Study Title: Progesterone for the treatment of cannabis withdrawal

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A. SPECIFIC AIMS

Substantial evidence demonstrates sex and gender differences in the behavioral, biological, and clinical correlates of substance use disorders. Men tend to initiate use earlier and have higher lifetime prevalence rates of disorder, but women demonstrate more severe withdrawal, more rapid progression from first use to disorder, and greater likelihood of comorbid psychiatric disorder. A growing literature suggests that the ovarian hormones progesterone and estradiol may play a key role in these differences. Evidence from preclinical and clinical research suggests that estradiol enhances drug sensitivity and related behavior, while progesterone attenuates drug sensitivity and behavior. As such, recent clinical trials investigating exogenous progesterone as a potential pharmacologic intervention have shown attenuated subjective and physiological effects of cocaine and nicotine in drug-dependent women, and improved cognitive performance in female smokers. While progesterone has shown promise as a treatment for women with cocaine and nicotine use disorder, it has not yet been tested for cannabis.

To date, there are no approved pharmacologic interventions for cannabis use disorder (CUD) despite numerous clinical trials. Cannabis withdrawal is one potential target for CUD medication development research as withdrawal increases risk of relapse. Important gender differences in cannabis withdrawal have been identified warranting gender-based investigation. Several studies have found that women experience more severe and impairing withdrawal symptoms, primarily physiological (e.g. stomach aches, headaches, nausea) and mood-related (e.g. irritability, mood swings), compared to men. As a naturally occurring sex hormone, progesterone may effectively address these gender differences. The proposed pilot study investigates the feasibility and efficacy of exogenous progesterone administration for cannabis withdrawal among female cannabis users.

Specific Aim 1: Test the feasibility of exogenous progesterone administration among cannabis users.

Hypothesis 1: Exogenous progesterone administration will induce normative elevations in progesterone comparable to the luteal phase of female menstrual cycle and will be well-tolerated by participants.

Specific Aim 2: Examine the efficacy of exogenous progesterone on cannabis withdrawal.

Hypothesis 2: Compared to placebo, progesterone will attenuate withdrawal symptoms among heavy-cannabis-using women.

Exploratory Aim: Examine the effect of exogenous progesterone on cognitive functioning during cannabis withdrawal.

Exploratory hypothesis: Compared to placebo, progesterone will enhance cognitive functioning among heavy-cannabis-using women.

B. BACKGROUND AND SIGNIFICANCE

Overview of the Problem.
Sex and gender differences in behavioral, biological, and clinical correlates of substance use disorders are myriad (Becker et al., 2017), yet there exists a dearth of gender-informed treatment options. Ovarian hormones have been identified as potential mechanisms of these disparities (Moran-Santa Maria et al., 2014), and recent clinical trials have begun to examine their utility as possible pharmacotherapeutic agents (Evans & Foltin, 2006; Fox et al., 2013; Sofuoglu et al., 2001; 2004; 2011). The ovarian hormone progesterone has shown promise as a treatment for female cocaine and nicotine users, but has not yet been tested for cannabis. Gender differences in cannabis withdrawal, which is associated with relapse (Davis et al., 2016), are pronounced and several studies report more severe and impairing withdrawal symptoms in women compared to men (Copersino et al., 2010; Herrmann et al., 2015; Sherman et al., 2017). Developing pharmacological interventions for cannabis withdrawal remains an important priority given the significant cognitive, psychiatric, and physical consequences of heavy cannabis use.

Sex and gender differences in substance use disorders are myriad and must be considered in treatment development research. Across substances of abuse men are at greater risk for lifetime use disorder diagnosis (Becker & Hu, 2008). In contrast, females show greater abuse liability, more rapid progression from use to disorder, more severe withdrawal symptoms, and greater barriers to care (Becker et al., 2017). Cannabis withdrawal in particular is one area of disparity worthy of further investigation. Two studies examining "most recent serious quit attempt" have shown that compared to men, treatment-seeking cannabis-dependent women reported more severe withdrawal symptoms, particularly mood (e.g. mood swings, irritability) and physiological symptoms (e.g. nausea, upset stomach) (Copersino et al., 2010; Herrmann et al, 2015). Another study examined acute cannabis withdrawal symptoms (i.e. "past 24 hours") among 302 treatment-seeking adults in a pharmacotherapy trial and found greater impairment in functioning as a result of more severe withdrawal symptoms among women compared to men (Sherman et al., 2017). Given the greater severity and impact of cannabis withdrawal in women and the association between cannabis withdrawal and relapse (Davis et al., 2016), targeted gender-based treatment development for cannabis withdrawal is a priority.

