VIVITROL ASSOCIATED WITH BEHAVIORAL-RELAPSE PREVENTION STRATEGY AS TREATMENT FOR CANNABIS USE DISORDER

Principal Investigator: Bernard Le Foll, MD PhD
Head Translational Addiction Research Laboratory, CAMH

Co-Investigators: Tony George, MD
Clinician Scientist, CAMH

Benedikt Fischer, Ph.D
Chair in Addiction Research, University of Auckland

Lena Quilty, PhD
Psychologist and Independent Scientist, Clinical Research, CAMH

Jose Trigo, PhD
Senior Research Scientist, Battelle, Baltimore

Principal Investigator Signature: _____ **Date:** _____
(dd/mm/yy)

Qualified Investigator Signature: _____ **Date:** _____
(dd/mm/yy)

INTRODUCTION

Cannabis exposure, use disorders and treatment in North America

Cannabis is the most widely used illicit substance worldwide [1]. Those who have used cannabis at least once (aged 15 to 64) are estimated to be 128-232 million, or 2.7 to 4.9% of the world's population [2]. There is a high prevalence of use in North America and a gradual increase since 2007 [2]. Cannabis use prevalence has important implications for public health [3-5] and its use has been associated with a variety of health problems including cognitive [6] and respiratory impairment [7], psychotic episodes [8], injury risk [9] and dependence [10, 11]. Research indicates that about 8% of those who ever use cannabis may develop cannabis dependence [12, 13]. However, there is currently no approved pharmacotherapy for cannabis dependence [14, 15]. Due to the significant impact of problematic cannabis use on individuals and society, and thereby, the increasing demand for treatment, several research teams have focused on developing medications for cannabis dependence treatment [14, 16]. These studies have mainly tested the potential utility of pharmacotherapies available for other indications (e.g. cannabinoid drugs, antidepressants, anxiolytics, and antipsychotics).

Cannabis use prevalence is important for public health [5, 17, 18], as it could be shown, that the number of problem users and cannabis-attributable problems depend on overall prevalence. Research indicates that about 10% of those who ever use cannabis become regular daily users [19], which in turn is a strong risk factor for any kind of cannabis-attributable health problems including cannabis use disorders. In 2008, 4.2 million Americans had past year dependence or abuse, representing 1.7 percent of the total population aged 12+; this made up 60.1% of all illicit drug dependence or abuse. In 2007, 15.8% of people entering drug abuse treatment programs in the UWS reported cannabis as their primary drug of abuse (61% of those under 15), representing nearly 288,000 treatment admissions [20]. In Canada, where the study will take place, treatment for problematic cannabis use consists mainly of cognitive behavioral interventions. This is similar to the common practice in the US and worldwide. Despite the fact that this approach is similar for other psychoactive and no novel treatments have been added, a consistently increasing number of individuals with cannabis problems have been admitted to treatment. Specifically, in the past decade, some 25 - 30% of admissions to publicly funded addiction treatment programs across Canada involved individuals with cannabis related problems [21, 22]. According to the Drug and Alcohol Treatment Information System (DATIS), admissions to publicly funded addiction treatment services in 2009/2010 in the province of Ontario, a 38.2% of total cases admissions involved cannabis as a problem substance [23], which represents an increase from previous reports [24].

Interactions between Opioids and Cannabinoids

Opioids and cannabinoids share some common characteristics on their ability to modulate pain, produce sedation, hypotension and motor depression [25-28]. In fact, opioids and cannabinoids have been shown able to modulate their function at many different levels including cross-tolerance, mutual potentiation, and receptor cross talk in pre-clinical models [25, 27-31]. Moreover, specific receptors for both the endogenous opioid system and the endogenous cannabinoid system (i.e., CB1 and μ-opioid receptors) have an overlapped distribution in the limbic system of rodents [32-34]. The intracellular signal response (i.e., G-protein activation) of μ-opioid receptors can be modulated by the stimulation of CB1 receptors [35, 36]. The administration of CB1 agonists is able to regulate the endogenous release of opioids [35, 37-41] and μ-opioid receptor density [42] and intra-accumbens infusions of the cannabinoid antagonist rimonabant decreased intravenous self-administration of heroin in rats [43]. On the other hand, it has been shown that the opioid antagonist naloxone was able to block THC-induced dopamine efflux in the NAc of rats [44]. In fact, studies have shown that opioid antagonists reduce both the discriminative stimulus and reinforcing effects of CB1 agonists [45-47], suggesting that opioid receptor antagonists could reduce cannabis abuse liability.

Based in the pre-clinical research mentioned above it is plausible to think that intervening in the endogenous opioid system might have consequences as well in the endogenous cannabinoid system and its function in humans (and vice versa; indeed, it has been shown that cannabinoids were able modulate opiate dependence [48, 49]). Therefore, several studies have tested the effects of different doses of naltrexone (0, 12, 25, 50, or 100 mg capsules) in cannabinoid effects both in marijuana smokers and nonmarijuana smokers [50, 51]. These early studies found that this oral form of naltrexone enhanced the subjective and cardiovascular effects of marijuana [51]. These effects seem to vary with marijuana use history [50, 51]. Those findings were surprising as the blockade of mu opioid receptor decreased reinforcing effects of THC in animals. More recently, it has been shown that chronic administration of naltrexone (e.g. 16 days) decreases cannabis self-administration and the subjective effects of cannabis in daily cannabis users [52]. Moreover, ongoing open label clinical trials are currently testing the effects of both long-acting injectable naltrexone (Vivitrol®) and oral naltrexone (Revia®, 50 mg per day) in cannabis-dependent patients (ClinicalTrials.gov Identifiers NCT02088177 and NCT01560013, respectively). The duration of treatments in these trials is 2 months (2 injections) for Vivitrol® and 35 days for Revia®. The safety and effectiveness of long term (i.e. 12 weeks) injectable extended-release naltrexone has been recently tested in patients with opioid dependence showing promising results [53]. However, in spite of the evidence showing clear interactions between the opioid and the endocannabinoid systems, no randomized clinical trial has yet evaluated the long-term efficacy of long-acting naltrexone Vivitrol® (380 mg, 4 mL intramuscular injection) in cannabis dependent subjects that are treatment seekers in comparison with placebo.

This project will test the safety and effectiveness of long term (i.e. 12 weeks) administration of the injectable extended-release of naltrexone; Vivitrol®. Vivitrol® is primarily used in the management of alcohol and opioid dependence. Naltrexone maintenance (e.g. oral) seems a promising treatment for cannabis use disorder (CUD). Therefore, administering Vivitrol® may have therapeutic properties for treatment of cannabis use disorder. The data collected will be used to ensure that the administration schedule we have planned for the subsequent future randomized clinical trials is appropriate.

In this study we will focus on the tolerability and effectiveness of the antagonist at the μ-opioid receptor, Vivitrol®, to reduce cannabis use, increase abstinence rates and reduce cannabis withdrawal and craving.

