a larger decrease in average pain (1.06; 95% CI: 0.72, 1.40) compared to the placebo group (0.34; 95% CI: 0.01, 0.66) (p = 0.003).

Our proposed study is modeled on the publication by Smith et al (20), and we will use the same primary outcome measures, which are the change in Brief Pain Inventory-Short Form (BFI-SF) and the Functional Assessment of Cancer Therapy, Gynecologic Oncology Group, Neurotoxicity subscale (FACT/GOG-Ntx) to assess pain and numbness. However, unlike the publication of Smith et al (20), we will only enroll volunteers diagnosed with breast cancer who have neuropathy secondary to paclitaxel or docetaxel.

Despite cannabis legalization for medical use, there are few placebo-controlled studies investigating its clinical efficacy. Additionally, most cannabis available today has been bred to be high in THC, at the expense of CBD. Cannabis that is high in THC can produce side effects, which could be aversive to many patients. Our objective is to test the effects of cannabis that is high in CBD, with moderate levels of THC, so that we can maximize the anti-neuropathic properties and reduce the intoxicating effects. The cannabis products will be provided by Tilray and dispensed at the lab visits. Subjects will be asked to bring the bottles with any remaining capsules that weren't taken.

Specific Aims and Hypotheses

Concisely state the objectives of the study and the hypothesis or primary research question(s) being examined. There should be one hypothesis for every major study procedure or intervention. For pilot studies, it is important not to overstate the study's objectives. If there are no study hypotheses, describe broad study goals/aims.

Aim 1: Effect of cannabis on pain and numbness in TIPN. Breast cancer patients with TIPN who have an interest in participating in a placebo-controlled trial of cannabis will be recruited. The volunteers will be randomized into two groups: active cannabis product (n=48) versus placebo (n=48). The active cannabis group will receive up to three capsules a day containing 100 mg and of CBD and 5 mg of THC, for a maximum total of 300 CBD and 15 mg THC. The doses will be titrated up and subjects will take the dose they tolerate best. The placebo condition contains negligible levels of CBD and THC (<0.1 mg). The cannabis will be provided by Tilray, Inc. We hypothesize that subjects receiving the active treatment will experience an improvement in neuropathy symptoms, measured with the change in BPI-SF (for pain) and FACT/GOG-Ntx scores (to measure paresthesia, numbness, and function).

Aim 2: Effect of cannabis on sensory deficits and tactile acuity in TIPN. These outcome measures will be obtained in the same subject groups to assess additional measures of neuropathy: 1) the tactile acuity cube, used to assess spatial acuity; and 2) mechanical sensitivity measured with von Frey filaments. We will also measure sleep and changes in medication. Our hypothesis is that the active group will experience an improvement in these measures over the placebo group.

Inclusion/Exclusion Criteria

This section details your study sample(s) and addresses the requirement for risk minimization.
You may choose to divide your sample by population (healthy controls vs. subjects) or by procedure (subjects who will have an MRI) and then define different sets of criteria for each.

For each sample, create or insert a table to describe detailed criteria for study inclusion and exclusion and the method you will use to ascertain each criterion. The method of ascertainment may describe tests, scales and instruments. When

relevant, indicate the level of training of the person who will make the assessment (e.g. clinical interview by a psychiatrist).

Inclusion/Exclusion Criteria needs to be numbered and listed in outline form (see Table template below).

CRITERION	METHOD OF ASCERTAINMENT
Inclusion:	
1. Participants with breast cancer (stage **I**, II or III), experiencing TIPN due to paclitaxel or docetaxel, who have completed chemotherapy. Participants must have an ECOG score, which measures level of function, of 2 or better. Participants must have a score of 2 or 3 score for sensory neuropathy, as assessed by the Common Toxicity Criteria Adverse Events (CTCAE).	Medical Assessment, interview with study clinician, Eastern Cooperative Oncology Group (ECOG) scale and Common Toxicity Criteria Adverse Events (CTCAE) scale. The ECOG (range 0 to 5) describes a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability. The CTCAE describes the severity of toxicity for patients receiving cancer therapy (range 0 to 5). Subjects are required to have a score on the neuropathy sensory scale of 2 (sensory alteration or paresthesia, interfering with function, but not interfering with activities of daily living) or 3 (sensory loss or paresthesia interfering with activities of daily living), but not above.
2. Able to give informed consent and comply with study procedures.	Medical Assessment, interview with a study clinician.
3. Ages of 21-60.	Medical Assessment, interview with a study clinician, intake questionnaire.
Exclusion:	
1. Meet DSM-V criteria for current major psychiatric illness, such as bipolar disorder, major depression, or psychosis. Subjects with a current substance use disorder will be excluded.	Medical Assessment, interview with study clinician. Score of ≥ 17 on the Hamilton Depression Rating Scale. Urine toxicology screen (for cannabis, opioids, cocaine, amphetamines**).**
2. Diagnosis of a major medical or neurological disorder, including hypertension or orthostatic hypotension, cardiovascular	Medical Assessment, laboratory studies, interview with a study physician.

disease, or neurodegenerative disorders (movement disorders, dementia) that would exclude cannabinoid use. Subjects with renal or hepatic impairment will not be included. Subjects with a history of peripheral neuropathy resulting from other causes will be excluded. Subjects taking warfarin will also be excluded.		
3. Current use of cannabis	Medical Assessment, urine toxicology, interview with a study clinician	
4. Women who are not practicing an effective form of birth control (condoms, diaphragm, birth control pill, IUD) or currently pregnant	Medical history, urine HCG. A urine HCG test will be performed at lab visits on women of childbearing potential.	

We will randomize 96 subjects into two groups (48 per group). The subjects will be females only. We expect 50% to be Caucasian, 25% to be African American, and 25% to be Hispanic or other.

Study Procedures

Provide a clear, concise narrative of study procedures with special attention to the subjects' involvement. Detail the overall study timeline and location of study procedures, list all interventions, assessments and interviews, estimate the duration of each procedure, provide dosing schedules, identify study personnel involved in each procedure, and provide credentials for relevant personnel. For complicated study designs, we strongly encourage attaching tables, flow-charts, and study algorithms.

The study investigators include the following:

Dr. Diana Martinez, MD: research psychiatrist at the NYSPI and CUMC. Dr. Martinez is a study PI.