Ovarian hormones are an important mechanism of sex and gender differences in substance abuse. A growing literature suggests that the ovarian hormones progesterone and estradiol, which fluctuate naturally during the menstrual cycle, may play a key role in sex and gender differences in substance abuse (Moran-Santa Maria et al., 2014). Preclinical research has shown that when progesterone levels are low (during the estrous phase in rats) females evidence greater cocaine seeking-behavior (Feltenstein & See, 2007) and are more diligent in self-administration of cocaine (Roberts et al., 1989; Hecht et al., 1999) than males. Numerous preclinical studies have also shown progesterone administration to attenuate reinforcing effects of cocaine (Frye, 2007; Evans & Foltin, 2010) and reduce drug-reinstatement and self-administration of cocaine (Anker et al., 2007; Larson et al., 2007) and nicotine (Mello et al., 2010). One preclinical study examined the effect of pregnenolone, a precursor to progesterone, on THC administration in rats and found suppressed THC-induced effects including hypothermia, locomotor suppression, and analgesia, as well as dampening of neurobiological effects in reward-related brain regions (VTA, NAc) (Vallee et al., 2014). Clinical research in nicotine, amphetamine, and cocaine users supports these findings. Women in the luteal phase of the menstrual cycle, when progesterone is high, showed decreased subjective cocaine (Evans, Haney, & Foltin, 2002; Sofuoglu et al., 1999) and amphetamine (Justice et al., 1999) effects compared to women in the follicular phase, while female smokers randomly assigned to quit during the luteal phase had lower relapse rates than those assigned to quit during the follicular phase (Allen et al., 2008).

Progesterone may address gender differences in cannabis withdrawal and improve outcomes for female cannabis users. Recent clinical trials have investigated exogenous progesterone as a potential pharmacologic intervention. Compared to placebo, progesterone has been shown to attenuate subjective and physiological effects of cocaine in female cocaine users (Evans & Foltin, 2006; Sofuoglu et al., 2002; 2004), as well as decrease cue-induced craving and cortisol response in early abstinent cocaine-dependent women (Fox et al., 2013). In a 12-week trial, progesterone reduced weekly cocaine use in post-partum cocaine-dependent women compared to placebo (Yonkers et al., 2014). Exogenous progesterone, compared to placebo, has also been shown to attenuate craving and subjective effects of smoking (Sofuoglu et al. 2001; 2011), and improve cognitive performance in women but not men (Sofuoglu et al., 2011). While progesterone has shown promise as a treatment for women with cocaine and nicotine use disorders, it has not yet been tested with respect to cannabis. Progesterone may effectively target cannabis withdrawal symptoms in women, thus reducing relapse rates improving daily functioning. The proposed pilot study investigates the feasibility and efficacy of exogenous progesterone administration for cannabis withdrawal among female cannabis users.

C. PRELIMINARY STUDIES

Capacity of Research Team. Completion of the proposed research will require experience with measuring cannabis withdrawal and gender-based substance use disorder research. As detailed below, the research team has the expertise to successfully complete the proposed work and a proven track-record in similar research areas.

Experience with measuring cannabis withdrawal. Dr. McRae-Clark (mentor) has conducted numerous NIH-funded studies with cannabis-dependent individuals that included regular assessment of cannabis withdrawal symptoms (K23DA15540; R21DA018221; R21DA022424; R01DA026782; R21DA034089). In a study of 87 cannabis-dependent individuals (McRae-Clark et al., 2011) craving responses to marijuana cues was assessed using the marijuana craving questionnaire (MCQ) and exposure to the cues produced a significant increase in the MCQ total score ($p=0.005$). Additional clinical trials assessing buspirone for cannabis dependence (McRae-Clark et al., 2015), vilazodone for cannabis dependence (McRae-Clark et al., 2016), and the effect of oxytocin on craving and stress response in cannabis-dependence all included assessments of cannabis withdrawal. Dr. Sherman recently completed a pilot study examining a cognitive bias modification paradigm on cue-reactivity in cannabis-dependent adults which also included assessment of withdrawal symptoms (under review). These studies demonstrate the team's ability to assess cannabis withdrawal in cannabis dependent adults.

Experience with gender-based research. Drs. McRae-Clark and Sherman have conducted numerous gender-based studies in substance-abusing populations including as part of the Specialized Center of Research (SCOR) on Sex/Gender Factors Affecting Women's Health (P50 DA016511-14). In recent studies Dr. Sherman has examined baseline gender differences among treatment seeking cannabis-dependent adults (Sherman et al., 2017), which included important findings on withdrawal symptoms, as well as a study on motivation for change and cannabis outcomes in a pharmacotherapy trial (Sherman et al., 2016). In addition, recently completed gender-based studies include a gender-based investigation of yohimbine and drug cues on impulsivity in cocaine users (Moran-Santa Maria, Baker, McRae-Clark, et al., 2016), and a review of menstrual phase cycle research with recommendations for assessment and future research (Allen, McRae-Clark, et al., 2016).