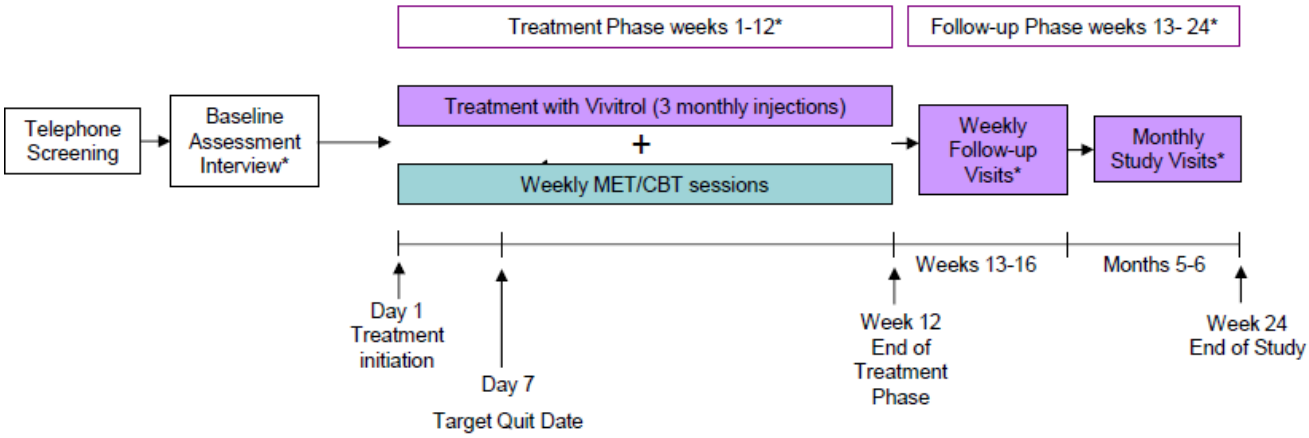
OVERVIEW

The study will be open label, with no placebo control. Ten male and female subjects seeking treatment for cannabis dependence subjects will undergo study procedures as outlined below. Treatment with Vivitrol® will start at day 1 (week 1) and a target quit date will be set up at Day 7 (but subjects will be allowed to stop using cannabis before if they are willing and able to). There will be a total of 12 weeks (3 injections, 1 every 4 weeks) of exposure to Vivitrol®. Study visits will occur weekly during the medication phase of the study. Motivational Enhancement Therapy and Cognitive Behavioral Therapy (MET/CBT) will also start at Week 1 and therefore, all participants will receive a combination of pharmacotherapy (Vivitrol® 4 mL intramuscular injection) associated with MET/CBT for 12-weeks in accordance with the intervention practices shown to be effective in treatment of cannabis dependence [54]. The intervention will be adapted from the Brief Counseling for Marijuana Dependence manual published by the Substance Abuse and Mental Health Services Administration (SAMHSA). In addition, to ensure compliance a Contingency Management plan will be implemented with $5 voucher that will be provided at each visit that is attended and at which biological samples have been provided, but with 5$ voucher loss for a missed appointment. The vouchers will be provided at end of treatment phase and at end of the follow-up phase.

At study visits, vital signs and self-report ratings will be collected. The subjects will have to come once per week (during treatment phase) to the center to assess cannabis and other substances usage

and will be asked to provide urine samples (see Summary of Study Assessments). As there may be compliance issues, a contingency management approach will be also implemented.
Following the medication phase, participants will have a follow-up weekly for another four weeks and then monthly until the 3 month follow up visit after the treatment starting date. We are planning to enroll 10 subjects.

Study Flow Schema



*Please see Summary of Study Assessments for tests administered during this period

Subjects will be pre-screened initially during a telephone interview in which basic medical, psychiatric, and substance abuse histories will be obtained without personal identifiers, contact information will be collected only for eligible participants as for pre-screening. The qualified subjects will then be assessed using the Structured Clinical Interview for *DSM 5* (SCID) and we will assess presence of CUD using *DSM 5* criteria. We will enroll a total of 10 subjects, that will be treated open-label (non blinded) with Vivitrol 380 mg.

Experimental group	**Experimental condition**
Group #1 **(n=10)**	Vivitrol® 380 mg, 4 mL intramuscular injection + MET/CBT

Summary of Study Assessments

Assessment	Baseline	Weekly (Weeks 1-12)	Weekly (Weeks 13-16)	Monthly (months 5-6)
Informed Consent	X			
Psychiatric Evaluation (including SCID)	X			
DSM5 criteria for CUD	X	X (week 12 only)	X (week 13 only)	X (end of trial)
Demographic	X			
Bloodwork (including CBC), Urinalysis	X	X (prior to 2nd and 3rd Vivitrol injections)		X (end of trial)
EKG	X	X (week 1 only)		X (end of trial)
Physical Exam	X			X (end of trial)
Urine Toxicology	X	X (before Vivitrol administration)	X	X
Vital Signs, Carbon Monoxide	X	X	X	X
Serum Pregnancy Test (Females only)	X	If needed	If needed	If needed
Urine Pregnancy Test (Females only)	X	X	X	X
FTND, Cigarette, alcohol and caffeine Time-line Follow-Back (TLFB)	X	X	X	X
Smoking Diary	X	X	X	X
Cannabis TLFB, Marijuana withdrawal checklist (MWC), Marijuana Craving Questionnaire (MCQ)	X	X	X	X
Beck Depression Inventory-II (BDI-II), Hamilton Anxiety Scale (HAM-A), Hamilton Depression Rating Scale (HDRS), Brief Psychiatric Rating Scale (BPRS), Profile of Mood States, Drug Effects Questionnaire (DEQ), Addiction Research Center Inventory marijuana scale, St Mary's Hospital Sleep Questionnaire (SMHSQ)	X	X	X	X
SAFTEE	X	X	X (week 13 only)	X (end of trial)
ASI, World Health Organization Disability Assessment Schedule (WHODAS)	X	X (week 12 only)	X (week 13 only)	X (end of trial)
Urine for THC metabolite analysis	X	X	X	X
Vivitrol® administration		X (once every 4 weeks)		
MET/CBT		X		

Trial Objectives and Purpose:

Primary and Secondary Outcome Measures

Our primary outcome measures: 1) for tolerability will be the number of subjects that drop out because of SAEs and 2) for piloting efficacy will be the seven-day point prevalence cannabis abstinence at the end of medication phase and at the 3 month follow-up;

Secondary outcome measures will be 1) percentage of days of cannabis use over the study duration until the 3 month follow-up; 2) amount of cannabis use over the study duration until the 3 month follow up. 3) effects on withdrawal symptoms scores, craving scores and number of urine samples screen as positive.

Abstinence status will be also based on the urine samples collected during the trial.

PRELIMINARY RESULTS

A CUD treatment clinic has been set up at the Addiction Medicine Service (AMS)/Concurrent Outpatient Medical & Psychosocial Addiction Support Service (COMPASS) that is using the CBT-MET approach as standard of care. We have recruited subjects for pharmacotherapy trial for CUD at CAMH. Those preliminary results demonstrate the feasibility of recruiting the subjects for this study.