Dr. Margaret Haney, PhD: Director of the Cannabis Research Laboratory. Dr. Haney is a study PI.

Dr. Frances Levin, MD: Director of the Division on Substance Use Disorders at CUMC

Dr. Craig Blinderman: MD: Director of the Adult Palliative Medicine Service at CUMC. Dr. Blinderman has extensive experience with cannabis and medially ill patients.

Dr. Jonathan Wai, MD: Dr. Wai is a psychiatrist and fellow in the Division on Substance Use. He will assist Dr. Martinez with the study procedures.

Dr. Caroline Arout, PhD, a Research Scientist II at the NYSPI in the Cannabis Research Laboratory. She will assist Dr. Haney with study procedures.

Dr. Marisa Weiss, MD, a radiation oncologist and Chief Medical Officer of Breatcancer.org. Dr. Weiss will assist us with advertising and outreach.

Dr. Amy Tiersten, MD, Professor of Medicine and breast cancer specialist at Mount Sinai. Dr. Tiersten will provide input and advice on the study design.

Covid-19 Procedures:

- Infection Control/PPE – Guidelines. During all onsite research procedures participants and the study team will be required to wear a mask, a face shield (when appropriate) and maintain a minimum of 6ft distance between other people unless a study procedure absolutely necessitates otherwise (placing of EKG leads, blood draw)

-Frequent hand washing or hand sanitizing will be practiced by the research team and the participants.

-Research participants will only come on-site if absolutely necessary for study procedures.

-Clinical research teams will screen their participants for COVID symptoms (night before and day of onsite visit, documenting this in the chart), and escort them in and out of the building.

-COVID/COVID-like symptoms in participants will be reported to the IRB via PRISM as an SAE.

Screening and Recruitment:

Subjects will be recruited from the New York City area with advertisements and flyers. Subjects will undergo a phone screening followed by a virtual screening for those who meet criteria. Remote (not written) consent may be obtained. Subjects will be provided with the study CF prior to a virtual visit, either an electronic (via encrypted email) or paper (via standard mail) version. If verbal consent is to be obtained, study personnel will ensure that the participant has an electronic (via encrypted email) or paper (via traditional mail) copy of the consent form and has had sufficient time to read it through and form questions. Remote contact will be made between an approved member of the study team and the participant via a HIPAA compliant communication method (WebEx, secure telephone, secure zoom account). Study personnel will discuss the document, the study, and any other questions the participant might have. The consent process will include discussion of the technology HIPAA-compliant platforms to be used and any concerns the participant may have, such as access to a private space in which to take calls, or accessibility—access at home to adequate devices, cell signal, or wifi. A note to file will be added to the participants chart to document that the participant had access to a copy of the form, discussed it with a member of the research staff, and gave verbal consent. This note will indicate the date that consent was given and be signed by the consenter, this note will be written the same day as the consent process.

The consent discussion will include the following language:

“You should exercise caution when traveling in public and follow public health guidelines, such as wearing masks in public and avoiding crowds. It is important for you to stay informed about public health recommendations and guidelines regarding COVID-19, such as those issued by the Centers for Disease Control (CDC.gov) and local government guidelines and directives. If you have questions about how you will travel for appointments, or do not feel safe traveling, please let us know, and know that you can call to reschedule visits.”

After the consent discussion, participants will be asked to read and electronically sign a copy of the consent form. The consent form will be signed using Redcap or by having the subject email a signed signature sheet using encrypted email. The consenter will also sign the document, a copy of the document will be made available to the participant (either via secure email or hard copy). This will also be done the same day as the consent discussion.

The screening visits will include a medical and psychiatric assessment and a description of study procedures, including the potential side effects. The Hamilton Depression Rating Scale will be obtained at screening, as well as a urine toxicology test. A urine HCG test will be performed on women of childbearing potential.

Additional screening instruments include:

1) The Eastern Cooperative Oncology Group (ECOG) scale, which describes a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.). The scale goes from 0 (normal activity) to 4 (bedridden). For this study, subjects are required to have an ECOG score of 0 (normal activity), 1 (symptomatic but ambulatory) or 2 (ambulatory, but unable to work).

2) The Common Toxicity Criteria Adverse Events (CTCAE) (22). This scale, established by the National Cancer Institute (NCI), standardizes definitions for adverse events, to describe the severity of toxicity for patients receiving cancer therapy. The scale goes from 0 (not present) to 5 (terminal). For this study, subjects are required to have a score on the neuropathy sensory scale of 2 (sensory alteration or paresthesia, interfering with function, but not interfering with activities of daily living) or 3 (sensory loss or paresthesia interfering with activities of daily living), but not above. The score on the CTCAE scale for motor neuropathy must be less than 2 (symptomatic weakness interfering with function but not activities of daily living). The scales are attached at the end of the protocol.

Participants will be asked to provide permission for us to contact their treating oncologist. The oncologist will be sent a letter, by fax, informing them of the study procedures and that their patient wishes to participate in this study. We will also request the patients' lab results (complete blood count and metabolic panel) so that subjects will not need to undergo another blood draw. If we are unable to obtain the labs from the oncologist, we will obtain a CBC and metabolic panel on subjects who agree to this. Potential volunteers with a history of cardiac disease, such as arrhythmia or a past myocardial infarction, will be excluded. Subjects with a history of orthostatic hypertension will also be excluded. Subjects with renal or hepatic insufficiency will not be included (liver function tests exceeding 2 x normal, BUN/CR > 22).

Subjects who are included will have been diagnosed with stage **I**, II or stage III breast cancer, and are no longer taking chemotherapy. The expected relative five-year survival for stage **I** and II is 93% and 72% for stage III.

The following medications, which are moderate or strong inhibitors, inducers, substrates of liver enzymes or drugs with high protein binding, will not be permitted: clarithromycin, itraconazole, erythromycin, fluconazole, clopidogrel, rifampin, sulfamethoxazole, warfarin, any opioids, warfarin, anti-epileptic medications (including carbamazapine, phenytoin, valproic acid, and gabapentin but excepting of clonazepam or diazepam).

