NEW YORK STATE PSYCHIATRIC INSTITUTE

INSTITUTIONAL REVIEW BOARD

MEMORANDUM

June 11, 2018

TO: Dr. John J. Mariani

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

SUBJECT: APPROVAL NOTICE: CONTINUATION
Expedited per 45CFR46.110(b)(1)(f)(8)(c)

Your protocol # **6623** entitled **QUETIAPINE PHARMACOTHERAPY FOR CANNABIS DEPENDENCE** (version date 06-11-18) and Consent Forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **July 8, 2018** to **July 7, 2019.**

Consent requirements:

X Not applicable: (RECRUITMENT COMPLETED. DATA BEING ANALYZED)

☐ 45CFR46.117 (c)(2) waiver of documentation of consent for the telephone interview.

☐ 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:

√ **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.**

AW/Scr

Signed copy on file at IRB

Protocol Title:
Quetiapine Pharmacotherapy for Cannabis Dependence

Version Date:
06/11/2018

Protocol Number:
6623

First Approval:
07/09/2012

Clinic:
Substance Treatment And Research Services (STARS)

Expiration Date:
07/07/2019

Contact Principal Investigator:
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Telephone: 646-774-6140

Co-Investigator(s):
Frances Levin, MD

Research Chief:
Herbert Kleber, 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 an annual continuation without modifications

Division & Personnel

Division

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

Application for Continuation of Research

Status

Current Status of Study:
All research interventions were completed. Only data analysis is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.
Participants have been enrolled and retained with a similar pattern to prior cannabis use disorder treatment trials conducted by our research group. Enrollment is completed and all participants have completed all study procedures. Data analysis is ongoing.

Funding

Have there been any changes in funding status since the prior approval?
No
Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?
Yes

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
No
Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?
No
Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?
Yes
Is the study covered by a certificate of confidentiality?
Yes
Certificate expiration date (mm/dd/yyyy)
09/30/2019

Overall Progress

Approved sample size
150

Total number of participants enrolled to date
130
Number of participants who have completed the study to date
70
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
No
Comments / additional information

Sample Demographics

Specify population
cannabis dependent adults
Total number of participants enrolled from this population to date
130
Gender, Racial and Ethnic Breakdown
There were 130 individuals enrolled into the treatment study. One hundred and one were male. There were 31 Hispanic, 4 Asian, 50 Black, 37 Caucasian, 6 more than 1 race, and 2 unknown or not reported.

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
0
Did the investigator withdraw participants from the study?
No
Did participants decide to discontinue study involvement?
No

Procedures

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

✓ Psychiatric Assessment
✓ Medication Trial
✓ Use of Placebo or Sham Treatment
✓ Off-label Use of Drug or Device

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 is currently funded
Source of Funding
Federal
Institute/Agency
NIDA
Grant Name
Quetiapine Pharmacotherapy for Cannabis Dependence
Grant Number
1R01DA031826
Select one of the following
Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?
Yes
Subcontracted?
To
Name institution(s)
Columbia University

Study Location

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

Lay Summary of Proposed Research

Lay Summary of Proposed Research
Despite a benign public perception, marijuana use disorders represent a significant public health problem. Because the only existing evidenced-based clinical strategies for treating marijuana dependence are behavioral interventions, the development of safe and effective pharmacotherapy for marijuana dependence is an important unmet public health need. The ideal pharmacotherapy for marijuana dependence would: 1) be safe and well tolerated when administered to patients using marijuana; 2) reduce marijuana intake and promote abstinence; and 3) treat the symptoms of marijuana withdrawal. The development of safe and effective pharmacotherapies for marijuana dependence is an important unmet public health need.
Quetiapine, an effective atypical antipsychotic that acts by blocking serotonin type 2A, dopamine type 2, histamine type 1, and adrenergic receptors, is a promising treatment for substance use disorders. In animal models, quetiapine blocks the enhancement of reward by cocaine, which is likely due to its actions on both dopamine and non-dopamine neurotransmission. Clinical studies of quetiapine have shown benefit for the treatment of alcohol and cocaine use disorders. Conceptually, the clinically prominent effects of quetiapine, namely sedation, anxiolysis, mood stabilization and appetite stimulation, are a good match for the symptoms of marijuana withdrawal. Most importantly, an open-label dose-finding study of quetiapine for the treatment of marijuana dependence conducted by our research group determined that quetiapine was well-tolerated and associated with reductions in marijuana use indicating that it is a promising agent deserving of further study in marijuana-dependent outpatients.
The proposed research project is a randomized double-blind placebo-controlled clinical trial to evaluate the efficacy of quetiapine for the treatment of marijuana dependence over a 12-week period. All participants will receive Medical Management, a medication adherence focused psychosocial intervention that facilitates compliance with study medication and other study procedures, promotes abstinence from marijuana and other substances, and encourages mutual-support group attendance. All participants will receive voucher incentives for compliance with study visit attendance, returning study medication bottles, and completing other study procedures, with the objective of achieving a highly compliant sample. The goal of this phase II clinical trial is to build on our promising open-label pilot study results and examine the efficacy of quetiapine on participants' marijuana consumption under placebo-controlled double-blind conditions using an abstinence-initiation model, where participants will be using marijuana regularly at study entry, reduce their use, and then achieve abstinence. The specific aims of the projects are to determine whether quetiapine is superior to placebo in 1) reducing marijuana use and 2) achieving abstinence.

