Study: #7662 “A randomized controlled trial of Lorcaserin for Cannabis Use Disorder”

PI: Christina Brezing, MD
NCT# **NCT03637842**
Protocol approved: 9-21-2018

NEW YORK STATE PSYCHIATRIC INSTITUTE

INSTITUTIONAL REVIEW BOARD

MEMORANDUM

September 21, 2018

TO: Christina Brezing, MD

FROM: Dr. Edward Nunes, Co-Chair, IRB
Dr. Agnes Whitaker, Co-Chair, IRB

SUBJECT: **APPROVAL NOTICE**

Your protocol # **7662** entitled **A RANDOMIZED CONTROLLED TRIAL OF LORCASERIN FOR CANNABIS USE DISORDER** (version date 09-21-18) and consent forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **September 21, 2018 to July 8, 2019.** (Reviewed by the Full Board on 07-09-18.)

Consent requirements:

☐ Not applicable:

☐ 45CFR46.116(d) waiver or alteration of consent (phone screen)

√ Signature by the person(s) obtaining consent is required to document the consent process.

☐ Documentation of an independent assessment of the participant's capacity to consent is also required.

Approved for recruitment of subjects who lack capacity to consent: √ No ☐ Yes:

Field Monitoring Requirements: ☐ Routine √ Special: ***Submit a report on the quality assurance chart monitoring of the first two participants who complete the study.***

√ **Only copies of consent documents that are currently approved and stamped by the IRB may be used to obtain consent for participation in this study.**

√ **A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.**

√ **Changes to this research may be not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.**

√ **All serious and/or unanticipated problems involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website at http://irb.nyspi.org for Adverse Event Reporting Procedures and additional reporting requirements.**

CC: RFMH Business Office (1K23DA045080 – 01A1)

ENC: CF, HIPAA form, Significant Other Contact Form

EN/AW/Scr

Signed copy on file at IRB

Protocol Title:
A Randomized Controlled Trial of Lorcaserin for Cannabis Use Disorder

Version Date:
09/21/2018

Protocol Number:
7662

First Approval:
09/21/2018

Clinic:
Substance Treatment And Research Services (STARS)

Expiration Date:
07/08/2019

Contact Principal Investigator:
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Research Chief:
Frances Levin, MD

Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting a new protocol

Division & Personnel

Division

What Division/Department does the PI belong to?
Division on Substance Use Disorders
Within the division/department, what Center or group are you affiliated with, if any?
Division on Substance Use Disorders/STARS

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.
None

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Psychiatric Assessment
✓ Collection of Biological Specimens
✓ Medication Trial
✓ Use of Placebo or Sham Treatment
✓ Off-label Use of Drug or Device
✓ Internet-based Data Collection or Transmission

Population

Indicate which of the following populations will be included in this research

✓ Adults
✓ Adults over 50
✓ Substance Users

Research Support/Funding

Will an existing internal account be used to support the project?
No
Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract application is a pending review or a funding decision
Source of Funding
Federal
Institute/Agency
NIH/NIDA
Grant Name
A RANDOMIZED CONTROLLED TRIAL OF LORCASERIN FOR CANNABIS USE DISORDER
Grant Number
1K23DA045080 – 01A1
Select one of the following
Single Site

Business Office
RFMH
Does the grant/contract involve a subcontract?
No

Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
This protocol describes research conducted by the PI at other facilities/locations
No

Lay Summary of Proposed Research

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The primary purpose of this study is to investigate the effect of lorcaserin on reductions in cannabis use and multiple constructs of impulsivity in outpatient treatment-seeking individuals with cannabis use disorder (CUD). Additionally, we will make use of the technological application of ecological momentary assessments (EMA), to collect real-time data at key time intervals during the study on participants' use of cannabis and other substances in addition to measuring impulsive traits through self-initiated, fixed and random phone prompts. This will be a 13-week randomized, double-blind, placebo-controlled trial, with week 1 focused on baseline assessments of impulsivity (through EMA in vivo and at study visits), weeks 2-3 of medication lead-in, and week 4 targeting a reduced cannabis use/quit day through week 13. The primary aims are to (1) Examine the effect of lorcaserin compared to placebo, on reductions in cannabis use among treatment-seeking outpatients with CUD, (2) Examine the effect of lorcaserin compared to placebo on behavioral and self-report measures of impulsivity among individuals with CUD during the medication lead-in phase (weeks 2-3). The secondary aim is to examine whether reductions in impulsivity (during weeks 2-3) mediates the effect of lorcaserin on cannabis use (during weeks 8-13), if the primary hypotheses are supported. Finally, we will explore the effect of lorcaserin compared to placebo on (1) drop-out rates, (2) time to discontinuation from study, (3) treatment adherence, and (4) nicotine use.

Background, Significance and Rationale

Background, Significance and Rationale

There are no FDA approved medications for CUD. The development of safe and effective pharmacotherapy for CUD is an important, unmet public health need and one goal of this project. A variety of medications have been tested in randomized controlled treatment trials for CUD. The primary strategies of these medication trials for treatment-seeking individuals with CUD primarily targeted withdrawal, craving, specific symptoms of withdrawal (ie: sleep, anxiety), co-occurring disorders (ie: ADHD,40 depression30, 31, 35), and glutamatergic modulation. None of these past medication strategies demonstrated clear efficacy

in adults in a fully powered trial, and none utilized the proposed mechanism of action of lorcaserin, pharmacologically via serotonin 5HT2C receptor activity or via a proposed effect by reducing impulsivity.