The following medications will not be excluded, but will be flagged (as an alert for a potential interaction): fluvoxamine, fluoxetine, paroxetine, buproprion, duloxetine, melatonin, ramelteon, tasimelteon, theophylline, tizanidine, repaglinide, gemfibrozil, mirabregon, verapamil, indometacin, canagliflozin, flurbiprofen, ibuprofen, lumiracoxib, valdecoxib, nateglinide, troglitazone, ertugliflozin, oxazepam, lorazepam, diazepam, clonazepam.

In order reduce in-person contact, there will be two screening visits. The first visit will be done using Webex and/or telephone. This visit will include the physicians' assessment (medical, psychiatric history, review of medications); the assessments (listed above), and a review of inclusion and exclusion criteria with the subject. Of subjects who meet criteria, based on the virtual visit, an in-person screening visit will be done. This includes the ECG, physical exam, pregnancy test, and lab work. If subjects already have lab work (from their primary care doctor or oncologist) they will be asked to bring it to the in-person screening visit.

<u>Study Entry</u>

Once the subject is entered into the study they will perform a baseline (pre medication) visit, followed by weekly visits for 8 weeks.

In the event that a subject attends the in-person screening visit and has a normal ECG, normal physical exam, and normal labs (brought with them), we will combine the in-person screening visit and the baseline visit into one lab visit.

The outcome measures and procedures for each visit are included here:

1) The Brief Pain Inventory-Short Form (BPI-SF), a short, self-administered questionnaire using a 0 to 10 scale, developed to quantify measures of pain (23).
2) The Functional Assessment of Cancer Therapy Taxane (FACT/GOG-TAX) and the 38-item neurotoxicity score (FACT-NTX), which asks about Quality of Life, well-being, in addition to neuropathy specific questions about and discomfort, numbness, tingling, and functional changes (trouble feeling small objects in hand or trouble walking) (24).
3) Promis Sleep Questionnaire: The 8-item Patient-Reported Outcomes Measurement Information System (PROMIS™) Sleep Disturbance questionnaire has been developed by the American Psychiatric Association as part of the NIH Roadmap Initiative. It is a 5-point Likert scale(1 = “not at all,” 2 = “a little bit,” 3 = “somewhat,”, 4 = “quite a bit,” and 5 = “very much”) where participants will rate 8 measures of sleep over the past 7 days.
4) Medication Questionnaire: Participants will be asked to report on the medication use at baseline and at the weekly visits, including the dose, schedule, and any side effects. Adjuvant drug use will be assessed at study completion using an ordinal rating scale that indicates whether the doses are unchanged, increased, or decreased. The presence of additional drugs would be graded as an increase, whereas discontinuing a drug would be graded as a decrease in analgesic/adjuvant dose.
5) Mechanical sensitivity using von Frey filaments (2.83, 3.61, 4.31, 4.56, 5.07 and 6.65) purchased from North Coast Medical (Gilroy, CA). Beginning with the smallest size, the filament will be applied to the palm of the hand that is most affected, or the dominant hand is the neuropathy is the same bilaterally. For each filament size, four positive trials and one negative trial (no touching of skin) will be performed. The mechanical sensitivity threshold is the filament size where the subject reports three correct answers on the positive trial and is correct on the one negative trial.
6) The Tactile Acuity Cube (TAC) test will be used to assess spatial acuity, as described previously (25). The cube is comprised of 6 sides each containing a grating with widths of increasing size (from 0.75 mm to 6.0 mm). Shielded glasses will be used as subjects are asked to turn up the palms of the dominant hand on a table. The gratings of the cube will be applied for 2 seconds to the finger pad of the index finger and the subject will be asked to say whether the grating is vertical or horizontal to the long axis of the finger. A narrower grating will be used if the subject answers correctly, and a wider grating if the subject answers incorrectly.

The schedule for the scales and tests at laboratory visits is as follows:

Visit	Scales (items 1 to 4, above)	In person lab visit	TAC	Mechanical Sensitivity	Blood levels
Baseline	x	x	x	x	

Week #1	x				
Week #2	x	X*	x	x	
Week #3	x				
Week #4	x	x	x	x	x
Week #5	x				
Week #6	x	X*	x	x	
Week #7	x				
Week #8	x	x	x	x	x

In order to reduce in-person contact, the visits on weeks 2 and 6 are optional (X*). Participants can opt out of these in-person visits if they wish. However, participants will be asked to decide ahead of time about attending these visits, so that the appropriate amount of drug is dispensed.

Participants who choose to attend all study visit will be given two weeks' worth of medication on each in-person lab visit. Participants who choose to opt out of the in-person visits of week 2 and 4 will receive 4 weeks of study medication. If participants who opt out of the weeks 2 and 6 in-person visits will still perform these visits virtually. While the TAC and mechanical sensitivity tasks will not be done, a study PI will still review their medications, concomitant medication use, and any adverse events.

All questionnaires will be obtained using Qualtrics.

Subjects will be asked to answer the following questionnaires daily:

1. Questions about taking their medication:

    a) How many doses did you take today? (1, 2, or 3)
    b) Have you made sure that no one else can access the dose? (yes or no)

2. The Brief Pain Inventory-Short Form (BPI-SF).

3. Promis Sleep Questionnaire.

On a weekly basis, subjects will be asked to complete the full FACT/GOG NTX (38 items).

In the lab visits, subjects will be asked to complete the following: Medication Questionnaire, the TAC, and mechanical sensitivity test. They will be seen by Drs. Haney or Martinez to review their study medication. This will include a discussion of how well the medication was tolerated and whether there were any problem with the medication. We will also ask about concomitant medications subjects are taking. On the weeks that subjects are not seen in the lab they will be contacted by phone to ask about these same issues.

<u>Cannabinoids:</u>

The cannabinoid capsules (two weeks' worth) will be provided during the visits. Subjects will begin with one capsule (100 mg CBD and 5 mg THC) in the evening. If the patient reports tolerating 1 capsule day for about 3 days, she will be instructed to take 2 capsules/day for several 3-5 days. If that is tolerated well, the dose will then be increased to three capsules per day. Participants will be encouraged to escalate doses on days they plan to be home in case they experience discomfort. The dose will then be increased to two and then three capsules per day, as long as these doses are tolerated well. The dose increase will occur over 7 to 10 days. Subjects who cannot tolerate more than one capsule per day can stay at that dose. Subjects who tolerate two a day will remain at that dose, and those who tolerate 3 capsules per day will be maintained at that dose. In our experience, there is a great degree in how non-cannabis smokers experience the intoxicating effects of THC, which is why subjects will self-titrate the effects. Thus, we expect that some subjects will take only one capsule daily, while others will take up to 3 a day. In a previous study by Tilray, performed in subjects undergoing chemotherapy and experiencing nausea and vomiting, subjects titrated up to 15 mg THC daily and 70% of subjects tolerate that dose.