Background, Significance and Rationale

Background, Significance and Rationale
Marijuana is the most widely-used illicit drug in the United States with approximately 15.2 million individuals reporting past-month use, according to the 2008 National Survey of Drug Use and Health (NSDUH) (SAMHSA, 2009). The 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) estimated past-year and lifetime prevalence of marijuana abuse to be 1.1% and 7.2%, respectively, and past-year and lifetime marijuana dependence to be 0.3% and 1.3% (Stinson, et al., 2005; Stinson, et al., 2006). There are no efficacious pharmacotherapies for marijuana use disorders, which are the most prevalent illicit drug use disorders in the United States. The development of safe and effective

pharmacotherapy for marijuana dependence is an important unmet public health need.
The primary psychoactive component of marijuana, delta-9-tetrahydrocannibinol (THC), exerts its effects on the endocannabinoid system, which influences the main neurotransmitter systems (GABA, glutamate, biogenic amines, opioids and acetylcholine) of the central nervous system. The primary reinforcing effects of marijuana use are mediated by mesolimbic dopamine release. The marijuana withdrawal syndrome, characterized by anxiety, insomnia, irritability and anorexia, is triggered when a marijuana-dependent individual discontinues or reduces marijuana use.
Quetiapine, an atypical antipsychotic, which acts as an antagonist at serotonin, dopamine, histamine, and adrenergic receptors, is a promising treatment for substance use disorders. In animal models, quetiapine blocks the enhancement of reward by cocaine, which is likely due to its actions on both dopamine and non-dopamine neurotransmission. Clinical studies of quetiapine have shown benefit for the treatment of alcohol and cocaine use disorders. Clinically, the prominent effects of quetiapine, namely sedation, anxiolysis, mood stabilization and appetite stimulation, are a good match for the symptoms of marijuana withdrawal. Mechanistically, antagonism at serotoninergic, noradrenergic, and dopaminergic receptors suggest that quetiapine may be of value in treating cannabis dependence, since medications that increase biogenic amine levels have been shown to adversely affect cannabis withdrawal and cannabis use. Recently analyzed data from our research group found that venlafaxine, a serotonin-norepinephrine reuptake inhibitor, was associated with significantly more severe marijuana withdrawal and lower rates of abstinence rate than placebo. These data are consistent with findings that bupropion, a dopamine-norepinephrine reuptake inhibitor, worsens marijuana withdrawal. Most importantly, an open-label dose-finding study of quetiapine for the treatment of marijuana dependence conducted by our research group determined that quetiapine was well-tolerated and associated with clinically significant reductions in the amount and frequency of marijuana use. Taken together, these findings support our hypothesis that the biogenic amine antagonism of quetiapine make it a potentially promising candidate medication for treating cannabis dependence.
The proposed research project is a randomized double-blind placebo-controlled clinical trial to evaluate the safety and efficacy of quetiapine for the treatment of marijuana dependence over a 12-week period. Medical Management, a medication adherence focused psychosocial intervention, will be used to facilitate compliance with study medication and other study procedures. Participants will receive voucher incentives for compliance with study visit attendance, returning study medication bottles, and completing other study procedures, with the objective of achieving a highly compliant sample. The goal of this phase II clinical trial is to build on our promising open-label pilot study results and examine the efficacy of quetiapine on participants' marijuana consumption under double-blind placebo-controlled conditions.

Specific Aims and Hypotheses

Specific Aims and Hypotheses
Specific Aims: To determine whether quetiapine is superior to placebo in 1) reducing marijuana use and 2) promoting abstinence in marijuana-dependent outpatients.
Primary Hypotheses:
A) Quetiapine will significantly reduce marijuana consumption as compared to placebo. The primary outcome measure will be the daily dollar value of marijuana used averaged over a one-week period as recorded by the Timeline Followback method and confirmed by creatinine-normalized quantitative urine THC levels.
B) Quetiapine will significantly promote abstinence from marijuana use as compared to placebo. The

primary outcome measure will be the number of abstinent days per week as recorded by the Timeline Followback method and confirmed by creatinine-normalized quantitative urine THC levels.
Secondary Hypotheses: Quetiapine will be superior to placebo in reducing: 1) the proportion of urine toxicology samples negative for cannabinoids; 2) symptoms of marijuana withdrawal, as measured by the Marijuana Withdrawal Checklist; 3) craving as measured by the Marijuana Craving Questionnaire; and 4) sleep disturbance as measured by the Medical Outcomes Study Sleep Scale. Quetiapine administration will be associated with superior study retention as compared to placebo.

Description of Subject Population

Sample #1

Specify subject population
Cannabis-dependent individuals
Number of completers required to accomplish study aims
110
Projected number of subjects who will be enrolled to obtain required number of completers
150
Age range of subject population
18-60

Gender, Racial and Ethnic Breakdown
The study includes women and minorities; the study does not exclude any potential participants on the basis of race or gender. Both males and females will be recruited. All eligible subjects will be accepted; however, past experience with recruitment for cannabis dependence suggests that the approximate gender distribution for this study will likely be 25% female and 75% male. Previous and ongoing studies at the clinical site (STARS) have had samples comprised of approximately 45% whites, 24% blacks, 31% Hispanics, less than 5% Asian, and less than 1% Native American, Alaska Native, Native Hawaiian, or Other Pacific Islander. We anticipate a similar representation in this project. We will make every effort to recruit minority patients and women in order to ensure the generalizability of our findings to the overall treatment population.
Description of subject population
Cannabis-dependent adults from age 18-60 seeking outpatient treatment.

Recruitment Procedures

Describe settings where recruitment will occur
Recruitment and screening will be conducted at the New York State Psychiatric Institute Substance Treatment and Research Service (STARS). Screening of potential participants at STARS is covered by an umbrella screening protocol, #6582R: Evaluation of Potential Substance Abuse Research Participants (PI:John J. Mariani, MD).
How and by whom will subjects be approached and/or recruited?
Participants will be recruited using previously successful methods for substance use disorder

pharmacotherapy trials at conducted at the Substance Treatment and Research Service (STARS). Clinical trials at STARS have historically drawn a broad sample of patients from the greater New York City metropolitan area. Screening of potential participants at STARS is covered by an umbrella screening protocol, #6582R: Evaluation of Potential Substance Abuse Research Participants (PI: John J. Mariani, MD). As per protocol #6582R, a standardized telephone interview is initially conducted and prospective patients who meet screening eligibility criteria are scheduled for the first screening visit. The screening evaluation process takes place in one to two visits over a one-week period. The Mini International Neuropsychiatric Interview (MINI Version 6) for DSM-IV (Sheehan DV & Lecrubier, 2009) is conducted to determine current and lifetime DSM-IV (MINI) Axis I diagnoses. A medical history and physical and laboratory examination is conducted. Eligible potential participants will be offered the opportunity to participate in the research treatment study and obtain informed consent using the IRB-approved consent form will be obtained by the research psychiatrist.
How will the study be advertised/publicized?
A combination of radio, print, cable television and Internet advertising will be directed at prospective patients in the New York City metropolitan area who have been experiencing problems related to marijuana use and are seeking treatment. Outreach to other clinical sites and individual clinicians will be accomplished by targeted mailings, phone solicitations of clinic directors, and the use of clinically oriented e-mail newsgroups and other Internet resources.
Do you have ads/recruitment material requiring review at this time?
No
Does this study involve a clinical trial?
Yes
Please provide the NCT Registration Number
NCT01697709