Impulsiveness is seen as a predisposing factor that promotes the acquisition of behaviors linked with substance use. Pre-clinically, it is seen as a factor in the transition from controlled to uncontrolled substance use and contributes to risk of relapse during periods of abstinence. Clinically, impulsivity is seen as both a predictor and consequence of substance use. Impulsivity has been shown to reduce treatment adherence and negatively impact treatment outcomes in CUD. Thus, baseline impulsivity may influence the effectiveness of medication treatments.Further, impulsive traits are associated with negative cannabis use consequences.Though promising work has demonstrated behavioral training may reduce impulsivity, no studies to date have targeted reductions in impulsivity as a means of substance abuse treatment. Despite the importance of distinguishing the role subtypes of impulsivity play in substance use, impulsivity has never been assessed systematically across constructs in a clinical treatment trial for CUD, or other substance use disorders .

Serotonin has long been implicated as an important neurotransmitter in substance use. The serotonergic medications investigated for CUD to date have targeted a variety of serotonin system components (e.g. 5HT1A and 5HT2A receptors and 5HT reuptake pumps), but not the 5HT2C system. This is important because serotonin either increases or decreases mesolimbic dopamine, dependent upon the receptor activated, and as a consequence has differential effects on incentive motivation. Extensive neurochemical and eletrophysiological data indicates the inhibitory influence of serotonin on mesolimbic dopamine is mediated by 5HT2C receptors, with agonists decreasing dopamine release and neuronal activity. The study proposed now would be the first to target the 5HT2C receptor, using lorcaserin.

5HT2C receptor agonists alter neurobiological systems and behavior relevant to drug use. 5HT2C receptors are also implicated in impulsivity and thought to indirectly impact substance use through its effects on this system.

Lorcaserin is a selective 5HT2C receptor agonist that was approved by the FDA in 2012 for the treatment of obesity. A recent randomized controlled trial of lorcaserin for cigarette smoking demonstrated dose-related increases in smoking cessation as compared to placebo. These findings, in conjunction with extensive preclinical work, suggest lorcaserin has potential for the treatment of substance use disorders, including CUD through either direct effects on drug use behavior or indirect effects on reductions in impulsivity. Preliminary results of our pilot study investigating tolerability of lorcaserin in CUD further supports its investigation in a larger trial (see below). While the impact of lorcaserin as a monotherapy on CUD (Primary Aim; Goal 1) will be important to elucidate, the findings of this study may also have implications for the treatment of other substance use and behavioral health disorders, by targeting reductions in impulsivity.

Preliminary data: To date, an ongoing, 10 week, open label pilot study of lorcaserin (20mg/day) assessing tolerability in CUD has enrolled 9 participants, 2 currently active, 4 completers, and 3 drop-outs, 2 of which dropped without follow up immediately following consent (never received medication), providing only baseline assessments. The third participant who dropped reported a desire to become pregnant and left the study (week 3). Thus far, lorcaserin has been well tolerated with mild adverse effects noted in two participants (50% of completers) including headache and nausea which resolved with dose reduction to

10mg/day. One of these participants ultimately titrated back to 20mg/day. All 4 participants, who completed the trial, reduced their cannabis use including 1 participant who achieved abstinence (Mean baseline cannabis use=$17.13/day, SD=$13.57/day; Mean end of study cannabis use=$4.31/day, SD=$4.45/day, Mean dollar reduction per day in cannabis use= $12.81, SD=$10.20). Mean dollar of cannabis used per day was selected given recent notable variability in cannabis products used by participants, including edibles and variable potencies of smoked cannabis, generally reflected in price. This has previously been demonstrated as a feasible means of measuring changes in cannabis use.91 This pilot also included a mobile health sensor with feedback through participant smart phones. All completers to date reported liking the use of the mobile health intervention in the context of their treatment throughout the study, finding it "easy to use," and "useful." Only one screening participant (out of 13) did not have an up-to-date phone operating system and was excluded on this basis. This preliminary pilot data demonstrates lorcaserin is well tolerated at FDA approved doses, leads to reductions in cannabis use, and implementation of a mobile health intervention on participants' own cell phone is feasible and has high likability.

In Summary, CUD currently has no efficacious medication treatments. It is a disorder that has been closely linked with impulsivity, but treatment strategies to date have not targeted this. Lorcaserin, a 5HT2C receptor agonist, has preclinical, clinical, and early pilot data supporting its use in treating substance use, including CUD, directly and indirectly through reducing impulsivity. In this proposal, we will investigate the effectiveness of lorcaserin for the treatment of CUD in addition to its impact across multiple constructs of impulsivity that translate from the preclinical literature. We will make use of EMA to improve our understanding and temporal resolution of impulsive traits and cannabis use.

Specific Aims and Hypotheses

Specific Aims and Hypotheses

Cannabis use disorder (CUD) is a major public health problem associated with significant psychiatric and medical morbidity, poor performance, and legal consequences.4 4.2 million people in the United States meet criteria for CUD.5 15% of all admissions for substance abuse treatment were related to cannabis as the primary, presenting problem in 2014 and 86% of those admissions were referred for ambulatory care.6 Despite the large number of patients with CUD seeking outpatient treatment, we have limited options available. While evidence-based practices (EBP), and specifically psychotherapies, have been studied to treat CUD and various approaches have been shown to have clinical utility,7-9 many patients have difficulty achieving significant reductions in their use or sustained abstinence.10 This is further complicated by patients' limited access to EBPs,11 frequent poor adherence by therapists in the community to EBP interventions,12-14 and challenges in treating CUD with EBPs when available in community settings.10 Finding effective medications for the treatment of CUD is essential. There are no FDA approved medications for CUD. A number of pharmacological treatment trials for CUD have been performed.1* While some agents have shown promise,15-17 no medication strategy has emerged as clearly efficacious in producing abstinence.1,18 As the changing legal landscape influences patients' goals for reductions in cannabis use as compared to abstinence only, and with increasing support from the research community, future studies need to identify medications that lead to reductions in cannabis use.
Impulsivity has been linked to the predisposition,19 severity,20 and poor treatment outcomes21, 22 in cannabis users and CUD, making it a prime pharmacology target. Notably, there is an entwined relationship between cannabis and impulsivity. Impulsivity as a neurobehavioral trait is associated with cannabis use,