METHODS:

Subjects

Inclusion criteria

- Adult (18-64) male or female (gender to be analyzed as a covariate)
- Understand and willing to comply with study requirements and restrictions
- Willing to use appropriate contraceptive method throughout the study
- Otherwise healthy as judged by investigator based on medical history, physical exam, vitals, ECG and labs
- DSM 5 criteria for current CUD
- Report cannabis as primary drug of abuse
- Have cannabis positive urine drug screen
- Treatment seeking cannabis smoker

Exclusion criteria

- Meets DSM 5 diagnostic criteria for a current severe mental disorder, including substance-related and addictive disorders, other than CUD, tobacco use disorder, and caffeine-related disorders
- Unstable medical conditions
- Pregnant or breast-feeding
- Positive urine drug test for opioids (including methadone, morphine, buprenorphine) or benzodiazepines (unless prescribed) at baseline
- Any IM gluteal administration 30 days prior to baseline
- Participation in a clinical trial of a pharmacological agent within 30 days prior to baseline
- Known intolerance and/or hypersensitivity to naltrexone, carboxymethylcellulose, or polylactide-coglycolide
- Any finding that, in the view of the principal investigator, would compromise the subject's ability to fulfill the protocol visit schedule or visit requirement (e.g. unadjudicated charges and/or pending parole hearings)

Pre-study Screening and Baseline/follow up evaluations and questionnaires that will be used:

a) Structured Clinical Interview for DSM 5 severe mental disorders, including substance-related and addictive disorders, other than CUD, tobacco use disorder, and caffeine-related disorders.
b) DSM 5 Criteria for CUD for the past month at baseline, end of treatment and end of follow-up
c) Demographic assessments.
d) Psychiatric/Medical Evaluation and Physical Examination by study physician Weight (kg) and Vital Signs (Temperature, Pulse, Blood Pressure and Respiration Rate). Carbon monoxide will be taken at each study visit to assess exposure to smoke (will reflect both cannabis and tobacco exposure).
e) 12-lead Electrocardiogram (EKG).
f) Blood work, including complete blood count (CBC), electrolytes, renal and liver function tests will be carried out at baseline and prior to the 2nd and 3rd Vivitrol injections.
g) For female subjects, a serum pregnancy test (beta-HCG) at inclusion (and when deemed needed) and weekly urine pregnancy test will be performed. Female subjects will be asked if they are lactating.
h) Ten-panel urine toxicology screen at baseline, and at each study visit to ensure absence of illicit drug use.
i) Substance use assessment including the age of first use, age of regular use, number of days in the past 30 days that the substance was used, number of days in the past week that the substance use used, and the amount of the substance used per using day (i.e. joints per day for cannabis).
j) Cannabis Use will be assessed by toxicology and self-report. Participants will provide a urine sample every week (see assessment schedule). The timeline follow-back (TLFB) will be used to assessing the number of days cannabis was smoked, the amount smoked, and the amount of money spent on cannabis since their last appointment. Smoking diaries will also be completed daily outlining how much cannabis was obtained at a time, how many days that amount lasted, and what amount, if any, was shared.
j) Addiction Severity Index self-report version.
k) Cannabis Withdrawal will be assessed using the Marijuana Withdrawal Checklist with 16 4-point items indicating severity during the prior 24 hours [55]. Cannabis craving will be assessed using the *Cannabis Craving Questionnaire (MCQ) [56].*
l) The sleep disturbance will be assessed using the St Mary's Hospital Sleep Questionnaire (SMHSQ), a self-report instrument developed for use with psychiatric and medical in-patients [57].
m) The Hamilton Anxiety Scale (HAM-A), will be used to assess the affective and vegetative symptoms of anxiety [58].
n) Depressive symptoms will be assessed using the Beck Depression Inventory-II (BDI-II - a self-report depression rating scale has been used extensively in depression treatment research [59]) and the Hamilton Depression Rating Scale (HDRS), 21-item version, a clinical administered rating scale for depression with well-established reliability and validity [60]; The Profile of Mood States [61] will also be used.
o) Psychotic symptoms will be assessed using the Brief Psychiatric Rating Scale (BPRS)
p) Cigarette smoking history including timeline follow-back (TLFB) for the past one week [62]; Pack-Years (average daily smoking consumption in packs per day multiplied by the years smoked); Fagerstrom Test for Nicotine Dependence (FTND).
q) Alcohol and caffeinated beverage use TLFB for the past one week [62].
r) The SAFTEE will be used to monitor for treatment-emergent medication side effects.
s) Participants will complete the Drug Effects Questionnaire (DEQ). The DEQ has five items (feel, high, dislike, like, and more) measured on a 100 mm visual analog scale; the revised Addiction Research Center Inventory marijuana scale [66] will also be used
t) The World Health Organization Disability Assessment Schedule (WHODAS) will be used to

monitor disability status at baseline and at the end of treatment and follow-up.

Pharmacological Treatment: Vivitrol® 380 mg, 4 mL intramuscular injection

Pilot Study in 10 subjects:

There is currently limited information to guide us on the Vivitrol® dosage to use in cannabis dependent individuals that likely have developed strong tolerance to cannabinoids. We are planning to administer Vivitrol® (380 mg, 4 mL intramuscular injection) every 4 weeks. Only eligible participants will be administered study medication (i.e. as per inclusion/exclusion criteria). On the day of the scheduled injection of Vivitrol® participants will be observed by qualified staff (i.e. staff performing injection) for 5-10 minutes for possible injection site reactions. Following injection of study medication the subjects will remain at CAMH facility for rest of study assessments (approx. 30 min to 1 h), so study staff will be able to monitor possible systemic AEs post-dosing. Medications and supportive measures will be available at CAMH clinic as per expected side effects of study medication. Additionally, participants in the study will be regularly assessed during the trial (see above schedule of assessments) for changes in health status, these assessments include ECG, vitals and CBC. The subjects in this study will be treatment-seekers that fit our inclusion/exclusion criteria and that will be treated open-label to ensure good tolerability. These 10 subjects will allow us to determine if our schedule for dosing is appropriate for the subsequent RCTs.

Biological sample collection (excludes samples used for general health assessments)

Urine samples will be collected weekly. All participants will have urine samples collected on the weekly visit. At any point that biological samples are taken, information about the last time the participant may have smoked cannabis and last used the study medication will be collected. All urine samples will be taken at the beginning of the visit to standardize the time. Each urine sample obtained will have creatinine measures and THC quantification determined by the CAMH laboratory. Appropriate temperature control until analysis will be maintained.

Biological sample collection for general health assessments

Urine and blood samples for general health assessments will be collected at Baseline and at the end of trial (see Summary of Study Assessments).