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement
Screening of potential participants at STARS is covered by an umbrella screening protocol, #6582R: Evaluation of Potential Substance Abuse Research Participants (PI: John J. Mariani, MD).

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Cannabis dependent individuals
Create or insert table to describe the inclusion criteria and methods to ascertain them

Criterion	Method of Ascertainment
1) Meets DSM-IV-TR criteria for	MINI International Neuropsychiatric

current marijuana dependence	Interview for DSM IV and psychiatric assessment
2) Reports using marijuana an average of 5 days per week over the past 28 days	Timeline Follow-Back (TLFB) procedure modified for marijuana (MJ-TLFB)
3) Between the ages of 18 and 60	Demographic information
4) Able to provide informed consent and comply with study procedures	Psychiatric assessment
5) Seeking treatment for cannabis dependence	Initial Contact Interview

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

Criterion	Method of Ascertainment
1) Individuals with a lifetime DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder	MINI International Neuropsychiatric Interview for DSM IV and psychiatric assessment
2) Individuals meeting current DSM-IV criteria for any other psychiatric disorder that may, according to the investigator's judgment, require either pharmacological or non-pharmacological intervention over the course of the study	MINI International Neuropsychiatric Interview for DSM IV and psychiatric assessment
3) Participants prescribed psychotropic medication	Psychiatric assessment
4) Known history of allergy, intolerance, or hypersensitivity to candidate medication (quetiapine)	Psychiatric assessment and medical history
5) Pregnancy, lactation, or failure to use adequate contraceptive methods in female patients who are currently engaging in sexual activity with men	Medical history and serum HCG
6) Unstable medical conditions, such as poorly controlled hypertension, which might make participation hazardous	Medical history, physical examination, electrocardiogram,

	and serum and urine laboratory testing
7) Diabetes (whether controlled or not), **meeting criteria for metabolic syndrome as defined by the NCEP (any 3 of the following: a. obesity [waist circumference > 40 inches], b. hyperglycemia [fasting glucose > 100 mg/dl or Rx], c. dyslipidemia [TG > 150 mg/dl or Rx], d. dyslipidemia [HDL cholesterol; 40 mg/dl (male), 50 mg/dl (female) or Rx], e. hypertension [130 mmHg systolic or > 85 mmHg diastolic or Rx]. Participants with a BMI > 35 will be excluded.**	Medical history, physical examination, and serum and urine laboratory testing
8) Participants with a current DSM-IV diagnosis of an alcohol of substance use disorder (abuse or dependence) other than marijuana or nicotine dependence	MINI International Neuropsychiatric Interview for DSM IV and psychiatric assessment
9) Positive confirmed result on urine toxicology screen	Urine toxicology
10) Are legally mandated to particpate in a substance use disorder treatment program	MINI International Neuropsychiatric Interview and psychiatric assessment
11) Increased risk for suicide	MINI International Neuropsychiatric Interview and psychiatric assessment
12) QTc prolongation (screening electrocardiogram with Qtc > 450 msec for men, QTc > 470 msec for women) or history of QTc prolongation or using concomitant medications which prolong QTc interval	Electrocardiogram and medical history

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
After determining study eligibility as part of the STARS screening protocol (#6582R PI- Dr. Mariani), potential participants will be offered the opportunity for study enrollment. participants will be provided with the study consent cover form (information sheet), study consent form, and consent quiz. Participants will be instructed to read the study consent cover form and study consent form and then complete the consent quiz. The study psychiatrist will then review the study consent quiz with the participant, correcting any errors and answering any questions about the quiz and consent form. The study psychiatrist will review all screening materials (psychiatric evaluation form, medical history and physical examination form, ECG, and laboratory reports) and complete the eligibility criteria checklist. The potential participant will then be given the opportunity to sign the consent form and the study psychiatrist will then sign the consent form documenting consent. Finally, the study psychiatrist will then complete the study consent note, documenting the consent process.
Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form
✓ Information Sheet

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Bisaga, Adam, MD
Brezing, Christina, MD
Dakwar, Elias, MD
Luo, Sean, MD
Mariani, John, MD
Marino, Leslie, MD
Naqvi, Nasir, MD
No
Nunes, Edward, MD

Shulman, Matisyahu, MD
Vaezazizi, Leila
Vaughan, Barney, MD
Williams, Arthur
Type in the name(s) not found in the above list

Adam Bisaga, MD
Edward Nunes, MD
Elizabeth Evans, MD

Study Procedures

Describe the procedures required for this study

Design Overview: In a 12-week randomized double-blind placebo-controlled clinical trial, we will evaluate the efficacy of quetiapine for the treatment of marijuana dependence in 150 outpatients. Participants will be randomly assigned to treatment under double-blind conditions with either a fixed dosing schedule of quetiapine or placebo. All participants will receive Medical Management, a medication adherence focused psychosocial intervention that facilitates compliance with study medication and other study procedures, and promotes abstinence from marijuana and other substances. All participants will receive progressive voucher incentives for compliance with study visit attendance and completing other study procedures, with the objective of achieving a highly compliant sample. The primary outcome measures will be: 1) the daily dollar value of marijuana used averaged over a one-week period as recorded by the Timeline Followback method and confirmed by creatinine-normalized quantitative urine THC levels; and 2) the number of abstinent days per week as recorded by the Timeline Followback method and confirmed by creatinine-normalized quantitative urine THC levels. Secondary outcome measures will include: 1) the proportion of urine toxicology samples negative for cannabinoids; 2) symptoms of marijuana withdrawal, including insomnia, anorexia, anxiety, and craving; and 3) study retention.