and acute and chronic use of cannabis has been shown to exacerbate impulsivity, with some mixed evidence likely attributable to diverse constructs of impulsivity used across studies. While we may not be able to fully determine which came first—the impulsivity or the cannabis use, further research is needed to demonstrate whether reductions across constructs of impulsivity can lead to improvements in CUD, and vice versa. Over the last two decades, 5HT2C receptor agonists have been shown to alter neurobiological systems of addiction and relevant drug use behavior in the preclinical literature by increasing inhibitory control on mesolimibic dopamine processes and resultant incentive motivation based behaviors,23 both directly and indirectly, particularly with regards to their impact on reducing impulsivity.24 In 2012, lorcaserin, a selective 5HT2C receptor agonist, was approved by the FDA, allowing for clinical exploration of its role in the treatment of substance use disorders, including CUD.25 Recently, a fully powered clinical trial of lorcaserin for tobacco smoking cessation was positive.26

The primary purpose of this study is therefore to investigate the effect of lorcaserin on reductions in cannabis use and multiple constructs of impulsivity in outpatient treatment-seeking individuals with CUD. Additionally, we will make use of the technological application of ecological momentary assessments (EMA), to collect real-time data at key time intervals during the study on participants' use of cannabis and other substances in addition to measuring impulsive traits through self-initiated, fixed and random phone prompts. This will be a 13-week randomized, double-blind, placebo-controlled trial, with week 1 focused on baseline assessments of impulsivity (through EMA in vivo and at study visits), weeks 2-3 of medication lead-in, and week 4 targeting a reduced cannabis use/quit day through week 13. This "proof of concept" study will provide Dr. Brezing with training in randomized controlled trial operations, multiple constructs to measure impulsivity, utilization of technology as a measurement tool, and identification of outcomes that may prove important to reductions in cannabis use.

Primary Aims:

(Aim 1) Examine the effect of lorcaserin compared to placebo, on reductions in cannabis use among treatment-seeking outpatients with CUD, **with the primary outcome measured by average weekly mean episodes of any cannabis use (including edibles, vaping, and other variable potency cannabinoid products) per day**.

(Aim 2) Examine the effect of lorcaserin compared to placebo on behavioral and self-report measures of impulsivity among individuals with CUD during the medication lead-in phase (weeks 2-3).

Secondary Aim: If the hypotheses of the Primary Aims are supported, we will examine whether reductions in impulsivity (during weeks 2-3) mediates the effect of lorcaserin on cannabis use (during weeks 8-13).

Exploratory Aims: To explore the effect of lorcaserin compared to placebo on (1) drop-out rates, (2) time to discontinuation from study, (3) treatment adherence, and (4) nicotine use.

Description of Subject Population

Sample #1

Specify subject population
Adults with cannabis use disorder
Number of completers required to accomplish study aims
60

Projected number of subjects who will be enrolled to obtain required number of completers
90
Age range of subject population
18-70

Gender, Racial and Ethnic Breakdown
The study described in the present application seeks to include women and minorities; the study does not exclude any potential participants on the basis of race and gender. Based on previous studies conducted at STARS, the sample is expected to include approximately 50% Caucasian, 22% Hispanic, 24% African-American, 4% other racial groups. Approximately 30% will be women. This profile is representative of the areas from which our treatment program draws patients in New York City and the greater metropolitan area.
Description of subject population
We plan to enroll 90 participants into the study who meet criteria for current CUD and all other study criteria.

Recruitment Procedures

Describe settings where recruitment will occur
The location consists of one site: the Substance Treatment and Research Services (STARS) satellite location (STARS Downtown) situated at 3 Columbus Circle, 14th Floor, New York, NY 10019. STARS Downtown is leased by NY Presbyterian Hospital Department of Psychiatry.

Participants will be recruited using previously successful methods for substance use disorder pharmacotherapy trials conducted at STARS. The main method of recruitment will be media advertisement.
How and by whom will subjects be approached and/or recruited?
Participants may learn about STARS through advertisements, or they may be referred by current or past participants involved in clinical research at STARS, or by clinical care providers. Most individuals will initiate contact themselves by calling the clinic. We will also contact participants who previously completed cannabis use disorder trials who previously gave permission for us to do so.

The first phase of recruitment is a structured telephone interview. Individuals interested in receiving treatment for cannabis use disorder will be asked to come to STARS Downtown for additional screening as per protocol #6582R. Those participants who meet criteria for cannabis use disorder and all other inclusion/exclusion criteria will be asked if they are interested in participating in the study.

How will the study be advertised/publicized?
A combination of radio, print, cable television, internet, and subway advertising will be directed at prospective patients in New York City metropolitan area who have been experiencing problems related to cannabis use and are seeking treatment. All advertising is coordinated by the NYSPI Public Relations Office. This method has proven successful in several clinical trials at STARS. Advertisements are sent tot he Institutional Review Board for approval.
Do you have ads/recruitment material requiring review at this time?
No
Does this study involve a clinical trial?

Yes
YOU MUST REGISTER AT ClinicalTrials.gov IMMEDIATELY UPON RECEIPT OF IRB APPROVAL AND PRIOR TO ENROLLMENT OF THE FIRST SUBJECT. YOU WILL BE PROVIDED WITH A NCT REGISTRATION NUMBER ON REGISTRATION. PLEASE REVISE THIS SECTION OF THE PROTOCOL SUMMARY FORM TO INCLUDE THE NCT NUMBER AND RE-SUBMIT AS AN AMENDMENT TO THE IRB.