Psychological support: MET/CBT intervention

All subjects will receive a weekly MET/CBT session with a trained therapist. This is an adaptation of a nine-week MET/CBT intervention which has been previously studied for the treatment of cannabis dependence and has been found to be effective [54]. The intervention in the proposed study emphasizes th e development of motivation for change and the implementation of skills to reduce and abstain from cannabis use, using the Brief Counseling for Marijuana Dependence manual published by the Substance Abuse and Mental Health Services Administration (SAMHSA). In this intervention, use of empathic therapeutic style helps resolve ambivalence, increase discrepancies about personal goals and cannabis use, and elicit motivation to change. Once ambivalence about cannabis use is addressed, the sessions focus on the cognitive, behavioral and emotional changes necessary for dealing with cannabis dependence while supplying coping strategies for predictable obstacles. As studies of psychosocial interventions in cannabis dependence have shown that more intensive interventions have a more sustainable outcome [54], the MET/CBT sessions in the proposed trial will continue for 12 weeks. The current SAMHSA manual provides an outline for this intervention for 9 weeks and provides 4 additional elective topics. In this study, participants will receive the 9 weekly sessions as outlined and then provided 3 of these elective topics for a total of 12 weeks. These elective topics will be identical amongst all participants. Addition of this intervention will allow for the necessary conditions to assess the additive value of treatment with Vivitrol® for cannabis use disorder.

We will seek participant's permission to audio record the MET/CBT sessions. A proportion of these audio recordings will be reviewed by a member of the research team to confirm that the assessment measures and the psychotherapy are provided according to standardized instructions [63-65].
MET/CBT may be conducted remotely by video call (i.e. Webex) if necessary. Remote therapy sessions will be conducted in accordance with the CAMH Research Guidelines for Virtual Participant Sessions.

Remote (WebEx) session conduct: Participants who provide consent for email communication will be sent a WebEX link and related information using an email template. Participants will be reminded that email is not secure means of communication and that there are potential security risks associated with videoconferencing software; that they will be required to provide an emergency contact, an alternate contact number, and their current address to confirm their location in case there are safety concerns; that their audio (but not video) will be recorded; and that a member of the technical team may join the call if there are technical problems.
At the beginning of the session, the participant will be reminded that audio (but not video) will be recorded and the fixed location, emergency contact, and alternate contact number of the participant will be confirmed. Participants will be reminded of relevant contingencies; i.e., if there is a technical issue, a member of the technical team may join the call; if the participant unexpectedly drops off the WebEx call, the alternate contact information will be used to regain contact; and if there are any safety concerns, the participant's location and emergency contact information will be used to contact emergency services.

Recruitment:
Participants will be mainly recruited from individuals seeking treatment within the CAMH Addiction Program. Information about this study may be presented to individuals through a brochure that will be present within the clinics or potentially by a clinician directly to their patients. After reviewing the information in the brochure, interested parties can contact the study staff through the telephone number provided in this brochure to obtain further detailed information about the study. In addition, staff in clinics at CAMH may identify potential participants that are CAMH clients who indicated via the concurrent disorder screener collected by Access CAMH on initial intake that they would be interested in being contacted for research. Clinic staff would then contact the client to provide study details. Clinic staff will be provided with a script to use when contacting clients who have indicated interest in learning more about research projects they may be eligible for. CLEARR process for recruitment - a delegated Research Coordinator under the supervision of a CLEARR team recruiting clinician will identify potential participants and notify the client's clinician about the client's eligibility to participate in this research study. The clinician will then ask their client if they would be willing to meet with a study team member about participating in this study. Only with a clients' agreement will they be approached. If a client is enrolled in the study and consents to it, their participation in this study will be noted in their medical chart. Subjects will be also recruited from other addiction clinics or medical centers located in Toronto, by word of mouth, smoke paraphernalia shops (e.g. brochures/posters will be made available at these shops), local advertisement in Toronto newspapers, social online networks (e.g. facebook), and through posters distributed in and around the CAMH and the University of Toronto campuses and on the CAMH "find a study" registry. Ads will also be posted online on U of T bulletins, Craigslist and similar websites, local magazines such as NOW! Or Eye Weekly and other mass media as radio, TTC, tv (e.g. Tim's tv advertisement) or online advertisement platforms at google ads or in youtube (e.g. as inserted advertisement) may also be used to recruit prospective subjects. Ads and fliers will be will approved by CAMH's Research Ethics Board (REB). Subject eligibility will be initially determined through a telephone interview prescreening to assess potential eligibility.

Participant Compensation:
Once participants are deemed eligible to be enrolled in the study (following baseline assessments) the total monetary compensation provided to participants in this study will be $700. They will be provided

$200 upon completion of the first 4 weeks of the trial, $200 after completion of the 12 week medication phase and $300 after completion of the follow-up period.

Due to the frequent visits required to CAMH, participants will also be provided with TTC tickets (or its cash value if preferred by participants) during treatment and follow-up visits as required.

Contingency Management
Participants will be provided with a $5 voucher for each visit where a sample of urine or blood is collected, however for each missed appointment, a $5 value will be subtracted from the total amount. These vouchers will be provided at two separate times, after completion of the treatment phase of the study, and after completion of the follow-up period.

In order to engage participants and to maximize returns to CAMH for weekly visits, a "fish-bowl prize" system will be instituted where during each visit participants will have a chance to reach within a large bowl/drum and select a ticket which provides a chance to win a prize. These prizes will range from tickets containing motivational messages, a small prize such as a pen or notepad, a $5 gift card to Tim Hortons up to a to a maximum prize of $50 in the form of a gift card to a number of establishments including restaurants, grocery stores, or retail merchants.

Data analysis: All analyses will be implemented in SPSS v24.0. Associations with p-values of less than 0.05 will be considered statistically significant, and all tests will be 2-sided. The data will be screened prior to analysis to ensure that the underlying assumptions for all subsequent statistical procedures are met. Preliminary analyses will include chi-square tests, t-tests, and Mann-Whitney U tests.
Our Primary outcome measures will be: 1) tolerability which will be assessed by determining the number of participants who withdraw from the study because of SAEs and 2) pilot efficacy of this intervention will be assessed by assessing seven-day point prevalence cannabis abstinence one week after the end of medication phase; and at 3 month follow up. Secondary outcome measures will be: 1) percentage of days of cannabis use over the study duration until the 3 month follow up; 2) amount of cannabis use over the study duration until the 3 month follow up; 3) effects on withdrawal symptoms scores, craving scores and number of urine samples screen as positive and 4) DSM5 criteria for CUD at the end of treatment and follow-up as compared with baseline. Efficacy analyses of count variables (e.g. number of joints per week) will be performed using generalized estimating equations (GEEs), specifying a negative-binomial distribution for the counts. Linear mixed models will be used to analyze continuous, secondary outcome measures (e.g. mood and anxiety ratings, physiological measures). All efficacy analyses will be by intention-to-treat. Treatment week will measure changes within-subjects. Subjects will be considered abstinent based on self-report TLFB. Thus, standard urine sampling for THC metabolites will be use as a measure of abstinence in this study. Urine samples will be collected and analyzed for THC metabolites.

Procedure for accounting for missing, unused, and spurious data: In the final report the procedures used to deal with missing, unused or spurious data in statistical analyses will be described.