Summary. Our research group has significant experience with measuring cannabis withdrawal and conducting gender-based substance abuse research. Given the experience and resources of the research team, we anticipate timely completion of the current study.

D. RESEARCH DESIGN AND METHODS

D1. General Procedures:

Study Overview. The proposed study will investigate the effect of exogenous progesterone on cannabis withdrawal among female cannabis users. Forty heavy-cannabis-using women will be randomized based on nicotine dependent status to receive placebo or progesterone (200mg bid) over a consecutive 5-day period during the early follicular phase of their menstrual cycle and asked to abstain from cannabis. Menstrual phase will be determined by onset of menses and ovarian hormone levels. Following screening, within 3 days of onset of menses, participants will undergo study visit 1 (day 1 abstinence) which includes biochemical, subjective, and cognitive performance assessments, randomization, and medication instructions; they will take their first medication dose that evening. Participants undergo study procedures on study days 2-4 at home and will return to the clinic on study day 5 for repeat assessments. Salivary progesterone and estradiol levels will be collected daily, and cannabis withdrawal will be assessed twice daily, concurrent with medication adherence procedures. Primary outcomes include progesterone levels and cannabis withdrawal symptoms.

Recruitment. Women who use cannabis daily or near daily will be recruited from the community based on previously successful techniques used over the past 20 years by the research team. This will include a mix of community, print, and online advertising.

Screening and eligibility assessment.
Participants will be screened either by telephone or in person by the trained study personnel. A quick screen will be used to initially determine study eligibility; this questionnaire is focused on inclusion/exclusion psychiatric diagnoses, medical status, current medication regimen, ability and willingness to fill out the necessary assessments and commit to completion of study procedures. Potential subjects will be given a full description of the study procedures and asked to read and sign an IRB-approved Informed Consent Form if they are interested in participating.

A) Inclusion Criteria

1. Able to provide informed consent and function at an intellectual level sufficient to allow accurate completion of all assessment instruments and study procedures.
2. Age 18-45, with regular menses (every 25-35 days).
3. Report using cannabis at least 5 days per week, for at least the past year.
4. Consent to remain abstinent from alcohol for 12 hours prior to study visits, and all other drugs other than cannabis or nicotine for the duration of the study.
5. Consent to random assignment.

B) Exclusion Criteria

1. Participants who are pregnant, nursing, amennorheic, or using oral contraceptives.
2. History of major medical illnesses; including liver diseases, abnormal vaginal bleeding, suspected or known malignancy, thrombophlebitis, deep vein thrombosis, pulmonary embolus, clotting or bleeding disorders, heart disease, diabetes, history of stroke or other medical conditions that the investigator deems as contraindicated for the patient to be in the study;
3. Regular use of psychotropic medication (antidepressants, antipsychotics, or anxiolytics) and recent/current psychiatric diagnosis and treatment for Axis I disorders including major depression, bipolar affective disorder, schizophrenia or panic disorder.
4. Current suicidal or homicidal risk. Any subject who endorses suicidal ideation will be seen by a licensed clinician in the Addiction Sciences Division who will determine the best course of action to ensure patient safety.
5. Known allergy to progesterone or peanuts (vehicle for micronized progesterone).
6. Unwilling or unable to maintain abstinence from alcohol 12 hours prior to study visits, and all other drugs other than cannabis or nicotine for the duration of the study.
7. Meet DSM-5 criteria for moderate to severe substance use disorder (other than nicotine, cannabis, or alcohol) within the past year.

D2. Participant Procedures:

Medication administration and adherence monitoring. *Micronized progesterone (Prometrium; 200mg)*: Progesterone is a hormone released mainly during the luteal phase of the menstrual cycle and pregnancy, and has been used for over 50 years in the treatment of various disorders including ovarian failure, premenstrual symptoms, amenorrhea, dysfunctional uterine bleeding, menopausal symptoms and for contraception (de Lignieres, 1999; Simon, 1995). Because it is poorly absorbed and has extensive first pass metabolism, several synthetic progesterone derivatives have been synthesized and marketed. However, these synthetic progesterone derivatives have additional androgenic, corticosteroid and anabolic effects and have been associated with unfavorable side effects including fluid retention, androgenic effects and alterations in lipid profile (Goodman et al., 1996). Recently, micronized progesterone formulations that can be taken orally have been developed to overcome the poor absorption of progesterone and the unfavorable side effects of the synthetic progesterons (McAuley et al., 1996; Simon, 1995). The safety, tolerability and efficacy of micronized progesterone have been demonstrated in multiple studies. Acute effects of micronized progesterone on physiological, performance and subjective measures have been investigated over a wide dose range, from 200 to 2,000 mg/day (Freeman et al., 1995; Gron et al., 1997; Schweizer et al., 1995). Micronized progesterone provides a specific pharmacological tool to investigate the effects of this hormone, devoid of the additional pharmacological effects that synthetic progesterone derivatives have.