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement
Screening for this study will be covered by the Substance Treatment and Research Service (STARS) umbrella screening protocol #6582R (PI: John Mariani, MD). Trained research assistants and administrative assistants under the supervision of the principal investigator conduct the initial phone screening. Under protocol #6582R, patients who contact STARS interested in research trial participation are informed that they will be asked questions of a personal nature and asked to provide verbal consent for such questions. A "phone screen" form is completed by the phone screener, which asks basic demographic information, contact information (for scheduling purposes) and description of substance use to determine whether an in-person evaluation appointment is appropriate. Individuals are also informed that if they make an initial screening appointment this “phone screen” information will be forwarded to the clinician to facilitate the first meeting.

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Adults with Cannabis Use Disorder
Create or insert table to describe the inclusion criteria and methods to ascertain them

Inclusion Criteria	**Method of Ascertainment**
1. Individuals between the ages of 18-70*	ID with birth date
2. Meets DSM-V criteria for a current cannabis use disorder	MINI interview by therapist, Clinical interview with psychiatrist, DSM-V criteria review, and urine toxicology
3. Seeking treatment for cannabis use disorder	Participant self-report, MINI interview by therapist, Clinical interview by psychiatrist
4. THC-positive urine drug screen	Urine toxicology
5. Capable of giving informed consent and complying with study procedures	Clinical interview by psychiatrist
6. Has access to an Apple or Android mobile device capable of running EMA	Participant self-report, staff inspection of mobile device
7. Not underweight (Defined as BMI ≥18.5)	Calculation of BMI using weight and height of

	participant

Please note that individuals greater than 60 years of age at screening will receive a Montreal Cognitive Assessment (MoCA) to ensure adequate cognitive functioning for participation in the study. Individuals who score greater than or equal to 24 will be included.

Create or insert table to describe the exclusion criteria and methods to ascertain them

Exclusion Criteria	**Method of Ascertainment**
1.Lifetime history of DSM-V diagnosis of schizophrenia or schizoaffective disorder	MINI interview by therapist, Clinical interview by psychiatrist
2. Current DSM-V criteria for a psychiatric disorder supported by the MINI that in the investigator's judgment is unstable, would be disrupted by the study medication, or is likely to require new pharmacotherapy or psychotherapy during the study period. Individuals who are currently stable on psychotropic medication for at least 3months may be included if in the investigator's opinion the psychotropic medication is compatible with the study medication (lorcaserin).	MINI interview by therapist, Clinical interview and mental status exam by psychiatrist, contact with collateral information as needed and available
3.Individuals who meet DSM-V criteria for any moderate to severe substance use disorder other an cannabis, caffeine or nicotine use disorders. **(Individuals are not required to abstain from all substances and those who meet criteria for a co-occurring mild SUD can be included; though cannot meet criteria for a moderate or severe substance use disorder other than cannabis, caffeine or nicotine use disorders).**	MINI interview by therapist, Clinical interview by psychiatrist
4. Pregnancy, lactation, or failure to use adequate contraceptive method in female patients who are currently engaging in sexual activity with men	Clinical interview by psychiatrist, physical examination and medical history by psychiatrist or NP, urine pregnancy test, serum HCG
5. Unstable medical conditions, such as AIDS*, cancer, uncontrolled hypertension, uncontrolled diabetes, pulmonary hypertension or heart disease	Medical history and physical examination by psychiatrist or NP, laboratory tests (serum Chem-20 and CBC, urinalysis), ECG
6. Legally mandated to participate in a substance use disorder treatment program	Participant self-report, Clinical interview by psychiatrist
7. Current or recent history of significant violent or suicidal behavior, risk for suicide or homicide	Participant self-report, Clinical interview by psychiatrist
8. Currently meets DSM-V diagnosis for an eating disorder or is underweight (BMI <18.5)	MINI interview by therapist, Clinical interview by psychiatrist
9. Elevated liver function tests (AST and ALT > 3	Laboratory tests (serum Chem-20)

times the upper limit of normal) or impaired renal function	
. **10.** Known history of allergy, intolerance, or hypersensitivity to lorcaserin	Participant self-report, Clinical interview by psychiatrist
11. Concurrent use of migraine medications ergotamine (Cafergot, Ergomar) or dihydroergotamine (Migranal), 5HT2B receptor agonists like cabergoline, or medications metabolized by CYP2D6 (thioridazine, tamoxifen, metoprolol, aripiprazole, codeine, etc)	Clinical interview by psychiatrist
12. No access to an Android or Apple mobile device	Participant self report, staff inspection of mobile device

***Please note that individuals who are HIV+ will receive additional screening lab of CD4+ T-cell count. Individuals whose CD4 count is less than 200 cells/ µL (one of the CDC criteria) will be excluded.**

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
No
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes
Indicate NYSPI IRB #
6582R
Describe Study Consent Procedures
All participants are seen by a therapist **(either a licensed clinical psychologist with a masters or PhD or a licensed clinical social worker)** and one of our psychiatrists for a screening evaluation and mental status

examination as part of routine admission procedures at STARS (Evaluation of Potential Substance Abuse Research Participants, IRB #6582R: PI: Mariani). Consent to participate in screening procedures is obtained prior to the medical and psychological screening evaluations used to determine whether the participant will meet the study inclusion/exclusion criteria. Patients who have cannabis use disorder and appear to meet study criteria are told about the study and offered further evaluation. **Individuals over 60 years of age will also complete a Montreal Cognitive Assessment (MoCA) to screen for cognitive impairment. Individuals who score a 23 or less will not be included in the study (Carson, 2018).** for cognitive deficits. Individuals Final informed consent is obtained after full psychiatric and medical work up is complete. Part of the evaluation includes a discussion of study eligibility for each screening participant with clinical staff, research psychiatrists, and principal investigators at the weekly screening meeting at STARS. Participants receive an explanation of the study risks, benefits, treatments, procedures, and options for alternative treatments. They also take a quiz testing their understanding of the study. The psychiatrists who obtain consent work regular weekly shifts at STARS and are able to explain study consent to the participant. They are educated about new protocols and inclusion/exclusion criteria at the weekly screening meeting. Consent for contact of a significant other will also be requested for the purposes of finding a participant with whom we have a significant clinical concern **or in the event of an emergency**. Participants may refuse this consent and still participate in the study.
Indicate which of the following are employed as a part of screening or main study consent procedures