Screening Procedures: A standardized telephone interview will be conducted and prospective participants who meet screening criteria will be scheduled for an evaluation. The MINI International Neuropsychiatric Interview will be conducted to assess current and lifetime DSM-IV-TR diagnoses. A psychiatric evaluation, medical history, and physical and laboratory examination will be conducted. The research psychiatrist will offer eligible patients participation in the study and will obtain informed consent.

Randomization: Participants will be stratified by gender and randomly allocated (1:1) to receive quetiapine or placebo. The purpose of the stratification is to distribute this potential prognostic factor equally between treatment groups.

Medication Dosing Schedule: Quetiapine has been shown to be safe and effective in doses up to 800 mg per day for schizophrenia and acute mania, and up to 300 mg per day for bipolar depression and as an adjunct

for the treatment of major depressive disorder. The results of a dose-finding pilot study of quetiapine for the treatment of marijuana dependence conducted by our research group suggests that the ideal dosing for the proposed project is a single 300 mg dose every evening, achieved after a gradual three-week titration. Clinical experience with this medication for treatment of marijuana dependence indicates that a gradual upward titration of dose is advisable to maximize tolerability and that morning dosing was poorly tolerated. Quetiapine (immediate release formulation) will be administered in 25 and 100 mg capsules; placebo capsules will appear identical to the quetiapine capsules. Participants in both treatment arms will take the same number of pills on the same schedule. Study medication will be dispensed on a weekly basis starting with the baseline visit. Quetiapine will be titrated over a three-week period (see table 1) to the target dose of 300 mg or the maximum tolerated dose. The research psychiatrist will make dose reductions for tolerability if necessary.

Medication Adherence Enhancement: We will use a combination of the riboflavin marker procedure, where both the active and placebo medication capsules will contain riboflavin, and a Timeline Followback (TLFB) pill count interview with a weekly financial incentive for medication bottle return to both enhance and measure medication compliance. To emphasize adherence to the study medication regimen and enhance the reliability of the TLFB pill count data, a $10 cash incentive is provided for return of medication bottles and any unused medication. Participants are not provided reinforcement for ingesting medication—payment is tied solely to the return of the medication bottle. The results of riboflavin marker procedure and TLFB pill count interview are discussed with the participant by the research psychiatrist to enhance adherence to the study medication regimen.

Medical Management Psychosocial Intervention: Phase II pharmacotherapy clinical trials should employ a psychosocial intervention to promote adherence to the study medication regimen and study visit schedule, without inflating the placebo response rate. The psychosocial intervention for this study will be Medical Management used for Project COMBINE (Anton et al., 2006), modified for marijuana dependence. All participants will have a manual-guided (Pettinati et al., 2005) supportive behavioral treatment session with the research psychiatrist each week. This psychosocial intervention facilitates compliance with study medication and other study procedures, promotes abstinence from marijuana and other substances, and encourages mutual-support group attendance. Throughout the trial, Medical Management sessions will be recorded, and random sessions will be chosen for review by Dr. Mariani, who will provide ongoing supervision to other study physicians to prevent therapeutic drift. All study psychiatrists will be trained in providing Medical Management and refresher training sessions will be provided every 6 months. As director of Columbia's Substance Treatment and Research Service, Dr. Mariani has extensive experience conducting and supervising Medical Management and other similar medication adherence focused psychosocial intervention models. Our research group recently completed a 12-week cocaine dependence pharmacotherapy trial that employed a medication adherence-focused psychosocial intervention similar to Medical Management had an overall retention rate of 72%.

Study Visits and Voucher Incentives for Attendance: Study visits will occur twice weekly during the study period. The study visit schedule will allow for frequent clinical monitoring and the regular performance of study assessments. One visit per week will be with the research psychiatrist for a Medical Management session to perform study assessments and to monitor medication effects and compliance. The second visit each week will be for vital sign monitoring and completion of self-report measures. Progressive cash incentives will be provided for study visit attendance and compliance with other study procedures. Starting

at $2.50 for the first study visit, the value for each subsequent consecutive visit is doubled to a maximum of $25. Failure to attend study appointments, complete study assessments, and provide a urine sample will reset the value of the cash incentive back to the initial $2.50 from which the value can escalate again according to the same schedule. If an individual attends all visits, they could earn $563 in cash. This reinforcement schedule occurs independently from the cash received for bottle return described above and cash compensation for travel.

Study Termination: Participants will be unblinded at the conclusion of the study (end of week 12). Participants assigned to quetiapine will be offered to continue treatment with quetiapine and quetiapine treatment will be provided free of charge for one month. Participants assigned to placebo will not be offered quetiapine. Participants assigned to quetiapine who do not wish to continue quetiapine treatment will be tapered off study medication over a one-week period following the final study visit. There will be a follow-up visit with the research psychiatrist one week after the study conclusion to monitor the effects of the medication taper.

Ongoing Psychiatric and Medical Assessments: The research psychiatrist will conduct weekly assessments of the psychiatric and medical status of the study participants. Participants who meet criteria for clinical worsening (see RISKS section) or the development of unacceptable medical or psychiatric risks will be removed from the trial and referred for appropriate treatment.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation
Ongoing Psychiatric and Medical Assessments: The research psychiatrist will conduct weekly assessments of the psychiatric and medical status of the study participants.