Progesterone or placebo dosing will begin at 9pm on study day 1. On study days 2-4 participants will take medication at home at 9am and 9pm, and on day 5 the final dose will be taken at 9am. Capsules will be prepared by the MUSC Investigational Drug Services. Previous studies (Fox et al., 2013; Sofuoglu et al., 2001; 2011) have used twice daily administration during the follicular phase of 200mg progesterone in order to achieve stable levels of progesterone comparable to normal luteal phase levels (2-20 ng/ml). Safety and tolerability of micronized progesterone has been established in numerous studies with nicotine (Sofuoglu et al., 2001; 2011) and cocaine (Evans & Foltin, 2006; Fox et al., 2013; Reed et al., 2011 Sofuoglu et al., 2002; 2004) dependent individuals.

Adherence Monitoring. Participants will record themselves taking their morning and evening medication doses and then submit these videos to research staff via RedCap survey. Subjects may use their personal smartphones for video submission. If they do not have a smartphone, one will be loaned to them during the course of the study, as video submissions may only be completed on a smartphone (cannot be completed on a computer). A survey link will be sent to the subject via text message twice daily. Video capture will occur as part of the RedCap survey. Videos are automatically stored on some Android smartphones, and participants will be informed of that so they can delete the files, if necessary. Participants using iPhones (and using loaner iPhones from our group) will not have stored videos on their phone and nothing will need to be deleted.

Ovarian Hormones: *Progesterone* and *Estradiol* will be measured from salivary samples collected using the passive drool method. Saliva samples will be collected daily; in the lab on days 1 and 5, and at home on days 2-4. Participants will be trained on how to collect and store the samples by study personnel on study day 1.

Cannabis Withdrawal. The *Cannabis Withdrawal Scale (CWS; Allsop et al., 2011)* will be used to assess cannabis withdrawal symptoms. CWS is a 19-item self-report measure that assesses cannabis withdrawal symptoms in the past 24 hours (sample items: I felt restless; I had a headache; I had trouble getting to sleep at night) on a 10-point Likert scale (0=Not at All to 10=Extremely). To establish a baseline withdrawal score, the CWS will be administered in person on study day 1. CWS will then be administered once on study days 1 and 5, and twice daily on study days 2-4 as part of the RedCap medication adherence survey that will be sent via text message to the participant. Participants will be asked to respond with reference to the past 12 hours.

Cannabis Abstinence. Cannabis abstinence will be assessed using self-report, saliva drug testing, and cannabinoid levels. Self-report will be conducted using the TLFB (see *Instrumentation* section). Saliva drug testing will occur in person on Days 1 and 5, and participants will be trained to administer saliva screening. During days 2-4, participants will schedule a Skype/FaceTime call with study personnel and undergo drug screen procedures via teleconference. Cannabinoid levels will be assessed using urine toxicology collected on Days 1 and 5. Creatinine-corrected cannabinoid levels will be compared from Day 1 to Day 5 to confirm abstinence during the study period.

Cognitive Testing. The *Symbol Digit Modalities Test (SDMT; Smith, 1982)*, *Go/NoGo Inhibitory Control (IC) Task (Chikazoe et al., 2009), and Approach-Avoidance Task (Wiers et al., 2009)* will be used to assess cognitive functioning. The SDMT measures sustained attention, response speed, and visuomotor coordination. It involves filling in a blank space below a symbol with the appropriate symbol-paired number as quickly as possible for 90 seconds. The main outcome is number of correct responses. A computerized IC task will be used to assess response inhibition. During the IC task, participants are instructed to press a button in response to common (75% of trials) and rare (12.5%) Go stimuli while inhibiting responding to rare NoGo stimuli (12.5%). The task provides errors of omission and reaction times during Go trials, and errors of commission on NoGo trials, and has been used in substance abusing populations (Froeliger et al., 2017). The AAT will be used to assess cannabis approach bias – a measure of implicit cognitive bias towards cannabis cues. During the AAT, participants are asked to respond to cannabis-related or neutral images by pushing or pulling a joystick based on an irrelevant image feature (i.e. border color). Primary outcome is cannabis approach bias, and a higher score indicates greater bias.

Nicotine Dependence: The *Fagerstrom Test for Nicotine Dependence (FTND; Heatherton, et al., 1991)* will be administered at screening to inform randomization procedures.

Consent and Screening Interview. Potential participants will present to the Addiction Sciences Division (ASD) Research Clinic and will be given a full description of the study procedures and asked to read and sign an IRB-approved informed consent form. The Mini-International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998) will assess exclusionary psychiatric and substance use diagnoses during the past year, including frequency of cannabis use. Participants will provide a urine sample, which will first be tested for pregnancy and subsequently for substance use. Past month cannabis and all other substance use will be assessed using the Timeline Follow-Back (TLFB; Sobell & Sobell, 1992). A medical history and physical exam will be conducted to ensure that the individual is eligible to participate. Participants will provide expected date of menses onset for study personnel to follow-up prior to study day 1 visit.