Participants will be seen by a study investigator (Drs. Haney or Martinez) at the laboratory visits. Dr. Martinez is a board-certified psychiatrist. Dr. Haney is a psychologist with over 20 years of experience administering cannabis to research volunteers and managing neuropsychiatric side effects related to cannabinoids. The study assessments (TAC, mechanical sensitivity) may be done by other study personnel, but Drs. Haney or Martinez will see the subjects at lab visits.

Blood samples will be drawn at weeks 4 and 8 to measure cannabidiol levels. Samples will be sent to Dr. David Moody at The University of Utah who will perform the analysis, without identifying information.

Subjects will receive: 1) $40 for the screening visit, 2) $4 each day for completing the Qualtrics questionnaires; 3) $30 for each of the baseline lab visit (virtual and in-person) and $40 for each of the laboratory visits (weeks 2, 4 and 6, which last about 1 hour); 4) $140 for the end of study laboratory visit (week 8, about 3 hours). Thus, the total is up to $584.
We will provide transportation (car service) to all in-person lab visits. We will pay cash for the in-person visits.

Participants will be reimbursed for the medicinal cannabis application as well ($50).

Subjects will also receive a $100 referral/fee if they chose to participate in this program. For each individual a subject refers whom successfully enrolls and completes the baseline visit of the study, subjects will receive $100.

Participants will be paid for their virtual screening visit using an Amazon gift card, check, or virtual payment method subject to IRB and business office approval. These same methods will be utilized to pay participants for weeks 2 and 6 if necessary. Participants may also choose to defer payment until their next in-person visit, if they wish to receive cash.

The study procedures will take place at either of two locations of the Division on Substance Use Disorders: 1051 Riverside Drive or 3 Columbus Circle (STARS clinic).

End of study: At the end of the study, subjects will be informed of the dose of cannabis they received. If they wish to continue cannabis (or start if in the placebo group) they will be provided with medical marijuana certification for NY state by Dr. Martinez. They will be provided with the names and location of NYS dispensaries. Dr. Martinez will manage their medical marijuana care for 6 months after study end. They will be asked to be contacted monthly, where we will ask about any symptoms, and we will ask them to complete the primary

questionnaires (BPI, FACT-Tax, Promis sleep). After that time point, any subject wishing to continue medical marijuana will be assisted with finding another provider from the NY state approved list.

Additional study**:** All participants will be informed that they are eligible to participate in another study if they wish. That study will be performed by Dr. Thomas Brannagan at the Neurological Institute. For that study, subjects will undergo an eye exam (corneal microscopy), to measure peripheral nerve viability. Subjects will be informed that participation in the eye exam study is optional.

Criteria for Early Discontinuation

Define criteria that will be used to exit or drop subjects from the study. Indicate the time points when such criteria will be applied, and describe the rating instruments, parameters, and thresholds that will lead to a decision to terminate a subject's participation. In addition, explain procedures for managing subjects who are dropped from the protocol.

For treatment studies: To minimize risks to subjects, operationalized drop-out criteria should be defined so that subjects who worsen, or in some cases, fail to improve, are removed from the study and offered standard care. The threshold for drop-out should consider the level of risk associated with non-improvement for the specific disorder, the availability of alternatives, and the typical required duration of treatment. For example, emergence of suicidal intent, or psychosis, should prompt immediate clinical evaluation and withdrawal from the study.

Participants will be discontinued early in the event of worsening of their clinical status, as assessed by Drs. Martinez, Haney or Levin or the participant's oncologist. Any volunteer who is discontinued early will be asked to have a follow up appointment with their oncologist (within 4 days) and we will assist with obtaining that appointment if needed.

Blood and other Biological Samples

Describe how the sample will be used and indicate, when relevant, the amount of the sample. The IRB wants to know that the sample is sufficient for the purposes of the study, but that sampling is limited to what is minimally necessary.

If you've indicated that you intend to store a sample for future use, indicate where the sample will be stored, how long the sample will be stored, and to what purposes the sample will eventually be put. Check the IRB website at http://irb.nyspi.org/irbdnn/Policies/GeneticResearch/tabid/96/Default.aspx for specific guidance and additional information about future use of DNA samples.

We will draw a 4cc sample of blood at weeks 4 and 8 to measure cannabidiol and THC levels. Samples will be sent to Dr. David Moody at The University of Utah who will perform the analysis. Samples will be sent with codes and without identifying information.

Assessment Instruments

List all assessment instruments, indicate who will administer them, and provide an estimate the duration of each. The IRB wants to know that assessments instruments are appropriate measures for the purposes of the study and are no more burdensome than is necessary. The IRB will consider the burden of assessment instruments (in terms of time, sensitivity of material, etc.) in the risk/benefit analysis. Please attach copies or otherwise provide all non-standard instruments.

The scales and assessments include the following:

1) The Brief Pain Inventory-Short Form (BPI-SF), a short, self-administered questionnaire using a 0 to 10 scale, developed to quantify measures of pain (23).
2) The Functional Assessment of Cancer Therapy Taxane (FACT/GOG-TAX) and the 38-item neurotoxicity score (FACT-NTX), which asks about Quality of Life, well-being, in addition to neuropathy specific questions about and discomfort, numbness, tingling, and functional changes (trouble feeling small objects in hand or trouble walking) (24).
3) Promis Sleep Questionnaire: The 8-item Patient-Reported Outcomes Measurement Information System (PROMIS™) Sleep Disturbance questionnaire has been developed by the American Psychiatric Association as part of the NIH Roadmap Initiative It is a 5-point Likert scale(1 = “not at all,” 2 = “a little bit,” 3 = “somewhat,”, 4 = “quite a bit,” and 5 = “very much”) where participants will rate 8 measures of sleep over the past 7 days.
4) Medication Questionnaire: Participants will be asked to report on the medication use at baseline and at the weekly visits, including the dose, schedule, and any side effects. Adjuvant drug use will be assessed at study completion using an ordinal rating scale that indicates whether the doses are unchanged, increased, or decreased. The presence of additional drugs would be graded as an increase, whereas discontinuing a drug would be graded as a decrease in analgesic/adjuvant dose.
5) Mechanical sensitivity using von Frey filaments (2.83, 3.61, 4.31, 4.56, 5.07 and 6.65) purchased from North Coast Medical (Gilroy, CA). Beginning with the smallest size, the filament will be applied to the palm of the hand that is most affected, or the dominant hand is the neuropathy is the same bilaterally. For each filament size, four positive trials and one negative trial (no touching of skin) will be performed. The mechanical sensitivity threshold is the filament size where the subject reports three correct answers on the positive trial and is correct on the one negative trial.
6) The Tactile Acuity Cube (TAC) test will be used to assess spatial acuity, as described previously (25). The cube is comprised of 6 sides each containing a grating with widths of increasing size (from 0.75 mm to 6.0 mm). Shielded glasses will be used as subjects are asked to turn up the palms of the dominant hand on a table. The gratings of the cube will be applied for 2 seconds to the finger pad of the index finger and the subject will be asked to say whether the grating is vertical or horizontal to the long axis of the finger. A narrower grating will be used if the subject answers correctly, and a wider grating if the subject answers incorrectly.

Research Related Delay to Treatment

Research involving participants who are in need of treatment invariably involves delay to care, and this delay is associated with risk. Scheduling of procedures must be carefully organized to minimize delay. Other delay must involve only that minimally necessary to accomplish the aims of the research while respecting subject well- being and safety. Describe the delay, by virtue of research participation in this study, before a participant can receive treatment of known efficacy or standard care routinely offered in the community.

There is no delay to treatment and subjects will continue their regular care.

Clinical Treatment Alternatives

Describe what other treatment or assessment options are available to subjects who do not participate in research.

Other treatments for CIPN include duloxetine.

Risks/Discomforts/Inconveniences

"Risk" is a broad term used to convey the potential for harm, burden, and inconvenience related to research participation. Use this section to provide a comprehensive description of foreseeable physical, psychological, social, interpersonal, and economic risks introduced by the research. Include the source of the information. Consider both the probability and magnitude of harm and its impact. Describe the foreseeable harms associated with the research (untoward effects of a medication) and those related to delay to individualized treatment. Include data from the literature, and local data, if available, on risk rates and subject experiences with research procedures. Describe procedures in place to minimize risk. In general, please create a numbered list of risks/categories of risk, and in general put the list in the order of significance or level of risk, the most significant risks first followed by others.

1. Cannabis: CBD may cause somnolence, decreased appetite, diarrhea; fatigue, malaise, asthenia and poor quality sleep. The THC may cause intoxication. Participants are instructed to take the THC in the evening to help with sleep. Risks of THC include sedation, gait disturbance, tiredness, anxiety, concentration difficulties, dizziness, sleep disturbance, changes in food intake, restlessness, confusion, sleepiness, headache, nausea, dry mouth, pallor, flushing, sweating, and slurred speech.

   Subjects will be called the morning after taking the first cannabis dose to inquire about any side effects they may have experienced. If a volunteer reports side effects other than tiredness and sleepiness we will discuss reducing the dose of THC at bedtime. Subjects will be informed that taking capsules shortly after a heavy meal may increase intoxication relative to a lighter meal. The volunteers will be informed that they should contact the PI between study visits if needed due to concern over side effects. During the weekly visits, participants will be asked about side effects.

   There have been reports that smoking cannabis increases the risk of heart attack in patients with established heart disease. The risk of this with oral cannabinoids is not known, but subjects with cardiovascular disease will be excluded. Smoked cannabis can also cause increased heart rate and hypotension, and we will exclude volunteers with orthostatic hypotension. Due to the potential for cannabis to affect warfarin metabolism, subjects taking this drug will be excluded.

2. Risks associated with the psychological test battery include potential nervousness and frustration with the tasks. A member of the research team will carefully explain the tests before hand and will be available for questions during the tasks should they arise. Subjects will be informed that they can stop if they choose to.

3. COVID-19. There is risk of exposure to coronavirus 2019 (COVID-19) related to travel for research purposes and to the in-person visit to NYSPI. We will do everything that we can, in concordance with NYSPI policy, to minimize risk to research participants and staff posed by COVID-19.

Methods to Protect Confidentiality

Describe the data management plan and the methods you will employ to protect subject privacy and the confidentiality of research data. The section should detail how information will be collected, recorded, coded, stored, transmitted, and as applicable, shared with other investigators so as to minimize risks related to breach of confidentiality. Confirm that identifiers are removed, to the extent possible, from research data, and explain if there are links between subject identity and research data, or if the data is anonymous. Also, indicate where the data is stored, who is responsible for its

safekeeping, and who has access to subject identity and codes, if any, which cross-link research data and subject identity. Confirm that identifiable data is not collected, stored, or transmitted by mail, fax, on removable drives, laptops, or via the internet without proper protections, e.g. encryption.

Participants divulge information which is sensitive and may have adverse social consequences if released. We deal with issues of confidentiality by using coded records, storing signed consent forms in a locked cabinet, and try to the best of our ability to maintain confidentiality. Data are kept on a password-protected computer, and if there is any electronic transmission concerning the study, it will use numeric identifiers rather that participant names. We also point out to prospective participants that we cannot assure that their medical histories and other personal records might not become known. In addition, we inform volunteers that we must conform with NY State reporting requirements. In addition to a discussion of this topic, the information is clearly stated in our consent forms.

Following the NYSPI Remote Communications Guidance, confidentiality of remote communication is protected through the use of secure HIPAA compliant telecommunication (e.g. Webex, Facetime, or telephone) in combination with digital data collection procedures (through remote access to secure NYSPI systems and encrypted email).

Direct Benefits to Subjects

Describe only benefits to individual subjects that are likely to accrue during the study itself. Do not include subject compensation or treatment to be provided at the end of the study, as these do not figure into the IRB's risk benefit considerations. Do not describe diagnostic and evaluation components unless subjects receive clinical feedback. Do not describe the anticipated scientific benefits of the research. Some studies offer no direct benefit to subjects.