Drop out criteria during the screening and study period include:

1. Development of serious psychiatric symptoms as indicated by a Clinical Global Impression (CGI) improvement score of 6 (much worse than baseline) or greater for 2 consecutive weeks.
2. If the participant's continued marijuana use places him or her at risk for self-destructive behavior or other harm as indicated by a CGI improvement score of 6 (much worse than baseline) or greater for 2 consecutive weeks.
3. Development of serious medical conditions that may or may not be related to study participation (e.g., tardive dyskinesia, neuroleptic malignant syndrome, metabolic syndrome) as assessed by the AIMS, vital sign measurements, and monthly serum and urine laboratory studies.
4. If the participant becomes pregnant as assessed by monthly urine pregnancy testing.
5. Development of meeting criteria for **metabolic syndrome as defined by the NCEP (any 3 of the following: a. obesity [waist circumference > 40 inches], b. hyperglycemia [fasting glucose > 100 mg/dl or Rx], c. dyslipidemia [TG > 150 mg/dl or Rx], d. dyslipidemia [HDL cholesterol; 40 mg/dl (male), 50 mg/dl (female) or Rx], e. hypertension [130 mmHg systolic or > 85 mmHg diastolic or Rx]**. Patients will have their **waist circumference** calculated on a weekly basis. Serum glucose and lipid testing will be

performed monthly throughout the trial. Elevated fasting glucose values will be repeated within one week to confirm persistent hyperglycemia rather than a spurious reading.
6. Weight gain in excess of 7% from baseline. Weight will be measured weekly throughout the trial.
7. QTc prolongation (electrocardiogram with QTc > 450 msec for men, QTc > 470 for women).

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens
Blood samples (20 ml) for routine analyses (e.g., chemistry and hematology) will be taken at the time of medical screening. They will be repeated at monthly intervals. For women, a blood pregnancy test will be performed at screening and urine pregnancy testing will be performed each month throughout the study. Between 60-100 ml of blood will be drawn overall (initial screening visit, end of weeks 4, 8 and 12.)

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment
Study Assessments:

Adverse Effects measures: The Systematic Assessment for Treatment and Emergent Events (SAFTEE) as modified for Project COMBINE (Johnson, et al., 2005) has been adapted for quetiapine and will be performed weekly to identify adverse symptoms. The Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976) assists in the early detection of tardive dyskinesia in patients receiving dopamine antagonist medications.

Clinical Status measures: The Clinical Global Impression Scale-Observer (CGI) (Guy, 1976) will be used to measure the overall clinical status of the participant as well change from baseline in symptom severity. The Clinical Global Impression-Self (CGI-S) is a two-item scale that asks the subject to rate his or her current level of symptoms and estimate changes from baseline (Guy, 1976). The CGI-S will serve as the primary self-reported measure of overall functioning.

Concurrent Treatment measure: The Modified Treatment Services Review assesses the past-week exposure to health care, psychiatric, or substance use disorder treatment (McLellan, et al., 1992).
Marijuana Craving measure: The Marijuana Craving Questionnaire (MCQ) is a 47-item instrument that focuses on four primary constructs that characterize marijuana craving: compulsivity, emotionality, expectancy, and purposefulness (Heishman, et al., 2001).

Marijuana Use Outcome Measures: Marijuana use will be recorded by the Timeline Followback (TLFB) method (Litten & Allen, 1992) modified for marijuana and confirmed by creatinine-normalized quantitative urine THC levels. Because urine toxicology testing can detect THC for over one month in chronic regular users of marijuana (Buchan, et al., 2002), relying solely on urine THC levels as a measure of marijuana use outcomes is not feasible. A line of research to develop urine cannabinoid testing methods of greater utility shows promise (ElSohly, et al., 2001; Goodwin, et al., 2006; Huestis & Cone, 1998a, 1998b; Levin, et al.,

2010), but these methods are not yet validated for chronic daily marijuana users such as this project plans to recruit. However, urine THC levels can be used to confirm self-report data. We have developed a modification of the TLFB method to incorporate using a surrogate substance (dried oregano) to represent marijuana to enable participants to estimate the amount and dollar value used (Mariani, et al., 2010) during the baseline and study period. This data allows for an estimate of the amount of marijuana used in dollars, in a manner similar to how alcohol use outcomes are measured (e.g., drinks per drinking day). Prior analysis of marijuana use disorder self-report data suggests that quantifying marijuana use by units of use (e.g., joints, blunts, or pipes) is unreliable, but that estimated dollar value is a feasible method of measuring within subject changes (Mariani, et al., 2010). Our experience with substance use disorder clinical trials is that self-reported substance use data collected in a nonjudgmental and direct manner is reliable (i.e., highly correlated with urine toxicology testing results). Other substance (including nicotine and alcohol) use self-report data will also be gathered during the TLFB interview. Urine samples for quantitative urine THC levels and creatinine will be collected under directly-observed conditions during screening and at each study visit (twice weekly). Creatinine levels can be used to control for urine concentration variability and screen for adulterated samples. Creatinine-corrected quantitative urine THC levels will then be used to confirm self-reported marijuana use, using a method similar to that described by Preston et al. (1997) for cocaine dependence, where an obvious pattern of new use (i.e., level more than doubles in the past two days) overrides a self-report of no use.

Marijuana Craving report: A 6-item self-report instrument that asks participants to rate the frequency and intensity of marijuana craving.

Marijuana Withdrawal Measure: We will use the 22-item version of the Marijuana Withdrawal Checklist (MWC) (Budney, et al., 1999) that measures subject-rated severity of withdrawal symptoms on a scale of 0 ("none") to 3 ("severe") as the primary outcome measure of withdrawal. While this scale has not been empirically-validated, an alternative scale to measure symptoms of withdrawal has not yet been validated.

Medical Evaluation and Monitoring: A comprehensive medical history and physical examination will be performed during the screening process. An ECG will be performed at baseline and monthly throughout the study period. Serum pregnancy testing will be performed on all females during screening and urine pregnancy tests will be performed at baseline and weeks 4, 8 and 12. Complete blood count, electrolyte, lipid profile, and liver function tests will be performed during the screening process and monitored during the study at weeks 4, 8, and 12. Laboratory urinalysis will be performed during the screening process and monthly throughout the study. Temperature, pulse, and blood pressure will be measured at every study visit for data collection and safety monitoring purposes. Height and weight will be measured and baseline body mass index (BMI) calculated during screening. Weight will be recorded and monitored at each visit throughout the study period. **Abdominal circumference will be measured weekly.**

Medication Adherence Measures: The Structured Pill Count Interview is a Timeline Followback assessment of study medication compliance accounting for each dose of prescribed study medication during the study period. Ultraviolet light detection of a urinary riboflavin tracer (Del Boca, et al., 1996) to determine compliance with study medication therapy is performed in conjunction with the weekly medication compliance interview.