Procedures for reporting deviations from the original statistical plan: Any deviation from the planned statistical analyses will be described in the final report.

Power calculation: The goal is to collect pilot data to demonstrate tolerability and trend for efficacy of Vivitrol® for treatment of cannabis dependence. We are hypothesizing that the use of cannabis will decrease by at least 50% after treatment with Vivitrol®. Assuming Cannabis use of around 9.5 g (SD = 5) at baseline [as per paper], a sample of 10 subjects will give us 80% power to detect a decrease in cannabis use of 50% from baseline to the last time point. The power calculation was conducted through Monte Carlo simulation, where 5000 replications were conducted. It was also assumed that the

correlation between baseline and the last time point was 0.6. A Mixed Effect Model was adjusted for each replication, where Time was the only Fixed Effect and Subjects entered the model as Random Effects. The power in such simulation is defined as the proportion of the replications where the Time effect is significant at confidence level 0.05 and two tailed test. No dropout was assumed.

Termination of the Study
Reasons for withdrawing individual subjects from the study may include one or more of the following:

1) Severe side effects;
2) Major protocol deviation;
3) Subject lost to follow-up;
4) Withdrawal of consent;
5) Pregnancy

Any subject may be discontinued from the study at the discretion of the investigators if it is deemed to be in the best interest of the subject.

Study Documentation
Investigators will retain a subject identification code list if they need to contact subjects after the study. This list will contain the complete name, identification number, address and phone number of all subjects and will be held confidentially at the investigators site after completion of the study.
A CRF will be completed for each subject enrolled in the study. A subject screening log, noting reasons for screen failure, where applicable, will be maintained for all subjects. All information recorded on the CRFs for this study will be consistent with the subject's source documentation (e.g. medical records). The investigator will document the obtained informed consent and record all medication administration, medical history, results of laboratory tests and adverse events in the CRF. Laboratory printouts and psychometric assessments will be considered source documents and will be incorporated into the CRF without transcription in a confidential manner.

The data collected during the study will be typed or written onto the CRF and other study documents using a ballpoint pen. If an error is made, it will be crossed out with a single horizontal line, and the new information clearly recorded next to the error, initialed and dated. Correction fluid is not allowed at any time.

REDCap will be used as a case report form and as a data collection tool. Data collected directly into REDCap will be the following self-report questionnaires, which will be completed directly by the participant under the supervision of research staff: FTND, MWC, MCQ, BDI, POMS, DEQ, SMHSQ, WHODAS, ASI. The participant identity/identification number will be checked by research staff at the time any self-report questionnaires are administered. Where REDCap is used for the purpose of data collection (i.e. in the case of self-report questionnaires), the data entered into REDCap will be considered as source. Data may be collected on paper CRFs where REDCap is not available, and if so such data will later be transcribed into REDCap. Other study data collected on source documents (such as paper CRFs) will be transcribed into REDCap, with source documents retained securely. The investigators will maintain the accuracy and completeness of REDCap records for each participant. No PHI will be stored in REDCap. All data entered into REDCap will be stored in a de-identified manner (i.e. coded with participant number).

REDCap may also be used instead of a paper telephone screening form to capture data collected during an initial telephone interview for screening purposes. No PHI will be stored in the REDCap screening project. Instead, all data entered into REDCap will be stored in a de-identified manner (i.e. coded with participant screening number).

Archiving of Study Documentation
Study data and other essential documents will be retained in a secure setting by the investigators for a period of 25 years as required by Health Canada regulations.

Confidentiality
All personal study participant data collected and processed for the purposes of this study will be managed by the investigators and their research staff with adequate precautions to ensure the confidentiality of this data, and in accordance with applicable national and local laws and regulations on personal data protection. Study data will be de-identified or coded. A master linking log with identifiers will be kept and stored separately from the data. The ethics committees approving this research and Health Canada will be granted direct access to the study participant's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subjects, to the extent permitted by the law and regulations. In any presentations of the results of this study at meetings or in publications, the subject's identity will remain confidential.

Summary of risks and benefits to subjects:

Risks Associated with the Medication
Vivitrol® is a medication approved by the U.S. Food and Drug Administration for the treatment of alcohol and opioid dependence. Therefore, current evidence shows only the risks of using Vivitrol® associated with opioid and alcohol dependence. The risks of using Vivitrol® associated with cannabis use disorder are still unknown. Research staff and study physicians will be made aware of the serious adverse reactions that may be associated with Vivitrol® therapy in clinical use, which include: severe injection site reactions, eosinophilic pneumonia, serious allergic reactions, unintended precipitation of opioid withdrawal, accidental opioid overdose and depression and suicidality.

The adverse events seen most frequently in association with Vivitrol® therapy for alcohol dependence (i.e., those occurring in ≥5% and at least twice as frequently with Vivitrol® than placebo) include nausea, vomiting, injection site reactions (including localized swelling, itching of the skin, nodules and swelling), muscle cramps, dizziness or syncope, somnolence or sedation, anorexia, decreased appetite or other appetite disorders.

The adverse events seen most frequently in association with Vivitrol® therapy in opioid-dependent patients (ie, those occurring in ≥2% and at least twice as frequently with Vivitrol® than placebo) were hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache.

Female participants will be required to take measures to avoid becoming pregnant during the study. Acceptable contraceptive methods include: barrier methods of contraception (e.g. male condom, female condom, cervical cap, diaphragm, contraceptive sponge).

Note: No barrier method by itself achieves a highly effective standard of contraception. The proper use of diaphragm or cervical cap includes use of spermicide and is considered one barrier method. The cervical cap and contraceptive sponge are less effective in parous women. The use of spermicide alone is not considered a suitable barrier method for contraception.

When used consistently and correctly, "double barrier" methods of contraception (e.g. male condom with diaphragm, male condom with cervical cap) can be used as an effective alternative to the highly effective contraception methods described below. The consistent and correct use of a male condom in

association with spermicide may be considered an acceptable barrier method in some clinical trial settings, for this study the above decision will be at the discretion of the study physician.

Female participants that underwent or currently using highly effective methods of contraception (i.e. hormonal contraceptives, intrauterine device (IUD) or intrauterine system (IUS)), will be also eligible for the trial.

Potential participants will be informed of these and other additional information regarding study medication during the informed consent process.

Other warnings and precautions to follow with Vivitrol® include:

Vulnerability to Opioid Overdose: Following Vivitrol® treatment opioid tolerance is reduced from pretreatment baseline, and patients are vulnerable to potentially fatal overdose at the end of a dosing interval, after missing a dose, or after discontinuing Vivitrol® treatment. Attempts to overcome blockade may also lead to fatal overdose (see product information for Vivitrol® for more detail).

Injection Site Reactions: In some cases, injection site reactions may be very severe. Some cases of injection site reactions required surgical intervention see product information for Vivitrol® for more detail).