There are no known benefits to subjects. Subjects may experience an improvement in their neuropathy, but this is the research question.

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Statistical Analysis: All variables used in analysis will be examined for distribution, and any outliers will be identified. Baseline differences between the two groups will be assessed using two-sample t-tests.

Aim 1: Separate Mixed Effects models will be fit for each of the 2 primary outcomes (BPI-SF and FACT/GOG-Ntx). Change in the outcome measure, from baseline, will be the response variable, and the predictor variables will be baseline outcome value, time, treatment group, and the interaction of time and treatment group. If the interaction of time and treatment group is not significant, models will be re-fit with only the main effects. If they are related to the outcome, additional covariates include change in concomitant medications, change in sleep, and quality of life measures. Analyses will be performed using SAS Version 9.4.

Aims 2 & 3: Similar models to those in Aim 1 will be used to test for differential change between the treatment groups in the secondary and tertiary outcomes of vibratory perception threshold, mechanical sensitivity (von Frey test), spatial acuity (tactile acuity cube), and corneal nerve fiber length.

IRB# 7635
Version 08/23/21

Notice Regarding Coronavirus 2019 (COVID-19)

There is risk of COVID-19 infection during in-office visits and during travel for research purposes. The risk related to travel can be reduced by taking recommended precautions. These include always wearing a mask in public and while traveling, practicing hand hygiene, and staying at least 6 feet away from others. If you do not feel comfortable traveling to the medical center for an appointment, for example if the subway you would normally take is crowded, you can reschedule. We also suggest you remain informed about public health recommendations, such as CDC guidelines and local government guidelines and directives. In addition, we are taking the following steps to minimize the risk of COVID-19:

All research at the New York State Psychiatric Institute (NYSPI) has been modified to reduce in person visits and procedures.

- We now use technology (telephone and computer) to perform all possible research procedures (such as obtaining consent, clinical interviews, symptom scales, and other tests) remotely.
- Only tests and procedures that cannot be performed remotely will take place in-person.

We are monitoring research participants and staff for signs and symptoms of COVID-19.

- You will be contacted by study staff on the day prior to all visits and asked whether you have any symptoms consistent with COVID-19, you will be asked to complete an online COVID-19 screening questionnaire addressing these questions. Upon your arrival to NYSPI, we will again ask you questions about any possible COVID-19 symptoms, ask that you fill out the questionnaire, and take your temperature.
- If you are having any symptoms of COVID-19, we will postpone your visit and recommend you see a medical professional for evaluation.
- All staff are required to monitor themselves for any possible symptoms of COVID-19 and are instructed to stay home and not come to work if they are sick in any way.

We are taking extra precautions at NYSPI to reduce the risk of COVID-19 infection.

- When you enter NYSPI, you will be required to wear a face covering. If you do not have one, you will be given a surgical face mask and face shield.
- Staff will wear masks and other personal protective equipment as appropriate to the procedure (e.g., gowns, gloves, face shields).
- You will be asked to maintain physical distancing (at least 6 feet between you and other people) while at NYSPI where possible, unless specific research procedures require temporarily being closer to study staff.
- Alcohol-based hand sanitizer will be provided at the building entrance and many other areas.
- We are restricting visitor access to only those who are essential for our participants' care. Visitors will be screened for fever and symptoms of COVID-19 prior to entry and will be asked to wear face coverings and limit their movement within NYSPI.

We have increased routine cleaning and disinfection procedures in order to further protect research participants and staff from COVID-19.

- All equipment used by participants (e.g., EKG) will continue to be thoroughly disinfected before and after each participant's use.

SUMMARY SHEET for "The Effect of Dispensed Cannabis on Taxane-Induced Peripheral Neuropathy"

This first page of the consent form is an outline of the study. The full consent form starts on the next page and contains details of the procedures. This outline page is a guide to help you learn about this research study and decide whether or not you want to participate.

This page does not replace the consent form that you will be asked to read and sign. The consent includes the information you'll need to make a decision. Please read the consent form carefully, ask questions and take your time to speak to others, if you want, to before you make your choice. Remember, even if you agree to take part in research you can change your mind at any time.

PURPOSE: The purpose of this study is to find out whether different strengths of cannabis affect neuropathy, or impaired nerve function, in persons with breast cancer who have taken paclitaxel or docetaxel.

ALTERNATIVES: You do not have to participate in this study. You can continue your medical care without participating in this study.

PROCEDURES:

- This study involves the administration of cannabis (marijuana) in different strength capsules, to be taken by mouth. The cannabis used in this study may contain moderate levels of THC, which means that it could make you feel intoxicated. The cannabis capsules may include other components of the plant, such as cannabidiol. Cannabidiol (also called CBD) does not produce intoxication.

- It is very important that only **you** take the cannabis provided and that you keep them out of reach of all others (including pets).

- The study lasts for 8 weeks. There will be a baseline visit (before starting cannabis) and visits every two weeks. We will contact you daily by phone, with an automated questionnaire to remind you to take the capsules.

- Each week we will ask you to complete a series of questionnaires regarding your symptoms and an examination to assess the neuropathy. We will also ask you about any changes to your health. We will draw your blood twice during the study (at 4 and 8 weeks) to check levels of cannabinoids.

RISKS:

- The cannabis capsules may produce effects such as anxiety, paranoia, tiredness, shakiness, and heart pounding. If these symptoms occur, you should be aware that it may take several hours for them to resolve.

- You should not participate in this study if you have heart disease, problems with your blood pressure, or if you are taking certain medications. We will ask about all the medicines you are taking.

- You may find the effects of cannabis capsules to be enjoyable, and there is a risk that you could develop an excessive desire to use cannabis. You will meet with a clinician with expertise in addiction to discuss this issue throughout the study.

NEW YORK STATE PSYCHIATRIC INSTITUTE
COLUMBIA UNIVERSITY DEPARTMENT OF PSYCHIATRY
CLINICAL INVESTIGATION CONSENT FORM

Purpose of Study

The purpose of this research is to study the effects of cannabis on peripheral neuropathy associated with paclitaxel or docetaxel, types of chemotherapy often used to treat breast cancer. The symptoms of neuropathy include numbness and/or pain of the hands and feet, and can sometimes include problems walking normally or picking things up.