Mood and Anxiety Measures: A structured-interview version of the Hamilton Depression Scale (HAM-D) (Williams, 1988) will be used to assess depressive symptoms in clinical trials to assess baseline severity and changes associated with treatment. In addition to mood symptoms, the HAM-D has items that measure anxiety, irritability, and insomnia, which are symptoms of interest for this study.

Psychiatric Evaluation and Diagnosis: The 6. MINI International Neuropsychiatric Interview is a semi-structured diagnostic interview designed to assist researchers in making reliable DSM-IV-TR psychiatric diagnoses. The MINI will be performed during screening as part of a complete psychiatric diagnostic assessment.

Treatment Goal questionnaire: A 4-item self report portion and 3-item clinician administered portion query participants with regard to their marijuana use goals during the treatment study.

Quality of Life Measure: The World Health Organization Quality of Life Bref Instrument (WHOQOL-BREF), a 26 item self-report instrument designed to assess change in participant's quality of life (WHO-QOL Group, 1998).

Sleep Measure: The Medical Outcomes Study—Sleep Scale (MOS-SS) (Hays, et al., 2005) will be the primary outcome of sleep quality and length.
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
1

Drug #1

Name of the drug
quetiapine
Manufacturer and other information
Generic quetiapine will be obtained from a wholesale supplier
Approval Status
No IND is required
Choose one of the following options
FDA has determined that IND is not required

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes

Maximum duration of delay to any treatment
One-week, due to screening visits.
Maximum duration of delay to standard care or treatment of known efficacy
One-week, due to screening visits. All subjects receive an effective psychosocial intervention upon entering the study.
Treatment to be provided at the end of the study
At the conclusion of the study, patients will continue to be seen by the research psychiatrist for a weekly visit for up to four weeks. Subjects who received active quetiapine will have the option of continuing open-label treatment with quetiapine. Quetiapine will be provided free of charge during the four-week follow-up period. During this time period treatment goals will be reassessed and appropriate clinical referrals will be arranged. The cost of continuing treatment after transferring care will be the patient's responsibility. Subjects who are discontinued from study medication will be offered to continue to meet for weekly visits with the research psychiatrist for a period of time equivalent to the study period, if clinically appropriate.

Clinical Treatment Alternatives

Clinical treatment alternatives
Unfortunately, there is no known effective pharmacotherapy for cannabis dependence. Several psychotherapy methods have been shown to be effective for treating cannabis dependence. Alternatives treatments for substance abuse include other models of outpatient treatment or residential treatment. Patients are informed that they may request referral for other treatment options.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
bOne of the main risks of research participation involves drug administration. The target daily dose of quetiapine in the proposed study (300 mg) is within the currently-approved dosing ranges for schizophrenia, bipolar mania, and bipolar depression. The FDA has issued a boxed warning on all second-generation antipsychotics, including quetiapine, related to increased mortality in elderly patients with dementia-related psychosis. Quetiapine has also been shown to increase suicidality among children, adolescents, and young adults, although decreases in suicidal ideation and suicide attempts have been shown in other populations. All participants will be examined by clinicians who will administer the CGI on a weekly basis and the HAM-D on a bimonthly basis and remain attuned to any changes in mood or behavior.

Significant risks associated with quetiapine include hyperglycemia and diabetes mellitus, Neuroleptic Malignant Syndrome (NMS), orthostatic hypotension, leukopenia, neutropenia, agranulocytosis, tardive dyskinesia, cataracts, seizures, hypothyroidism, cholesterol and triglyceride elevations, hyperprolactinemia, transaminase elevations, cognitive and motor impairment, priapism, body temperature dysregulation, and dysphagia. The most commonly reported adverse reactions include dry mouth, sedation, somnolence, dizziness, constipation, asthenia, abdominal pain, postural hypotension, pharyngitis, weight gain, lethargy, hyperglycemia, nasal congestion, increased levels of alanine transaminase (ALT), and dyspepsia. Participants will be instructed not to drive or operate heavy machinery until they know how the medication will affect them.

Quetiapine is highly metabolized, with elimination occurring mainly via hepatic mechanism. Because of its primary central nervous system and hypotensive properties, quetiapine may lead to increased sedation when taken with other centrally-acting drugs, including marijuana, and may enhance the effects of hypertensive agents. It may also antagonize the effects of levodopa and dopamine agonists. CYP450 3A inhibitors (e.g., ketoconazole, erythromycin, protease inhibitors) may decrease clearance of quetiapine and thus raise quetiapine plasma levels, whereas hepatic enzyme inducers (e.g., phenytoin, carbamazapine, barbiturates, ridampicin) may increase the clearance of quetiapine and therefore reduce quetiapine plasma levels.

The teratogenic potential of quetiapine in pregnant women remains unknown, as there have been no well-controlled studies evaluating quetiapine in pregnant women. Therefore, women of childbearing potential must use adequate methods of contraception (e.g., barrier or hormonal contraceptive devices). Serum pregnancy tests will be conducted during screening and urine pregnancy tests will be performed monthly. If a female patient does become pregnant and wishes to continue the pregnancy, she will be withdrawn from study medication and offered continuing non-pharmacological treatment (i.e., psychotherapy).

The structured interviews, rating scales, and questionnaires should add no physical risk. However, because many of the interviews and assessments are time-consuming to complete and involve topics of a sensitive nature, some people have found them to be physically or emotionally tiring. Patients are informed prior to study entry that they can refuse to answer any questions and that they can request to stop at any time. If a participant becomes agitated during any of the interviews or assessments, he or she will be provided with therapeutic assistance.