Precipitation of Opioid Withdrawal: Opioid-dependent and opioid-using patients, including those being treated for alcohol dependence, should be opioid-free before starting Vivitrol® treatment, and should notify healthcare providers of any recent opioid use. An opioid-free duration of a minimum of 7-10 days is recommended for patients to avoid precipitation of opioid withdrawal that may be severe enough to require hospitalization (see product information for Vivitrol® for more detail). Participants will be advised to be off all opioids, including opioid-containing medicines, for a minimum of 7 – 10 days before starting Vivitrol® in order to avoid precipitation of opioid withdrawal, opioid use will be based in self-report and urine drug screen during baseline and before treatment initiation, only those participants showing absence of opioid in urine will initiate treatment with Vivitrol®. For those patients transitioning from buprenorphine or methadone they may be vulnerable to precipitation of withdrawal symptoms for as long as two weeks. Healthcare providers will therefore inquiry about any recent use of opioids or any history of opioid dependence before starting Vivitrol® to avoid precipitation of opioid withdrawal.

Hepatotoxicity: Cases of hepatitis and clinically significant liver dysfunction were observed in association with Vivitrol® treatment during the clinical development program and in the postmarketing period. Discontinue use of Vivitrol® in the event of symptoms or signs of acute hepatitis (see product information for Vivitrol® for more detail). The results of liver function tests and CBC prior to the 2nd and 3rd Vivitrol injections will serve as safety monitoring for treatment-emergent AEs and to better inform the clinical judgment regarding the safety of continued dosing of Vivitrol in the present study.

Depression and Suicidality: Monitor patients for the development of depression or suicidal thinking (see product information for Vivitrol® for more detail).

When Reversal of Vivitrol® Blockade Is Required for Pain Management: In an emergency situation in patients receiving Vivitrol®, suggestions for pain management include regional analgesia or use of non-opioid analgesics (see product information for Vivitrol® for more detail).

Study staff will recommend participants to inform their primary care physician/clinic of their participation on this study. Alternatively, if participants are agreeable (i.e. during the informed consent), study staff will notify their primary care physician(s) or specialist(s) of their participation in this study. Additionally, a wallet card will be provided to participants in this study to alert medical personnel to the fact that they are taking Vivitrol®.

Physicians should include the following issues in discussions with participants/patients for whom they prescribe Vivitrol®:

Advise patients that if they previously used opioids, they may be more sensitive to lower doses of opioids and at risk of accidental overdose should they use opioids when their next dose is due, if they miss a dose, or after Vivitrol® treatment is discontinued. It is important that patients inform family members and the people closest to the patient of this increased sensitivity to opioids and the risk of overdose.

Advise patients that because Vivitrol® can block the effects of opioids, patients will not perceive any effect if they attempt to self-administer heroin or any other opioid drug in small doses while on Vivitrol®. Further, emphasize that administration of large doses of heroin or any other opioid to try to bypass the blockade and get high while on Vivitrol® may lead to serious injury, coma, or death.

Patients on Vivitrol® may not experience the expected effects from opioid-containing analgesic, antidiarrheal, or antitussive medications.

Advise patients that a reaction at the site of Vivitrol® injection may occur. Reactions include pain, tenderness, induration, swelling, erythema, bruising, or pruritus. Serious injection site reactions including necrosis may occur. Some of these injection site reactions have required surgery. Patients will receive their injection from a healthcare provider qualified to administer the injection. Patients should be advised to seek medical attention for worsening skin reactions.

Advise patients that they should be off all opioids, including opioid-containing medicines, for a minimum of 7 – 10 days before starting Vivitrol® in order to avoid precipitation of opioid withdrawal. Patients transitioning from buprenorphine or methadone may be vulnerable to precipitation of withdrawal symptoms for as long as two weeks. Ensure that patients understand that withdrawal precipitated by administration of an opioid antagonist may be severe enough to require hospitalization if they have not been opioid-free for an adequate period of time, and is different from the experience of spontaneous withdrawal that occurs with discontinuation of opioid in a dependent individual. Advise patients that they should not take Vivitrol® if they have any symptoms of opioid withdrawal. Advise all patients, including those with alcohol dependence, that it is imperative to notify healthcare providers of any recent use of opioids or any history of opioid dependence before starting Vivitrol® to avoid precipitation of opioid withdrawal.
Advise patients that Vivitrol® may cause liver injury. Patients should immediately notify their physician if they develop symptoms and/or signs of liver disease.

Advise patients that they may experience depression while taking Vivitrol®. It is important that patients inform family members and the people closest to the patient that they are taking Vivitrol® and that they should call a doctor right away should they become depressed or experience symptoms of depression.

Advise patients to carry documentation to alert medical personnel to the fact that they are taking Vivitrol® (naltrexone for extended-release injectable suspension). This will help to ensure that patients obtain adequate medical treatment in an emergency.

Advise patients that Vivitrol® may cause an allergic pneumonia. Patients should immediately notify their physician if they develop signs and symptoms of pneumonia, including dyspnea, coughing, or wheezing.

Advise patients that they should not take Vivitrol® if they are allergic to Vivitrol® or any of the microsphere or diluent components.

Advise patients that they may experience nausea following the initial injection of Vivitrol®. These episodes of nausea tend to be mild and subside within a few days post-injection. Patients are less likely to experience nausea in subsequent injections. Patients should be advised that they may also experience tiredness, headache, vomiting, decreased appetite, painful joints and muscle cramps.

Advise patients that because Vivitrol® is an intramuscular injection and not an implanted device, once Vivitrol® is injected, it is not possible to remove it from the body.

Advise patients that Vivitrol® has been shown to treat alcohol and opioid dependence only when used as part of a treatment program that includes counseling and support.

Advise patients that dizziness may occur with Vivitrol® treatment, and they should avoid driving or operating heavy machinery until they have determined how Vivitrol® affects them.

Other events were observed during the Vivitrol® Clinical Studies (in alcohol- and/or opioid-dependent subjects treated with Vivitrol®), including events for which a drug cause was remote, events that were so general as to be uninformative, and those events reported only once that did not have a substantial probability of being acutely life-threatening (see product information for Vivitrol® for more detail).

Adverse Events Reporting
In the event of a serious adverse event (SAE), whether related to study drug or not, the Principal / Qualified investigator will notify REB of its occurrence and will submit the necessary documentation to their attention within timelines provided in CAMH SOP HSR207 Serious Adverse Event (SAE) Reporting. Only SAEs that are Serious unexpected adverse drug reaction (SUADR) will be reported to Health Canada as outlined in ICH E2A Clinical Safety Data Management Definitions and Standards for Expediting Reporting. While only SAEs and SUADRs will be reported as documented above, every adverse event will be assessed and recorded in the subject's research record by research staff working on the study and reviewed regularly by the Principal/Qualified Investigator. AEs will be documented and reported as mandated by current regulations.

The trial will be conducted in compliance with protocol, GCP, and applicable regulatory requirements.

Direct Access to Source data/documents: The PI and QI will permit trial-related monitoring, audits, REB review, and regulatory inspections, by providing direct access to source data/documents. This is outlined in the informed consent form. Monitoring will be conducted according to the study monitoring plan.