In this study, you will be asked to consume capsules daily for 8 weeks. You will need to come to our laboratory every two weeks for questionnaires and assessments. We expect to include 98 volunteers total. This study is funded by the Thompson Family Foundation.

In this study, different groups of volunteers will receive cannabis with different concentrations of Δ-9-THC and cannabidiol. The levels of Δ-9-THC may make you feel tired or intoxicated. Cannabidiol does not have perceptible effects. Neither you nor the research staff will know which type of cannabis you are receiving from day to day. At the end of the 8 weeks, we will refer you to a medical marijuana dispensary if you wish.

You should not participate in this study if you have heart problems, such as a prior heart attack or an arrhythmia. You should also not participate if you have problems with your blood pressure. Certain medications can interact with cannabis, and we will ask you about your medications.

Participation is Voluntary: Participation in this project is voluntary, and you may refuse to participate or discontinue participation at any time without loss of benefits to which you are otherwise entitled. You will be informed of any new findings or risks that arise that may affect your willingness to continue in this study. A decision not to participate in this study or to withdraw at any time will not affect your present or future medical care at either the Columbia University Medical Center or the NYS Psychiatric Institute. The investigator may also decide that your participation should be discontinued, if he/she thinks that this is better for you.

Participation in an Additional Study: There is another study that we invite you to participate in, if you wish, that looks at changes in the nerves in the cornea, which is the clear covering of the eyeball. This study involves two eye exams, at the beginning and after 8 weeks of cannabis administration.

If you are interested in hearing more information about this study, please check this box. ☐

Alternatives to Participation

This data is being collected for research only, to learn more about the effects of cannabis and neuropathy. The alternative is to not participate in the study.

Study Procedures

Consent and Screening

The screening process will take 2 visits. The first visit will be done virtually (via computer, telephone or cell phone) while the second visit will be in person. In an effort to minimize in person contact and travel you will be asked to provide verbal (not written) consent for the study outlined here. Before giving verbal consent you should have an electronic or paper copy of this form, have had sufficient time to read it, have discussed the risks of the screening procedures with a member of the research team, and had an

opportunity to ask questions. We will additionally ask you to indicate your consent through an electronic version of this form on a HIPAA compliant secure platform.

We will ask that you complete some written questionnaires on a computer or mobile phone. After this, we will schedule you for an in-person visit if you qualify and are interested in continuing your participation.

In the virtual visit, we will ask a series of questions regarding your health and medical diagnoses. We will also ask for your permission to notify your cancer doctor, so that they know that you are interested in participating in this study. We will also ask for copies of your lab work, so that we don't have to repeat them. If we can't get lab work from your doctor, we will draw your blood in the in-person screening visit.

The in-person screening visit will include an ECG, to look at your heart, a urine pregnancy test, a physical exam, and blood draw (if you don't have your lab results available). If you are pregnant, you will not be eligible to participate. We will test your urine for drug use before starting and occasionally throughout participation.

<u>During the Study</u>

The capsules will be supplied by Tilray, a Canadian company that provides cannabis products to medical patients. You will be given a weekly supply of capsules at each laboratory visit. You will start with one capsule in the evening and will slowly increase the number of capsules to a maximum of 3 per day. Please know that we will increase the number of capsules only if you are comfortable with this change. Sensitivity to cannabis products varies considerably between people. We expect that the many participants will tolerate 3 doses/day, but it is important that we find the dose that works well for you, without problematic side effects.

It is important that you not drive or operate machinery if you feel intoxicated in any way from the capsules. As the dose is raised it is important that you start with the additional capsule at a time when you are not driving or have important things to take care of. Taking capsules shortly after a heavy meal may increase intoxication relative to a lighter meal.

We will contact you once daily by text and/or email to ask you to answer questions about your study medication, pain you may be having, and about sleep. On one day a week we will ask that you complete a longer questionnaire that asks about quality of life, and about symptoms of neuropathy (numbness, and tingling or burning).

<u>Laboratory visits:</u>

We will ask that you attend visits every two weeks during the study. The first baseline visit will be before you start taking cannabis. We will ask you to fill out questionnaires, perform an exam, and assess your symptoms of neuropathy using the following assessments:

1) We will also ask you about the medications you are taking and how you are sleeping. We will ask you to fill these out using online questionnaires.
2) An exam where we determine how well you can detect touch using a cube with grooves of different sizes. For this test, you will wear shielded glasses and we will ask you to tell us the direction of grooves of different sizes. This test will be performed on the hand that you think is most affected by neuropathy. This test takes about 30 minutes.
3) An exam of sensitivity of the hand. You will again be asked to wear shielded glasses and this test will be performed on the hand that you think is most affected by neuropathy. Filaments of

different sizes will be placed on the palm of the hand and we will ask you if you can feel it or not. This test takes about 30 minutes.

At these visits we will perform some but not all of these tests (there is a schedule on the next page). We will ask to draw blood to check cannabinoid levels at 4 and 8 weeks after you start taking the cannabis. We will take less than a teaspoon of blood each of these times. At the visit of week 8, we will perform all of these tests again.

If you prefer to have fewer in-person visits at the lab, you can opt out of two lab visits (weeks 2 and 6). On the weeks that we do not see you personally we will talk to you by phone. However, you do not have to wait for this phone call to discuss any issues that you may have with the study or the medication (you can call any time). We will ask that you complete questionnaires every day. We will ask that you do these online even when you do not have a visit with us (by text or email).