Describe procedures for minimizing risks

i) 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 (including liver function tests), complete blood count, urinalysis, serum pregnancy test, and is designed, along with the clinical history, to detect chronic or unstable medical illnesses. A comprehensive psychiatric assessment, including a SCID interview, 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 those for whom participation would place them at an increased risk.

Females who are pregnant or lactating will be excluded from the study. Women of childbearing potential will be instructed to use an effective form of birth control before and throughout their participation in the study. Women of childbearing potential will receive clear explanations of effective birth control and be informed of the limitations of pregnancy testing, with an understanding that a negative test does not guarantee absence of pregnancy. The importance of using effective forms of birth control consistently will be emphasized, along with the understanding that even using an effective birth control method, there is still a chance that pregnancy could occur. Women of childbearing potential who cannot agree to consistently practice effective birth control, or who the investigator judges to be unreliable in practicing birth control will be excluded. Serum pregnancy tests will be conducted during screening and urine pregnancy tests will be performed monthly. Patients are instructed to inform their psychiatrist immediately if they suspect they may be pregnant. Prior to enrollment, based on all of the accumulated screening information, the Principal

Investigator, in communication with the consenting physician, will determine whether the risk/benefit ratio is acceptable for an individual to participate in the treatment protocol.

History of allergic or adverse reactions to quetiapine is exclusionary.

ii) During Study Procedures
In order to minimize the risk associated with the study medication, participants' mental status and physical health are monitored weekly during the study period by the Research Psychiatrist. Vital signs will be obtained at each study visit. Subjects will be monitored for signs and symptoms of adverse effects and dose adjustments will be made if indicated.

Although the risk of NMS and tardive dyskinesia are believed to be lower with quetiapine than with other neuroleptics, the emergence of NMS or any Extrapyramidal Symptoms (EPS) will be assessed by using the AIMS and SAFTEE throughout the study. Vital sign measurements and serum laboratory testing will be evaluated monthly to screen for any metabolic abnormalities.

Drop-out criteria during the screening and study period include:
1. Development of serious psychiatric symptoms as indicated by a Clinical Global Impression (CGI) improvement score of 6 (much worse than baseline) or greater for 2 consecutive weeks.
2. If the participant's continued marijuana use places him or her at risk for self-destructive behavior or other harm as indicated by a CGI improvement score of 6 (much worse than baseline) or greater for 2 consecutive weeks.
3. Development of serious medical conditions that may or may not be related to study participation (e.g., tardive dyskinesia, neuroleptic malignant syndrome, metabolic syndrome) as assessed by the AIMS, vital sign measurements, and monthly serum and urine laboratory studies.
4. If the participant becomes pregnant as assessed by monthly urine pregnancy testing.
5. Development of diabetes (whether controlled or not), hyperglycemia (fasting glucose > 100 mg/dl for two consecutive weeks), obesity (BMI > 30) and elevated lipids (cholesterol > 200 mg/dl; triglycerides > 150 mg/dl). Patients will have their BMI calculated on a weekly basis. Serum glucose and lipid testing will be performed monthly throughout the trial. Elevated fasting glucose values will be repeated within one week to confirm persistent hyperglycemia rather than a spurious reading.
6. Weight gain in excess of 7% from baseline. Weight will be measured weekly throughout the trial.

Participants may be removed from the trial if they repeatedly miss scheduled appointments or clinical worsening necessitates more intensive treatment (drop out criteria are defined above). Subjects who develop serious psychiatric symptomatology (e.g., psychosis, suicidal ideation, severe depressive symptoms) during the study period will be dropped from the study and appropriate clinical referrals will be made. A patient who's continued marijuana use, places them at risk for self-destructive behavior or otherwise places them at significant risk will be discontinued from the study. This would include, but not be limited to, patients who engage in destructive or violent behavior while intoxicated, report driving while intoxicated, or develop medical complications from their marijuana use. In all cases where subjects are discontinued from the study, the clinical research staff will assume clinical responsibility for the subjects until clinical referrals are operational.
Women of childbearing potential will be instructed to consistently use adequate methods of birth control (condom with spermicide, diaphragm with spermicide, oral contraceptives). During the

treatment trial, there will be periodic discussion reviewing the importance of using adequate methods of contraception consistently. Serum pregnancy tests will be evaluated at baseline and urine pregnancy testing will be performed monthly throughout the trial. If a patient suspects that she may be pregnant, she will advised that it is important to let the study team know right away. The study team will conduct a pregnancy test and help the patient decide what to do next. If a patient does become pregnant, she will be withdrawn from study medication and will be offered continued non-pharmacological treatment at the clinic. Free condoms will be made available to participants and comprehensive reproductive education will be offered.

Although a patient might potentially attempt to overdose with quetiapine, those individuals who are risk for suicidality will be excluded. Subjects will be provided with a seven-day supply of medication on a weekly basis, although in the case of a planned absence greater quantities up to a two-week supply my be provided. All patients will be informed of the possible side effects and risks listed above through extensive discussions with the Research Psychiatrist during the consent process. Patients will be warned that risks, as yet unknown, may occur when combining study medication with marijuana, other prescription medications, or street drugs. Patients will give informed consent before entering the study. Patients are instructed to call us if any untoward effects occur and are given the phone number of our 24-hour answering service. One of the Division on Substance Abuse affiliated physicians is on call 24 hours per day to answer questions and handle clinical emergencies.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
A Certificate of Confidentiality has been acquired for this study to offer protection for the privacy of subjects by protecting identifiable research information from forced disclosure (e.g., through a subpoena or court order). 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. We do, however, point out to prospective patients, that we cannot assure that their drug histories and other personal records might become known.

Upon entry to the study, the subject is informed that, if s/he agrees, the staff would prefer to have the contact information of someone who knows them well, to periodically assess how they are doing or to aid in case of emergency. Providing this information is not contingent on participating in the study. The subject, if he or she agrees, will then inform the individual that they may be contacted by the study staff. Only after the subject has informed the individual about the possible contact by the staff will the contact information be provided and the consent form addendum be signed.
Will the study be conducted under a certificate of confidentiality?