Tracking period between screening and study day 1 visit: Following screening visit participants will be asked to track their menstrual cycle and contact the clinic upon menses onset. Study personnel will reach out to participants 3 days prior to expected onset provided at screening as a reminder. Upon menses onset, participants will schedule study day 1 visit to occur within 3 days, or on Monday if onset occurs on the weekend (Friday-Sunday). *Study day 1 must occur on Monday, Thursday, or Friday in order to assure in-person visit on study day 5.* Participants will be asked to begin abstinence on Study Day 1.

Study day 1 visit: Participants will present to ASD and undergo urine toxicology, Breathalyzer, saliva testing, and TLFB. After all inclusion criteria and no exclusion criteria have been satisfied, the participant will be randomized to either the experimental (progesterone 200mg bid) or control (placebo) condition based on nicotine dependent status (FTND score of 4 or greater, versus 3 or below). Participants will then provide a saliva sample for progesterone and estradiol quantification, followed by cognitive testing, and then self-report assessments (see *Instrumentation* section). Participants will then receive medication instructions and review medication adherence procedures (see *Adherence* section). Participants will be instructed to take first dose of medication at 9:00pm that evening to minimize sedation. Participants will then be compensated and discharged.

Example study day 1 timeline

Time	Procedure	Duration
9:00 am	Saliva, breathalyzer, utox	15 mins
9:15	TLFB	15 mins
9:30	Saliva sample (hormones)	5 mins
9:35	Cognitive testing	15 mins
9:50	Self-report assessments (FrSBe, CWS, PANAS-X, CUDIT-R)	20 mins
10:10	Medication instructions	20 mins
10:30	Compensate/discharge	--
9:00 pm	First medication dose, CWS (at home)	--

Study days 2-4: Participants will be prompted by RedCap to complete medication adherence and CWS at 9am and 9pm. Each day participants will schedule a Skype/FaceTime call with study personnel to conduct saliva testing and adverse event assessment. Should an adverse event occur, trained personnel will assess via video conference to determine necessary procedures. Participants will also provide a saliva sample for hormone testing. Participants will be provided with labeled tubes for saliva collection and storage. They will fill out the date and time and place in the freezer to be stored until study day 5 when they will bring to ASD clinic for testing.

Study day 5 visit: Participants will present to the ASD clinic by 10am for final study visit. They will undergo saliva testing, urine toxicology, Breathalyzer, and TLFB, followed by hormone saliva sampling and cognitive testing. Participants will be debriefed, compensated, and discharged.

Example study day 5 timeline

Time	Procedure	Duration
9:00am	Last medication dose, CWS (at home)	--
9:00	Saliva, breathalyzer, utox	15 mins
9:15	TLFB	15 mins
9:30	Saliva sample (hormones)	5 mins
9:35	Cognitive testing, FrSBe	15 mins
9:50	Compensate/debrief	10 mins
10:00	Discharge	--

D3. Instrumentation:

Screening and Diagnostic Instruments. *Quick Screen:* This assessment will be used to quickly determine whether an individual meets inclusion or exclusion criteria for study entry when they first present. The instrument is designed to assess for substance use and obvious psychiatric, medical, and logistic exclusions.

Mini-International Neuropsychiatric Interview (M.I.N.I.): The M.I.N.I. is a brief structured interview that was designed to assess current DSM-5 diagnoses (including lifetime mood disorder diagnoses) using a series of questions in dichotomous format (yes/no). Earlier studies have found that the M.I.N.I. is similar in sensitivity, specificity, and inter-rater reliability to other more lengthy diagnostic interviews, such as the SCID-I/P (Sheehan & Lecrubier, 2003; Sheehan et al., 1998). This instrument will be used to assess inclusionary/exclusionary psychiatric diagnoses.

Substance-Related Instruments. *Timeline Follow-Back:* Time Line Follow-back (TLFB; Sobell & Sobell, 1992) is a calendar-based instrument designed to assess daily substance use. Study subjects will be asked to estimate the amount of substance consumed with the aid of visual cues designed to accurately quantify consumption. Cannabis use will be recorded in unique sessions per day and quantity (grams) per session.

Urine Drug Screening: Drug screens will be performed using the One Step Multi-Drug Test Dip Card (Drugconfirm™), a lateral flow chromatographic immunoassay for the qualitative detection of drug or drug metabolite in the urine at the following cutoffs (ng/ml): cocaine (300), amphetamines (1000), methamphetamine (1000), THC (50), opiates (2000), and benzodiazepines (300). Samples will then be sent to MUSC laboratory for creatinine correction processing. Results will be used to ascertain abstinence prior to study procedures, cannabinoid levels, and to substantiate self-reports of all substance use.