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Blevins, Derek
Brezing, Christina, MD
Dakwar, Elias, MD
Kidd, Jeremy
Luo, Sean, MD
Mariani, John, MD
Naqvi, Nasir, MD
Shulman, Matisyahu, MD
Wai, Jonathan, MD
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study
Standard Assessments (Weeks 1-13): The following will be completed at every study visit: vital signs, BMI, and TLFB for cannabis use (primary outcome measure). Once per week, participants will provide a urine sample tested for THC-COOH levels and have a study physician evaluation assessing participant's medical and psychiatric status, **in addition to use of substances other than cannabis, and will** include Clinical Global Impressions (CGI) scales for patients' overall well-being and cannabis use. **If a CGI of 6 or more is noted, the study physician and staff will review with participants at his/her next visit to the clinic.** Participants who clinically worsen as measured with CGI ≥ 6 for 2 consecutive weeks will be

further evaluated by a clinician and case reviewed at the clinic lab meeting as to whether discontinuation from the study is appropriate. If it is clinically determined the participant should be discontinued, he/she will be given referrals for treatment.

Baseline Assessments (Week 1): Prior to randomization and start of study medication, participants will complete baseline assessments in addition to screening and the standard assessments described above. These include EMA prompted through their phone regarding their cannabis, tobacco, other substance use and self-report of impulsivity, study visit assessments including impulsivity measure battery and Fagerstrom Test for Nicotine Dependence (FTND).

Randomization: Participants will be randomly allocated (1:1) to receive lorcaserin or placebo and stratified by the severity of cannabis use at baseline. Severity of use will be categorized as "high" verses "low" users. High users will be defined as those who use 5 or more days per week, averaged per week over the course of the last 1 month. Low users will be defined as those who use less than 5 days per week, averaged per week over the course of the last 1 month. This study will inform future research on stratification for impulsivity.

Medication Dosing Schedule (Weeks 2-13): Participants will begin medication on Day 8 of week 2. Participants will take 1 dose of lorcaserin 10mg on Day 8. On Day 9, participants will take lorcaserin XR 20mg per day and continue this dose for the remainder of the treatment trial if tolerated. Flexible, reduced dosing is available for participants with immediate release lorcaserin.

The medication lead-in phase occurs during weeks 2-3.

During this time, participants will also complete daily EMA regarding cannabis use, other substance use including nicotine, and self-report of impulsivity in addition to study-visit assessments. Participants will be instructed to have a target reduce use or quit day, consistent with the participant's treatments goals, by Day 22 of the trial (start of week 4) though are encouraged to attempt to achieve reductions in cannabis use throughout the study and following any relapses. On the first day of week 13, participants will take 1 dose of lorcaserin 10mg before discontinuation.

Study Procedures (Weeks 2-13): Medication Adherence Measurement and Study Procedure Enhancement:Quantitative urine riboflavin in blinded pill casings and a Timeline Followback (TLFB) pill count interview will measure medication adherence. All patients will receive Medical Management (psychosocial treatment) to enhance medication and study procedure adherence and troubleshoot medication-related issues. Participants will receive compensation for returning medication bottles, regardless of taking medication ($5/visit), completing EMA (% of $20/week), and attending study visits ($5/visit) as a form of contingency management. We previously found this contributes to high rates of bottle return (over 90% in a recent CUD trial) and improves treatment adherence measures. $5/visit is given for transportation costs. Study Assessments: Impulsivity Battery: (1) Choice Impulsivity- (1a) Monetary Choice Questionnaire (delay discounting) 27-item assessment requiring subjects to select choices between larger-later sums of money available with a delay or smaller-sooner sums of money available immediately. (1b) Beads Task: Computerized task where subjects are presented with up to 20 drawn beads from two jars and asked to infer from which jar the beads were drawn. (2) Motor/Action Impulsivity- (2a) 4-Choice Serial Reaction Time task (4-CSRTT): The 4-CSRTT is the human analog computerized task based on the rodent 5-CSRTT to assess premature responding. When four boxes appear on the screen, subjects hold down the space bar, indicating the cue onset time. After a specified time, a green circle target appears briefly and randomly in one of the four boxes. Subjects release the space bar and touch the box in which the target appeared. (2b) Stop Signal Task assesses response inhibition. (3) Self-report of Personality Traits- (3a) EMA –Patients complete a training session at baseline on how to complete EMA assessments through their phone that are created with Ilumivu software package. Participants can initiate event-contingent surveys on