Yes, we have already received a Certificate of Confidentiality

Direct Benefits to Subjects

Direct Benefits to Subjects
Participants marijuana use and associated symptoms may improve with study participation. A complete physical and psychiatric evaluation will be performed free of charge.

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.
Participants will be paid $10 for each screening visit in order to cover transportation costs. In addition, participants earn $50 for completion of the entire screening process, which may require up to four visits. Subjects will receive $10 in cash for each visit during treatment to cover transportation costs, and will earn an additional $10 in cash for each visit that they return their medication bottle. The purpose of reimbursing patients for returning medication bottles is to monitor compliance with study medication. Reimbursement is not dependent on subjects taking study medication; subjects will be reimbursed whether or not they have taken the prescribed medication.

Progressive cash incentives will be provided for study visit attendance and compliance with other study procedures. Starting at $2.50 for the first study visit, the value of the cash incentive for each subsequent consecutive visit is doubled to a maximum of $25. Failure to attend study appointments, complete study assessments, and provide a urine sample will reset the value of cash incentives back to their initial $2.50 from which the value can escalate again according to the same schedule. If an individual attends all visits, they could earn $563 in cash. This reinforcement schedule occurs independently from the cash received for bottle return described above and cash compensation for travel.

The total compensation a patient may earn for completion of the screening process and the entire study is $733.

References

References
American Psychiatric Association. (2000). Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association.
Anton, R. F., O'Malley, S. S., Ciraulo, D. A., Cisler, R. A., Couper, D., Donovan, D. M., et al. (2006). Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. Jama, 295(17), 2003-2017.

Buchan, B. J., M, L. D., Tims, F. M., & Diamond, G. S. (2002). Cannabis use: consistency and validity of self-report, on-site urine testing and laboratory testing. Addiction, 97 Suppl 1, 98-108.
Budney, A. J., Novy, P. L., & Hughes, J. R. (1999). Marijuana withdrawal among adults seeking treatment for marijuana dependence. Addiction, 94(9), 1311-1322.
Del Boca, F. K., Kranzler, H. R., Brown, J., & Korner, P. F. (1996). Assessment of medication compliance in alcoholics through UV light detection of a riboflavin tracer. Alcohol Clin Exp Res, 20(8), 1412-1417.
ElSohly, M. A., deWit, H., Wachtel, S. R., Feng, S., & Murphy, T. P. (2001). Delta9-tetrahydrocannabivarin as a marker for the ingestion of marijuana versus Marinol: results of a clinical study. J Anal Toxicol, 25(7), 565-571.
Goodwin, R. S., Gustafson, R. A., Barnes, A., Nebro, W., Moolchan, E. T., & Huestis, M. A. (2006). Delta(9)-tetrahydrocannabinol, 11-hydroxy-delta(9)-tetrahydrocannabinol and 11-nor-9-carboxy-delta(9)-tetrahydrocannabinol in human plasma after controlled oral administration of cannabinoids. Ther Drug Monit, 28(4), 545-551.
Guy, W. (1976). Clinical Global Impression. In ECDEU Assessment Manual for Psychopharmacology, revised Rockville, MD: US Department of Health, Education, and Welfare. 217-222
Hays, R. D., Martin, S. A., Sesti, A. M., & Spritzer, K. L. (2005). Psychometric properties of the Medical Outcomes Study Sleep measure. Sleep Med, 6(1), 41-44.
Heishman, S. J., Singleton, E. G., & Liguori, A. (2001). Marijuana Craving Questionnaire: development and initial validation of a self-report instrument. Addiction, 96(7), 1023-1034.
Huestis, M. A., & Cone, E. J. (1998a). Differentiating new marijuana use from residual drug excretion in occasional marijuana users. J Anal Toxicol, 22(6), 445-454.
Huestis, M. A., & Cone, E. J. (1998b). Urinary excretion half-life of 11-nor-9-carboxy-delta9-tetrahydrocannabinol in humans. Ther Drug Monit, 20(5), 570-576.
Johnson, B. A., Ait-Daoud, N., & Roache, J. D. (2005). The COMBINE SAFTEE: a structured instrument for collecting adverse events adapted for clinical studies in the alcoholism field. J Stud Alcohol Suppl(15), 157-167; discussion 140.
Levin, F. R., Mariani, J. J., Brooks, D. J., Xie, S., & Murray, K. A. (2010). Delta9-tetrahydrocannabivarin testing may not have the sensitivity to detect marijuana use among individuals ingesting dronabinol. Drug Alcohol Depend, 106(1), 65-68. PMCID: PMC2815025
Litten, R., & Allen, J. (1992). Measuring Alcohol Consumption: Psychosocial and Biochemical Methods. Totowa, NJ: The Humana Press Inc.
Mariani J.J., Brooks D, Haney M, Levin FR. (2010). Quantification and comparison of marijuana smoking practices: Blunts, joints, and pipes. Drug and Alcohol Dependence. DOI:10.1016/j.drugalcdep.2010.08.008. PMC Journal - In Process.
McLellan, A. T., Alterman, A. I., Cacciola, J., Metzger, D., & O'Brien, C. P. (1992). A new measure of substance abuse treatment. Initial studies of the treatment services review. J Nerv Ment Dis, 180(2), 101-110.
Pettinati, H. M., Weiss, R. D., Dundon, W., Miller, W. R., Donovan, D., Ernst, D. B., et al. (2005). A structured approach to medical management: a psychosocial intervention to support pharmacotherapy in the treatment of alcohol dependence. J Stud Alcohol Suppl(15), 170-178; discussion 168-179.
Preston, K. L., Silverman, K., Schuster, C. R., & Cone, E. J. (1997). Assessment of cocaine use with quantitative urinalysis and estimation of new uses. Addiction, 92(6), 717-727.
Swift, R. M. (2003). Topiramate for the treatment of alcohol dependence: initiating abstinence. The Lancet, 361(9370), 1666-1667.