Saliva Drug Screening: In addition to urine testing, participants will provide a saliva sample to verify abstinence from cannabis use through use of OraLab® testing (Varian, Inc.). This test is able to detect THC in saliva for up to 14 hours, which allows verification of abstinence in the past 12 hours as indicated in procedures.

Breathalyzer: To ascertain abstinence from alcohol prior to study visits, subjects will have their breath sampled for the presence of alcohol (Alco-Sensor III, Intoximeters Inc., St. Louis, MO)

Self-Report Instruments. The *Positive and Negative Affect Scale – Expanded Form* (PANAS-X; Watson & Clark, 1999) will be used to assess emotional states within the past few weeks. It is comprised of 60-item measure with two higher order dimensions (positive and negative affect) and 11 lower order subscales (e.g. guilt, hostility, sadness). Affective states are associated with relapse and therefore a baseline measure of affect is important to consider. The *Cannabis Use Disorder Test-Revised* (CUDIT-R; Adamson et al., 2010), will be used to assess cannabis use severity, and will be included as a covariate. The Frontal Systems Behavior Rating Scale (FrSBe; Grace & Malloy, 2001) will be used to measure behavioral syndromes associated with frontal lobe dysfunction. It consists of a total score and three subscale scores: apathy, disinhibition, and executive dysfunction, and has been used in substance-abusing populations as a self-report assessment of cognitive functioning (Bickel et al., 2011) in conjunction with objective behavioral measures.

Assessment Timeline

Assessments	**Screening**	**Study day 1 visit**	**Study days 2-4 visits**	**Study day 5 visit**
MINI	X			
Breathalyzer, UDS	X	X		X
Saliva (drug screen)	X	X	X	X
TLFB	X	X	X	X
FTND	X			
Medication		X	X	X
CWS (2x/day)		X	X	X
Saliva (hormones)		X	X	X
IC task		X		X
SDMT		X		X
AAT		X		X
FrSBe		X		X
CUDIT-R		X		
PANAS		X		

Participant Compensation. Participants will be compensated for participating in the study. Participants will receive $40 for screening assessment ($20 for interview and $20 for physical exam) and $50 for study days 1 and 5 visits. Participants will receive $20 for each completion of medication adherence and CWS. Participants will receive an additional $30 for each negative saliva cannabis drug screen and $10 for a positive saliva screening on Days 2-4. Participants will receive $10 for each salivary hormone sample collected on Days 2-4. Maximum potential compensation is $420 value in the form of cash. Subjects will be compensated for negative drug screens since it is absolutely crucial to maintain abstinence in order to observe withdrawal symptoms.

Summary of compensation schedule:

	Screening	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	
Attendance	$40	$50	--	--	--	$50	
Medication/CWS	--	$20	$40	$40	$40	$20	
Saliva Drug Screen	--		$30	$30	$30		
Saliva Hormones	--		$10	$10	$10		
Totals	**$40**	**$70**	**$80**	**$80**	**$80**	**$70**	**$420**

Confidentiality. Confidentiality will be maintained using procedures that are employed as standard policy. Confidentiality of all research data will be maintained by keeping all data in a locked file, limiting access to the computer database to only study personnel, and by using patient code numbers/initials as opposed to names on all paperwork. Any requests for the release of patient information will be referred to Dr. Sherman.

Data Management and Reduction. All paper-based assessments (other than laboratory reports) will be entered into REDCap, a secure, web-based application designed exclusively to support data capture for research studies. REDCap provides an intuitive interface for data entry (with data validation), audit trails for tracking data manipulation, and automated export procedures for data downloading to statistical packages such as SPSS and SAS. Completed assessments will be entered within two weeks after the information has been collected from the subject. Quarterly database management and data integrity audits will be conducted.

Statistical Considerations

Sample Size

Specific Aims 1 and 2 of the study are to test the feasibility of exogenous progesterone for cannabis withdrawal (1), and determine its efficacy in attenuating withdrawal symptoms in heavy-cannabis-using women (2). The maximum attainable sample size of 40 (20 per condition) will yield stable levels of plasma progesterone and estimates of cannabis withdrawal symptoms across groups.

Statistical Analyses

The hypothesis associated with Specific Aim 1 concerns the feasibility of exogenous progesterone in cannabis using women. It is hypothesized that participants receiving progesterone compared to placebo during the early follicular phase will demonstrate plasma progesterone levels comparable to the average range found in the mid-luteal phase. The hypothesis associated with Specific Aim 2 concerns the efficacy of exogenous progesterone in attenuating cannabis withdrawal symptoms in female cannabis users. It is hypothesized that participants receiving progesterone compared to placebo will show reductions in cannabis withdrawal symptoms. The exploratory aim is concerned with the impact of progesterone on cognitive performance. It is hypothesized that participants receiving progesterone compared to placebo will demonstrate better cognitive function at the end of the study period. These hypotheses will be tested using a random effects mixed model for repeated measures; this methodology allows the estimation of the variance associated with a random intercept for each subject and can accommodate partially missing data (Brown and Prescott, 1999). In addition to the primary analyses, contrasts of pertinent baseline characteristics will be performed between groups. If the groups differ significantly on any of these baseline characteristics, the corresponding variables will be used as covariates in the above analyses. To note, all analyses will be considered preliminary in nature, and will need to be confirmed by a larger study.