their substance use (ie: cannabis “hits” and method of intake, number of tobacco cigarettes, or alcohol drinks, if consumed) at any time. Impulsivity is assessed during an “end of day” survey using the Barratt Impulsiveness Scale-Brief,103 a 7 item short form of the BIS-11. Reminders to complete end of day surveys are triggered on
phones at 9:30pm but can be completed at any time when activities are done for the day. Responses are uploaded in real-time to a secure Ilumivu server. (3b) At Study Visits: UPPS-P Impulsive Behavior Scale104- 59 item questionnaire assesses 5 facets of impulsivity including sensation seeking, lack of premeditation, lack of perseverance, negative urgency, and positive urgency. Adverse Effects Measures: The Systematic Assessment for Treatment and Emergent Events (SAFTEE) will be performed weekly by the study physician to identify adverse symptoms.
Mood and Suicide Measures: Hamilton Depression Scale (HAM-D): We use a 25-item, structured interview version that incorporates the reverse vegetative symptoms of atypical depression but permits calculation of the standard 17 and 21 item scores that are imbedded in the scale. Completed at baseline, weeks 4, 9, and 13. Columbia Suicide Severity Rating Scale (C-SSRS) This is a comprehensive assessment that identifies whether someone is at risk for suicide, assesses the severity and immediacy of that risk, and gauges the level of support that the person needs. Completed at baseline, weeks 4, 9, and 13. Exploratory Assessments: Participant drop-out and time to drop-out will be assessed. Fagerstrom Test for Nicotine Dependence (FTND) This 6 item self-report questionnaire assesses severity of nicotine dependence and is completed at weeks 1 and 13. Treatment Adherence will be assessed by medication adherence (see above), % response to EMA, and visits attended. Following completion of the study, participants interested in continuing treatment will be given community referrals and bridged by the study physician until first available appointment.
Medication Management: The participants will receive weekly medication management as adjunct psychosocial support with the psychiatrist. During this visit each week, the psychiatrist will monitor for medication effects in addition to providing counseling aimed at adherence with study medication, compliance with study procedures, promoting goals toward abstinence or reduced use of cannabis, promotion of positive health behaviors, and encouraging engagement in other supports outside of the study (eg: mutual support meetings, relationships with family, friends).

You can upload charts or diagrams if any
Table 1_IRB_2018.pdf

Criteria for Early Discontinuation

Criteria for Early Discontinuation
Drop out criteria during the screening and study period include:
1) Any development of serious psychiatric symptoms **or worsening of any substance use, such as alcohol or other drugs, including cannabis (see details for cannabis under "2") ,** as indicated by the Clinical Global Impression (CGI) improvement score of 6 (much worse than baseline) or greater for 2 consecutive weeks will prompt a clinical evaluation and then clinical judgment as to whether the patient should be discontinued from the study, rather than a definitive discontinuation criterion. Such evaluation will be documented in the clinical chart, and based on other supportive assessments such as the C-SSRS. **Any evaluation that prompts a score of 6 or more on the CGI will be followed up by staff and discussed with the participant at his/her next clinic visit.**
2) A participant's continued marijuana use that ultimately places him/her at risk for self-destructive behavior

or other harm as indicated by a CGI improvement score of 6 or more (much worse than baseline) for 2 consecutive weeks will prompt a clinical evaluation and then clinical judgment as to whether the patient should be discontinued from the study, rather than a definitive discontinuation criterion. Such evaluation will be documented in the clinical chart, and based on other supportive assessments such as the C-SSRS. **Any evaluation that prompts a score of 6 or more on the CGI will be followed up by staff and discussed with the participant at his/her next clinic visit.**
3) Development of serious medical condition(s) that may or may not be related to study participation (e.g.,unhealthy weight loss, serotonin syndrome) as assessed by weekly visits with the psychiatrist, vital sign measurements, and weekly weigh-ins
4) If the participant becomes pregnant as assessed by monthly urine pregnancy testing
5) Weight loss resulting in the participant becoming underweight (BMI<18.5). BMI will be calculated weekly.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens
Blood samples (20ml) for routine analyses (ie: chemistry and hematology) will be taken at the time of medical screening. They will be repeated at 1 month following initiation of study medication and then end of study. Women will receive a serum pregnancy test at screening, followed by urine pregnancy testing every month throughout the study following initiation of medication. Quantitative urine toxicology will be collected at screening, followed by quantitative urine THC levels and creatinine twice weekly throughout the study.

Blood and Other Biological Sample(s)	Time Point(s) Collected
Blood chemistries, CBC, liver function tests	Screening, week 13
Serum pregnancy test	Screening
Urinalysis	Screening
Urine pregnancy test	Screening, week 2, 4, 9, 13
Quantitative urine toxicology and creatinine	Screening
Quantitative urine delta-9-THC and creatinine	Weekly following start of study

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment
Medical/Physiological Measurements
Vital Signs and Weight-5min
History and Physical Examination-30min
Electrocardiogram-15min
Pregnancy Test urine—5min
Pregnancy Test serum-5min
Urinalysis-5min
Urine testing for delta-9-THC and cannabinoids (At Screening)-5min
Quantitative urine toxicology with creatinine (weekly throughout study)-5min

Serum Laboratory Examination (CBC, Chem-7, LFTs)-5min

Interviews
Clinical Global Impressions Scale Observer (CGI-O)-5min
Timeline Follow-Back (TLFB)-10min
Hamilton Depression Scale (HAM-D)-5min
Systematic Assessment for Treatment Emergent Effects (SAFTEE)-3min
Columbia-Suicide Severity Rating Scale (C-SSRS)- 5min

Self-Reports
Fagerstrom Test for Nicotine Dependence (FTND)-5min
EMA self reporting on substance use and BIS-7-3min
-participants can self-initiate use of cannabis (log episodes of use) at any time of day through the EMA application
-Daily throughout the study, participants will receive a prompt in the evening asking about number of episodes of use of cannabis, number of cigarettes, and report of any of other substance use.
-During weeks 1, 2, 3, 4, and 13, participants will be asked to complete daily BIS-7 self-reports. The BIS (Barratt Impulsiveness Scale)-7 is an abbreviated version of the BIS-30. (Ansell, 2015)
UPPS-P Impulsive Behavior Scale-59 item questionnaire assesses 5 facets of impulsivity including sensation seeking, lack of premeditation, lack of perseverance, negative urgency, and positive urgency. -20min