Financing and insurance: The study is funded by the Alkermes Inc. This study is performed under usual arrangements for studies that are conducted at CAMH. No specific insurance has been taken.

Publication policy: Scientific publications of study data will be sought in peer reviewed journals and authorship will be in accordance with journal policies.

REFERENCES:

1. UNODC. *United Nations Office on Drugs and Crime. World Drug Report 2016*. 2016; Available from: https://www.unodc.org/doc/wdr2016/WORLD_DRUG_REPORT_2016_web.pdf.
2. UNODC. *United Nations Office on Drugs and Crime. World Drug Report 2015*. 2015; Available from: https://www.unodc.org/documents/wdr2015/World_Drug_Report_2015.pdf.
3. Fischer, B., et al., *Crude estimates of cannabis-attributable mortality and morbidity in Canada-implications for public health focused intervention priorities.* J Public Health (Oxf), 2016. **38**(1): p. 183-8.
4. Fischer, B., J. Rehm, and W. Hall, *Cannabis use in Canada: the need for a 'public health' approach.* Can J Public Health, 2009. **100**(2): p. 101-3.
5. Room, R., et al., eds. *Cannabis policy: Moving beyond stalemate*. 2010, Oxford University Press: New York, NY.
6. Crean, R.D., et al., *Effects of chronic, heavy cannabis use on executive functions.* J Addict Med, 2011. **5**(1): p. 9-15.
7. Tashkin, D.P., et al., *Respiratory and immunologic consequences of marijuana smoking.* J Clin Pharmacol, 2002. **42**(11 Suppl): p. 71S-81S.
8. Di Forti, M., et al., *Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study.* Lancet Psychiatry, 2015. **2**(3): p. 233-8.
9. Hartman, R.L., et al., *Cannabis effects on driving lateral control with and without alcohol.* Drug Alcohol Depend, 2015. **154**: p. 25-37.
10. Hasin, D.S., et al., *Prevalence of Marijuana Use Disorders in the United States Between 2001-2002 and 2012-2013.* JAMA Psychiatry, 2015. **72**(12): p. 1235-42.
11. Winters, K.C. and C.Y. Lee, *Likelihood of developing an alcohol and cannabis use disorder during youth: association with recent use and age.* Drug Alcohol Depend, 2008. **92**(1-3): p. 239-47.
12. Lev-Ran, S., et al., *Gender differences in prevalence of substance use disorders among individuals with lifetime exposure to substances: results from a large representative sample.* Am J Addict, 2013. **22**(1): p. 7-13.
13. Wagner, F.A. and J.C. Anthony, *From first drug use to drug dependence; developmental periods of risk for dependence upon marijuana, cocaine, and alcohol.* Neuropsychopharmacology, 2002. **26**(4): p. 479-88.
14. Marshall, K., et al., *Pharmacotherapies for cannabis dependence.* Cochrane Database Syst Rev, 2014. **12**: p. CD008940.
15. WHO. *World Health Organization. The health and social effects of nonmedical cannabis use*. WHO Library Cataloguing-in-Publication Data 2016; Available from: http://apps.who.int/iris/bitstream/10665/251056/1/9789241510240-eng.pdf?ua=1.
16. Copeland, J. and I. Pokorski, *Progress toward pharmacotherapies for cannabis-use disorder: an evidence-based review.* Subst Abuse Rehabil, 2016. **7**: p. 41-53.
17. Fischer, B., J. Rehm, and W. Hall, *Cannabis use in Canada - The need for a public health approach.* Canadian Journal of Public Health, 2009. **100**: p. 101-103.

18. Hall, W. and R. Pacula, *Cannabis use and dependence: Public health and public policy*. 2003, Cambridge University Press.: Melbourne.
19. United Nations Office on Drugs and Crime, in *World Drug Report 2010*. 2010: Vienna, Austria.
20. National Institute on Drug Abuse, *Marijuana*, in *An update from the National Institute on Drug Abuse*. 2010, National Institute on Drug Abuse.
21. Urbanoski, K., C. Strike, and B.R. Rush, *Individuals seeking treatment for cannabis-related problems in Ontario: demographic and clinical profile.* European Addiction Research, 2005. **11**: p. 115-123.
22. Rush, B. and K. Urbanoski, *Estimating the demand for treatment for cannabis-related problems in Canada.* International Journal of Mental Health and Addiction, 2007. **5**: p. 181-186.
23. Rotondi, N.K. and B. Rush, *Monitoring Utilization of a Large Scale Addiction Treatment System: The Drug and Alcohol Treatment Information System (DATIS).* Subst Abuse, 2012. **6**: p. 73-84.
24. Ialomiteanu AR, A.E., Mann RE, Rehm J. , *CAMH Monitor eReport: addiction and mental health indicators among Ontario adults, 1977–2009* in *CAMH Research Document Series*. 2011.
25. Manzanares, J., et al., *Pharmacological and biochemical interactions between opioids and cannabinoids.* Trends Pharmacol Sci, 1999. **20**(7): p. 287-94.
26. Massi, P., et al., *Comparative characterization in the rat of the interaction between cannabinoids and opiates for their immunosuppressive and analgesic effects.* J Neuroimmunol, 2001. **117**(1-2): p. 116-24.
27. Maldonado, R. and O. Valverde, *Participation of the opioid system in cannabinoid-induced antinociception and emotional-like responses.* Eur Neuropsychopharmacol, 2003. **13**(6): p. 401-10.
28. Corchero, J., J. Manzanares, and J.A. Fuentes, *Cannabinoid/opioid crosstalk in the central nervous system.* Crit Rev Neurobiol, 2004. **16**(1-2): p. 159-72.
29. Cichewicz, D.L. and E.A. McCarthy, *Antinociceptive synergy between delta(9)-tetrahydrocannabinol and opioids after oral administration.* J Pharmacol Exp Ther, 2003. **304**(3): p. 1010-5.
30. Vigano, D., T. Rubino, and D. Parolaro, *Molecular and cellular basis of cannabinoid and opioid interactions.* Pharmacol Biochem Behav, 2005. **81**(2): p. 360-8.
31. Parolaro, D., et al., *Cellular mechanisms underlying the interaction between cannabinoid and opioid system.* Curr Drug Targets, 2010. **11**(4): p. 393-405.
32. Pickel, V.M., et al., *Compartment-specific localization of cannabinoid 1 (CB1) and mu-opioid receptors in rat nucleus accumbens.* Neuroscience, 2004. **127**(1): p. 101-12.
33. Rodriguez, J.J., K. Mackie, and V.M. Pickel, *Ultrastructural localization of the CB1 cannabinoid receptor in mu-opioid receptor patches of the rat Caudate putamen nucleus.* J Neurosci, 2001. **21**(3): p. 823-33.
34. Salio, C., et al., *CB1-cannabinoid and mu-opioid receptor co-localization on postsynaptic target in the rat dorsal horn.* Neuroreport, 2001. **12**(17): p. 3689-92.
35. Corchero, J., et al., *Time-dependent differences of repeated administration with Delta9-tetrahydrocannabinol in proenkephalin and cannabinoid receptor gene expression and G-protein activation by mu-opioid and CB1-cannabinoid*