Potential Study Limitations

Duration. Due to protracted nature of cannabis withdrawal, a longer study period would be ideal. However, given the pilot nature of this study the 5-day design should allow ample time for acute withdrawal symptoms to present, while maintaining adherence to the withdrawal protocol in a non-treatment seeking sample. Variable dosing. Since progesterone has not yet been tested in cannabis users, testing dose-related effects would provide more information as to efficacious dosing. Given numerous studies have used the proposed dose of 200mg bid in cocaine and nicotine dependent individuals, the proposed dose can be assumed to elicit the desired effect safely with confidence.

Future Studies

Cannabis use continues to increase nationwide, yet treatments remain inadequate. Cannabis withdrawal is of particular concern because it precipitates relapse and there are marked sex differences in withdrawal severity and impairment. Progesterone is a novel pharmacotherapy that may address provide targeted treatment for female cannabis users, and if combined with psychosocial interventions could enhance treatment outcomes overall. Fully-powered clinical trials of progesterone for cannabis withdrawal and relapse prevention would be important next steps.

E. PROTECTION OF HUMAN SUBJECTS

1. RISKS TO THE SUBJECTS

a. Human Subjects Involvement and Characteristics

Admission into the study is open to men and women and to all racial and ethnic groups, age 18-65. Forty subjects will be recruited primarily through internet and newspaper advertisements. Inclusion/exclusion criteria that apply to all subjects are listed below:

A) Inclusion Criteria

1. Able to provide informed consent and function at an intellectual level sufficient to allow accurate completion of all assessment instruments and study procedures.
2. Age 18-45, with regular menses (every 25-35 days).
3. Report using cannabis at least 5 days per week, for at least the past year.
4. Consent to remain abstinent from alcohol for 12 hours prior to study visits, and all other drugs other than cannabis or nicotine for the duration of the study.
5. Consent to random assignment.

B) Exclusion Criteria

1. Participants who are pregnant, nursing, amennorheic, or using oral contraceptives.
2. History of major medical illnesses; including liver diseases, abnormal vaginal bleeding, suspected or known malignancy, thrombophlebitis, deep vein thrombosis, pulmonary embolus, clotting or bleeding disorders, heart disease, diabetes, history of stroke or other medical conditions that the investigator deems as contraindicated for the patient to be in the study;
3. Regular use of psychotropic medication (antidepressants, antipsychotics, or anxiolytics) and recent/current psychiatric diagnosis and treatment for Axis I disorders including major depression, bipolar affective disorder, schizophrenia or panic disorder.
4. Current suicidal or homicidal risk. Any subject who endorses suicidal ideation will be seen by a licensed clinician in the Addiction Sciences Division who will determine the best course of action to ensure patient safety.
5. Known allergy to progesterone or peanuts (vehicle for micronized progesterone).
6. Unwilling or unable to maintain abstinence from alcohol 12 hours prior to study visits, and all other drugs other than cannabis or nicotine for the duration of the study.
7. Meet DSM-5 criteria for moderate to severe substance use disorder (other than nicotine, cannabis, or alcohol) within the past year.

Targeted/Planned Enrollment Table

Total Planned Enrollment 40

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
	Sex/Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	0	0	0
Not Hispanic or Latino	40	0	40
Ethnic Category: Total of All Subjects*	40	0	40
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	16	0	16
White	24	0	24
Racial Categories: Total of All Subjects*	40	0	40

b. Sources of Materials

1. Research material obtained from individual subjects includes questionnaires and interviews with study personnel as well as breath and urine samples. To ensure confidentiality, all subject data will be letter/number coded, and only the investigators will have access to the master lists of codes.

2. The research material will be obtained specifically for research purposes. Written research material obtained will be stored in the Addiction Sciences Division, in an office that is locked when not in use.

c. Potential Risks

1. Risks due to micronized progesterone: Micronized progesterone is generally well tolerated. The most common adverse effect is sedation. Other less common adverse effects include menstrual irregularity, spotting or breakthrough bleeding, dizziness, cramps, nausea, fatigue, headache and breast tenderness (de Lignieres, 1999; Simon, 1995). Other side effects attributed to synthetic progesterone, including depression, fluid retention, pruritus, jaundice, rash and thrombotic disorders, are unlikely to occur. Recently there has been reports of increased risk of stroke, coronary artery disease, venous thromboembolism and breast cancer in postmenapousal women who have been on long-term hormone replacement treatment with estradiol and progestin (medroxyprogesterone) combination (Grady et al., 2002; Hulley et al., 2002; Nelson et al., 2002). While some of these adverse events develop after years of treatment, venous thromboembolism is seen within the first year of treatment (2002b). It is possible that progestins may contribute to thromboembolism seen during estradiol and progestin treatment and thromboembolism is listed in the PDR as one of the adverse events for medroxyprogesterone treatment (PDR, 2002). In contrast to synthetic progestins, progesterone is not known to cause thromboembolism (PDR, 2002).