Behavioral Tests
Monetary Choice Questionnaire (delay discounting) 27-item assessment requiring subjects to select choices between larger-later sums of money available with a delay or smaller-sooner sums of money available immediately.-5min
(1b) Beads Task:Computerized task where subjects are presented with up to 20 drawn beads from two jars and asked to infer from which jar the beads were drawn. Following their decision, they indicate their degree of confidence that their answer is correct without feedback.-5min
(2) Motor/Action Impulsivity- (2a) 4-Choice Serial Reaction Time task (4-CSRTT): The 4-CSRTT is the human analog computerized task based on the rodent 5-CSRTT to assess premature responding. When four boxes appear on the screen, subjects hold down the space bar, indicating the cue onset time. After a specified time, a green circle target appears briefly and randomly in one of the four boxes. Subjects release the space bar and touch the box in which the target appeared. Premature responding is defined as early release of the space bar before target onset- 5min
(2b) Stop Signal Task assesses response inhibition. A series of go stimuli in the form of left or right arrows are presented and subjects are instructed to respond as quickly as possible by pressing the respective button. The key outcome is the stop signal reaction time (SSRT).-5min

Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study
✓ Drug
Select the number of drugs used in this study
2

Drug #1

Name of the drug
Lorcaserin
Manufacturer and other information
Name of the drug
Lorcaserin (Belviq)
Manufacturer and other information
Lorcaserin (Belviq) is a weight-loss drug developed by Arena Pharmaceuticals. It has serotonergic properties and acts as an anorexiant.

An example of study medication label will appear as follows:
Protocol #
Participant ID: 001-ABC
Study Week: #2
Lorcaserin 10mg tablet
Directions for use: Take 1 tablet by mouth once
Dispense: 1 tablet
Caution: New Drug-- Limited by Federal (or United States) law to investigational use
Approval Status
IND is approved
IND#
129105
Who holds the IND/IND sponsor?
Other
Enter Name
Frances R. Levin, MD

Drug #2

Name of the drug
Lorcaserin XR
Manufacturer and other information
Lorcaserin XR (BelviqXR)
Manufacturer and other information
Lorcaserin XR (Belviq XR) is a weight-loss drug developed by Arena Pharmaceuticals. It has serotonergic properties and acts as an anorexiant.

An example of study medication label will appear as follows:
Protocol #

Participant ID: 001-ABC
Study Week: #3
Lorcaserin XR 20mg tablet
Directions for use: Take 1 tablet by mouth daily.
Dispense: 7 tablets
Caution: New Drug-- Limited by Federal (or United States) law to investigational use
Approval Status
IND is approved
IND#
129105
Who holds the IND/IND sponsor?
Other
Enter Name
Frances R. Levin, MD

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
No
Treatment to be provided at the end of the study
Upon study completion or at the point of dropout, participants will be provided with referrals to community practitioners and offered the option of continued medical management counseling, focused on goals for abstinence and utilization of additional resources in the community for up to four weeks following the end of the study.

Clinical Treatment Alternatives

Clinical treatment alternatives
Unfortunately, there are no FDA-approved medications for the treatment of cannabis use disorder. Several psychotherapy methods have been shown to be effective in treating cannabis use disorder and include: Relapse Prevention Therapy, a form of CBT; Contingency Management, a prize- or voucher-based incentive treatment; Motivational Enhancement Therapy (MET), a form of Motivational Interviewing; the combination of CBT and MET together; and family therapy. However, success rates for psychotherapies have been modest (less than 50%). During the study, participants are permitted to seek additional help from other providers (therapists and physicians outside of the study). Patients are informed that they may request referral for other treatment options.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
Study Medication Risks: One of the main risks associated with participation is drug administration.

Lorcaserin XR (or Bleviq XR©) was approved by the FDA for treating obesity, is generally well tolerated, and has low abuse potential. The target daily dose of lorcaserin in the proposed study (20mg) is the current FDA approved dose for the treatment of weight management. In clinical trials, headache was the only reported side effect to occur at a frequency much greater than placebo. Other possible side effects of lorcaserin include: constipation, dry mouth, headache, nausea, and dizziness. Some rare but serious side effects include hypoglycemia in patients with Type 2 diabetes, serotonin syndrome, agitation, confusion, hallucinations, arrhythmias, cardiac valve disease, depression, thoughts of suicide, and an erection lasting longer than 4 hours.
The combination of lorcaserin with other serotonergic medications (e.g., 5HT3 antagonist antiemetics, buproprion, triptans, SSRIs, SNRIs, TCAs, St. John's Wort, tryptophan), medications that impair the metabolism of serotonin (e.g., MAO inhibitors, dextromethorphan, tramadol, lithium), or antidopaminergic medications (e.g., antipsychotics) may enhance serotonergic effects, and this could result in rare but serious serotonin syndrome reaction. Signs of serotonin syndrome include: mental status changes (e.g., anxiety, agitated delirium, restlessness, and disorientation); easy startle, autonomic manifestations (e.g., diaphoresis, tachycardia, hyperthermia, hypertension, vomiting, and diarrhea); and neuromuscular hyperactivity (e.g., tremor, muscle rigidity, myoclonus, hyperreflexia, and bilateral Babinski sign).
The combination of lorcaserin with ergot derivatives is contraindicated. The use of these drugs together may increase the risk of developing valvular heart disease in addition to enhancing serotonergic effects that may result in serotonin syndrome.
The combination of lorcaserin with 5HT2B-R agonists (e.g., cabergoline) is contraindicated due to the increased risk of cardiac valvulopathy.
Lorcaserin is a moderate CYP2D6 inhibitor and may decrease the clearance of drugs metabolized by CYP2D6, and thus raise these other drug levels increasing the risk of toxicity.
Lorcaserin is contraindicated in pregnancy due to the fact that weight loss offers no clinical benefit in pregnancy and is advised against.