receptors in the caudate-putamen. Brain Res Mol Brain Res, 1999. **67**(1): p. 148-57.
36. Rios, C., I. Gomes, and L.A. Devi, *mu opioid and CB1 cannabinoid receptor interactions: reciprocal inhibition of receptor signaling and neuritogenesis.* Br J Pharmacol, 2006. **148**(4): p. 387-95.
37. Corchero, J., J.A. Fuentes, and J. Manzanares, *delta 9-Tetrahydrocannabinol increases proopiomelanocortin gene expression in the arcuate nucleus of the rat hypothalamus.* Eur J Pharmacol, 1997. **323**(2-3): p. 193-5.
38. Corchero, J., et al., *delta-9-Tetrahydrocannabinol increases prodynorphin and proenkephalin gene expression in the spinal cord of the rat.* Life Sci, 1997. **61**(4): p. PL 39-43.
39. Corchero, J., J.A. Fuentes, and J. Manzanares, *Chronic treatment with CP-55,940 regulates corticotropin releasing factor and proopiomelanocortin gene expression in the hypothalamus and pituitary gland of the rat.* Life Sci, 1999. **64**(11): p. 905-11.
40. Manzanares, J., et al., *Chronic administration of cannabinoids regulates proenkephalin mRNA levels in selected regions of the rat brain.* Brain Res Mol Brain Res, 1998. **55**(1): p. 126-32.
41. Valverde, O., et al., *Delta9-tetrahydrocannabinol releases and facilitates the effects of endogenous enkephalins: reduction in morphine withdrawal syndrome without change in rewarding effect.* Eur J Neurosci, 2001. **13**(9): p. 1816-24.
42. Corchero, J., et al., *Repeated administration with Delta9-tetrahydrocannabinol regulates mu-opioid receptor density in the rat brain.* J Psychopharmacol, 2004. **18**(1): p. 54-8.
43. Caille, S. and L.H. Parsons, *Cannabinoid modulation of opiate reinforcement through the ventral striatopallidal pathway.* Neuropsychopharmacology, 2006. **31**(4): p. 804-13.
44. Chen, J.P., et al., *Delta 9-tetrahydrocannabinol produces naloxone-blockable enhancement of presynaptic basal dopamine efflux in nucleus accumbens of conscious, freely-moving rats as measured by intracerebral microdialysis.* Psychopharmacology (Berl), 1990. **102**(2): p. 156-62.
45. Solinas, M. and S.R. Goldberg, *Motivational effects of cannabinoids and opioids on food reinforcement depend on simultaneous activation of cannabinoid and opioid systems.* Neuropsychopharmacology, 2005. **30**(11): p. 2035-45.
46. Braida, D., et al., *Intracerebral self-administration of the cannabinoid receptor agonist CP 55,940 in the rat: interaction with the opioid system.* Eur J Pharmacol, 2001. **413**(2-3): p. 227-34.
47. Navarro, M., et al., *Functional interaction between opioid and cannabinoid receptors in drug self-administration.* J Neurosci, 2001. **21**(14): p. 5344-50.
48. Scavone, J.L., R.C. Sterling, and E.J. Van Bockstaele, *Cannabinoid and opioid interactions: implications for opiate dependence and withdrawal.* Neuroscience, 2013. **248**: p. 637-54.
49. Scavone, J.L., et al., *Impact of cannabis use during stabilization on methadone maintenance treatment.* Am J Addict, 2013. **22**(4): p. 344-51.
50. Haney, M., *Opioid antagonism of cannabinoid effects: differences between marijuana smokers and nonmarijuana smokers.* Neuropsychopharmacology, 2007. **32**(6): p. 1391-403.

51. Cooper, Z.D. and M. Haney, *Opioid antagonism enhances marijuana's effects in heavy marijuana smokers.* Psychopharmacology (Berl), 2010. **211**(2): p. 141-8.
52. Haney, M., et al., *Naltrexone Maintenance Decreases Cannabis Self-Administration and Subjective Effects in Daily Cannabis Smokers.* Neuropsychopharmacology, 2015. **40**(11): p. 2489-98.
53. Tanum, L., et al., *The Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence: A Randomized Clinical Noninferiority Trial.* JAMA Psychiatry, 2017.
54. Nordstrom, B.R. and F.R. Levin, *Treatment of cannabis use disorders: a review of the literature.* Am J Addict, 2007. **16**(5): p. 331-42.
55. Budney, A. J., Moore, B. A., Vandrey, R. G., & Hughes, J. R. *The time course and significance of cannabis withdrawal*. J. Abnorm. Psychol., 2003. **112**(3), p. 393-402.
56. Heishman, S.J., Evans, R.J., Singleton, E.G., Levin, K.H., Copersino, M.L., Gorelick, D.A.. *Reliability and validity of a short form of the Marijuana Craving Questionnaire*. Drug and Alcohol Dependence 2009. **102**(1-3):p. 35-40.
57. Ellis, B.W., et al., *The St. Mary's Hospital sleep questionnaire: a study of reliability.* Sleep, 1981. **4**(1): p. 93-7.
58. Hamilton, M., *The assessment of anxiety states by rating.* Br J Med Psychol, 1959. **32**(1): p. 50-5.
59. Beck, A.T., Steer, R.A., & Brown, G.K., *Manual for the Beck Depression Inventory-II.* San Antonio, TX: Psychological Corporation, 1996.
60. Hamilton, M., *A rating scale for depression.* J. Neurol. Neurosurg. Psychiatry, 1960. **23**: p. 56-62.
61. McNair, D.M., M. Lorr, and L.F. Droppleman, *Manual for the profile of mood states*. 1971, San Diego, CA: Educational and Industrial Testing Services.
62. Sobell, L.C., et al., *Reliability of a timeline method: assessing normal drinkers' reports of recent drinking and a comparative evaluation across several populations.* Br J Addict, 1988. **83**(4): p. 393-402.
63. Blackburn, I.M., James, I. A., Milne, D. L., Reichelt, F. K., Garland, A., Baker, C., Standart, S. H., & Claydon, A. , *Cognitive therapy scale—revised (CTS-R).* 2001: Newcastle-upon-Tyne: Newcastle Cognitive and Behavioural Therapies Centre.
64. Carroll, K.M., et al., *Motivational interviewing to improve treatment engagement and outcome in individuals seeking treatment for substance abuse: a multisite effectiveness study.* Drug Alcohol Depend, 2006. **81**(3): p. 301-12.
65. Steinberg, K.L., Roffman, R. A., Carroll, K. M., McRee, B., Babor, T. F., Miller, M., Kadden, R., Duresky, D., & Stephens, R. , *Brief counseling for marijuana dependence: a manual for treating adults*. 2005.
66. Chait, L.D., Marian W.F., and Charles R.S. *'Hangover' effects the morning after marijuana smoking*. Drug and alcohol dependence, 1985. **15**(3): p. 229-238.