Below is a schedule of these visits:

Visit	Questionnaires (every week)	Laboratory Visits	Sense of touch tests	Test of Sensitivity	Blood level
Baseline	x	x	x	x	
Week #1	x				
Week #2	x	x (optional)	**x**	**x**	
Week #3	x				
Week #4	x	x	x	x	x
Week #5	x				
Week #6	x	x (optional)	**x**	**x**	
Week #7	x				
Week #8	x	x	x	x	x

End of the study:

Once you have completed the 8 weeks of visits, we will not be able to provide cannabis through our lab. Once you complete the study, we will provide you with New York State medical marijuana certification for 6 months after the study ends and we will help you find a dispensary near you. However, you will be responsible for purchasing the cannabis from the dispensary. If you wish to continue with medical marijuana after the six months, we will provide you with a list of medical marijuana doctors. We will ask that you contact us monthly during this time and that you complete the questionnaires**.**

Risks

You may experience side effects which could include: anxiety, sad mood, sleepiness, concentration difficulties, faintness, restlessness, confusion, lightheadedness, loss of coordination, clumsiness, shakiness, dizziness, stomach upset, headache, paleness, flushing, sweating, dry mouth, slurred speech, fatigue, itching, heart pounding, and changes in the pattern of heart beats. Additional potential side effects include: CBD may cause sleepiness, decreased appetite, diarrhea, fatigue, malaise; asthenia, and poor quality sleep

There is a risk of heart attack or stroke in patients using cannabis who have a known history of heart disease. There is also a risk of cannabis quickly lowering blood pressure, which can exacerbate orthostatic hypotension or hypertension, if you have this.

Cannabis can also interact with certain medications. We will review your medications with you each week to reduce the risk of a medication interaction.

There is little evidence that cannabidiol has effects that you may feel, although it is possible that you may feel sleepy. Cannabidiol is not listed as a carcinogen (a substance that causes cancer) by the International Agency for Research on Cancer. However, cannabidiol exposure may have a harmful effect on a fetus or a newborn, and you will not be allowed to participate in the study if you are pregnant or breastfeeding during the study, or if you cannot use an appropriate contraception method.

You may also feel that you are at risk for wanting to take cannabis too often. We will discuss this with you, and we will provide you with a referral if needed.

The risk of drawing blood includes a bruise at the site of the blood draw, and the potential for infection.

For females of childbearing age: If you are pregnant, you cannot participate in the study. A negative urine pregnancy test is required at the time of screening and urine pregnancy tests will be repeated weekly in females of childbearing potential. However, since these tests might not detect the very early phase of pregnancy, you should not participate in this study if you do not use a reliable contraceptive method, such as condoms, diaphragm, birth control pill, or IUD.

Benefits

The benefits of participating in the research relate primarily to the general scientific value of gaining a better understanding of the effects of cannabis on neuropathy.

Compensation

You will be compensated as follows: 1) $40 for the screening visit, 2) $4 each day for completing the Qualtrics questionnaires; 3) $30 for each of the baseline lab visit (virtual and in-person) and $40 for each of the laboratory visits (weeks 2, 4 and 6, which last about 1 hour); 4) $140 for the end of study laboratory visit (week 8, about 3 hours). Thus, the total is up to $584.

We will provide transportation (car service) to all in-person lab visits. We will pay you in cash for the in-person visits. We will pay you with a gift card for the virtual visits, which will be mailed to you. However, if you decide that you would rather be paid in cash for the virtual visits, we will hold your payment until you come to the lab.

If you are interested, you can refer other people to us who might be interested in this study. If you do, you will receive a $100 fee for each person you refer once that person successfully enrolls and completes an in-person baseline visit.

You will also be reimbursed the $50 medical marijuana card application when you complete the study (week 8).

Confidentiality

Records will be available to research staff, and to Federal, State and Institutional regulatory personnel (who may review records as part of routine audits). Your records will be kept in a locked room and information gathered on you will not be shared. However, because the study is regulated by the Food and Drug Administration (FDA) staff from this agency and other Department of Health and Human Services

(DHHS) agencies may review records that identify you. Institutional personnel can also review records as part of routine audits.

When results of this study are presented or published, your name will not be used. Your name and other personal identifying information will be stored in an electronically secure database at the New York State Psychiatric Institute. Research records will only be available to research staff and the Food and Drug Administration (FDA). Signed consent forms will be kept in a locked file and electronic data will be maintained on password-protected computers.

All biological specimens that we collect from you (blood and urine samples) will be disposed of, and not kept for future research. Biological specimens we collect from you will not be used for commercial profit or genetic testing.

De-identified data (data without your personal information) obtained from you in this study will be kept for future research or analysis either for the investigators of this study or may be shared with other researchers.

We will also maintain your information to contact you in case there are research studies in the future for which you might be eligible and interested, unless you let us know that you do not want to be contacted for participation in future research studies. Your name and contact information will be protected as described above.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Following the NYSPI Remote Communications Guidance, confidentiality of remote communication is protected confidentiality through the use of secure HIPAA compliant telecommunication (e.g. Webex, Facetime, or telephone) in combination with digital data collection procedures (remote access to secure NYSPI systems and encrypted email).

Research Standards and Rights of Participants

In Case of Injury:

Federal regulations require that research participants be informed about our institution's policy with regard to the provision of treatment and compensation for research-related injuries. In case of injury, New York State Psychiatric Institute will provide short term emergency medical treatment, which has been determined to be necessary by New York State Psychiatric Institute's doctors, and which is within the capability of New York State Psychiatric Institute to provide. In addition, we will provide assistance in arranging follow up care in such instances.

New York State Psychiatric Institute and Research Foundation for Mental Hygiene do not provide compensation or payment for treatment of research related injuries. However, you should be aware that you do not give up your legal right to seek such compensation through the court by participating in this research.

If you believe that you have sustained an injury as a result of participating in this research study, you should contact the Principal Investigator, Dr. Martinez at (646) 774-6160 so that we can review the matter and identify medical resources that may be available to you.

Questions:

The investigators will answer, to the best of their ability, any questions you may have now or in the future regarding study procedures or your response to them. If you have any questions, you can call the principal investigator, Dr. Diana Martinez, at (646) 774-6160. If you have any questions about your rights as a research participant, want to provide feedback, or have a complaint, you may call the NYSPI Institutional Review Board (IRB). An IRB is a committee that protects the rights of participants in research studies. You may call the IRB Office at (646)774-7155 during regular office hours.

You will be given a copy of this consent form to keep.

Statement of Consent

I voluntarily agree to participate in the research study described above.

_____

Signature of Subject Date

_____

Printed Name of Subject

Statement of the Physician Investigator

I have discussed the proposed research with the participant, and, in my opinion, the participant understands the benefits, risks and alternatives (including the alternative of not participating in the research) and is capable of freely consenting to participate in this research.

_____

Signature of Study Physician obtaining consent Date

_____

Printed Name of Study Physician