Other Risks: Blood draws may cause slight discomfort at the site of needle entry, can result in infection at the site if hygienic/sterile techniques aren't used, or can result in a small bruise.
Participants will receive compensation and incentives during the study that could pose a risk of providing more available funds to purchase cannabis.
The structured interviews, rating scales, and questionnaires should add no physical risk. The major disadvantage is the time required to complete them and that some of the questions might be embarrassing to participants. Our past experience with these measures indicates that they are acceptable to participants. However, some people have found them uncomfortable and/or tiring because the interviews/assessments are long and of a personal nature.
Describe procedures for minimizing risks
1) Screening Procedures
In order to minimize the risk associated with the study, subjects undergo a comprehensive medical and psychiatric evaluation during the screening procedure. The baseline medical evaluation consists of a physical examination, blood chemistry profile, complete blood count, urinalysis, serum pregnancy test, urine toxicology and is designed, along with the clinical history, to detect chronic and/or unstable medical illnesses. A comprehensive psychiatric assessment is performed during the screening process, and is intended to detect and assess all past and current psychiatric disorders. The eligibility criteria (see above) are designed to minimize the medical and psychiatric risks to participants by excluding those for whom participation would place them at an increased risk. Special attention will be given to patient's concurrent

use of medications. Participants on medications that meet exclusion criteria will not be included in the study. If participants have recently completed another study at STARS, we will ensure, as with other medications, that there are no drug-drug interactions with the possible recent exposure to other study medications or will ensure proper time for wash-out between studies.
2) Study Procedures
Participants will be informed about the possible side effects and risks (listed above) of taking lorcaserin both alone and in combination with other medications through extensive discussions with staff psychiatrist(s) during the consent process. Participants will be told to contact the clinic if they experience any adverse effects and given the number for the 24-hr physician on-call. All participants, both those not taking and taking concurrent medications, will be monitored closely throughout the study for possible signs and symptoms of serotonin syndrome and weight loss. Participants' mental status and physical health are monitored weekly during the study period by a psychiatrist. Vital signs will be obtained at each study visit. Weight will be assessed weekly to monitor for possible excessive weight loss and used to calculate BMI. At clinic visits, a physician will assess participants for signs and symptoms of adverse effects of lorcaserin, noting which if any symptoms are present, the severity of the symptoms, make adjustments to study medication dose, discontinue study medication, or withdraw participant(s) from the study if needed. Female participants who are engaging in sexual activity with men must use adequate methods of contraception which will be discussed repeatedly during the screening process. Serum pregnancy tests will be conducted during screening and urine pregnancy tests will be performed monthly during the study. If a female participant does become pregnant or wishes to become pregnant, study medication will be immediately discontinued, she will be withdrawn from the study, and offered continuing nonpharmacological treatment (psychotherapy).

Procedures to Minimize Other Risks:
With regards to the risks of blood draws, only staff trained in phlebotomy will draw blood from participants to minimize risks of infection. Participants will be warned of the possible associated discomfort and slight bruising following blood draws. They can decline blood draws at any time. We aim to reduce the risk of using reimbursements and incentives to buy drugs such as cannabis by keeping reimbursements at a low monetary value, earned in increments of $5. The additional monetary incentives for completion of study related activities are felt to be modest, appropriate, and limited. This payment schedule has been used successfully in treatment studies in our clinic and others with no observed effect of increased drug use. With regards to risks associated with interviews, rating scales, and questionnaires, patients are informed that they may refuse to answer any questions and may ask to stop at anytime. If participants become upset during the interviews/assessments, assistance will be made available to them.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
This study has a Certificate of Confidentiality. The Certificate of Confidentiality will allow investigators and others with access to research records to refuse to disclose information that could identify subjects in any civil, criminal, administrative, legislative, or other proceeding, whether at the Federal, State, or local level. The Certificate of Confidentiality is granted for studies that collect information that, if disclosed, could damage subjects' financial standing, employability, insurability, or reputation, or have other adverse consequences.

We use coded records (i.e., initials and numbers), store signed consent forms in a locked file cabinet, and try, to the best of our ability to maintain confidentiality. Only coded records will be entered into the computer and the security of electronic data is ensured at the level of the server, the user, and the database.

Ilumivu secure, encrypted servers will store anonymous data gathered through EMA. The data gathered includes self-report of substance use and impulsivity. Ilumivu will not have access to any information that identifies the participant, nor will they access the de-identified data collected from the EMA unless requested by the PI. Select STARS staff can access the de-identified data using a password to access the encrypted server where the data is stored. Access to this folder is limited to necessary study personnel. Only STARS has access to de-identifiers assigned by a STARS research coordinator at the time of EMA training.

Will the study be conducted under a certificate of confidentiality?
Yes, we will apply for the Certificate of Confidentiality

Direct Benefits to Subjects

Direct Benefits to Subjects
There are no direct benefits to the participants through their enrollment in the study. There is the potential benefit of reducing cannabis use with lorcaserin treatment and, in combination with a medication compliance enhancement therapy (medical management), may lead to reduction/cessation of marijuana use. Often patients entering and remaining in treatment studies for cannabis or other substance use disorders exhibit some improvement in personal, medical and psychiatric domains whether or not the specific medication is demonstrated effective.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.

For each visit participants attend, they receive $5. Over the course of the study, they can receive up $130 for visit attendance. They will also receive a $5 for each week that they bring in their medication bottle, for a maximum for $65. They will receive $5.50 per visit for transportation for a maximum of $143 in transportation compensation. During the study they will complete EMA. During the 5 weeks of the study, where the phone assessments include questions on impulsivity, they can be compensated a percentage of $20 for those 5 weeks based on a percentage of completion of the impulsivity questions, for a maximum of $100. They can receive a total of $438 with complete adherence to study visits and procedures.

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