2. Risks due to study procedures: Participants will be asked not to smoke cannabis for 5 days. During this cannabis abstinence period, participants may experience symptoms of cannabis withdrawal such as craving cannabis, mild anxiety, insomnia, irritability, restlessness, stomachache, headache, nausea, loss of energy or appetite, chills, diaphoresis, and feeling depressed.

3. Potential risks of rating scales and questionnaires: These are all non-invasive, should add no risk, and have been used without difficulty or any adverse events in our previous studies with this population. The only minor inconvenience could be the time taken to complete them. Some participants may feel uncomfortable disclosing personal thoughts and feelings. Careful efforts aimed at maintaining confidentiality have been effective in previous research, and only participants' code numbers will be recorded on the forms themselves to protect confidentiality.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent

Patients will be recruited through the use of advertisements (internet, newspaper). Medical records will NOT be reviewed to identify potential study subjects. The study PI, a Co-I, or other qualified study staff will obtain informed consent. The informed consent form includes a detailed description of the study procedures, along with statements regarding participants' rights to withdraw from the procedure at any time without consequences. The informed consent form will be explained to subjects in easy-to-understand language, and subjects will be instructed to read the form carefully prior to signing it. Consent will be documented by the signature of the participant on the informed consent agreement, accompanied by the signature of the individual obtaining the consent.

b. Protection against Risk

All study participants will be closely monitored for psychiatric stability. All sessions will be conducted under the supervision of experienced personnel. If during study visits withdrawal symptoms are excessively elevated for several hours, admission for an overnight stay can be arranged for which the participant will not be charged. If hospitalization is indicated, the patient will be hospitalized through the CDAP program at MUSC or an appropriate referral will be made. Participants will be carefully screened to rule out any medical conditions that may put them at increased risk for study participation including thrombophlebitis, deep vein thrombosis, pulmonary embolus, clotting or bleeding disorders, heart disease, diabetes or history of stroke. Subjects will be warned about these side effects and the physician will be alert to the earliest manifestations of thrombotic disorders including thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis. If any of these occur or be suspected, the study medication will be discontinued immediately. Participants will be cautioned regarding potential drowsiness from progesterone.

All participants will be fully informed that they may withdraw from the experiment at any time without penalty. All participant records will be kept in a locked filing cabinet, and confidentiality of all materials will be maintained. Offices also will be locked at times when not in use. To ensure confidentiality, all participant data will be coded by letters and/or numbers, and only the investigators will have access to the master lists of codes. All participant records will be kept in an office that will be locked at times when not in use. The research staff understands the importance of maintaining confidentiality. This method of maintaining confidentiality has been used for several years by our research group and has

been effective. All co-investigators and study personnel have completed (or will complete upon hiring) training in Good Research Practices as mandated by the MUSC IRB.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

Potential benefits include detailed assessment of substance use and referral for treatment. Participants in the progesterone condition may experience a reduction in withdrawal symptoms. The minimal risks are reasonable in relation to the potential benefits to be gained from the study.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

This study may provide important information concerning cannabis withdrawal and the potential utility of progesterone as a treatment for women experiencing cannabis withdrawal. The minimal risks of the investigation are considered reasonable in relation to the expected knowledge to be gained.

5. SUBJECT SAFETY AND MINIMIZING RISKS (Data and Safety Monitoring Plan)

a. Adverse Event Monitoring

Adverse events will be monitored throughout the study and all events will be followed to resolution or stabilization. All serious adverse events will be collected and reported immediately to the IRB, and the federal funding agency. A serious adverse event is one that meets any of the following criteria:

1. Fatal or life threatening
2. Requires or prolongs inpatient hospitalization
3. Results in persistent or significant disability/incapacity
4. Congenital anomaly
5. Important medical event that may jeopardize the patient or require intervention to prevent a serious outcome
6. Cancer
7. Overdose
8. Results in the development of drug dependency or abuse.

b. Data and Safety Monitoring Plan

Data will be reviewed on an ongoing basis to ensure that data integrity is maintained. Quarterly audits of 10% of data entry will be completed. Adverse events will be reviewed by the study team on a weekly basis to ensure tolerability of the intervention. If indicated, a Data and Safety Monitoring Board will be convened to further review safety or data concerns.

6. INCLUSION OF WOMEN AND MINORITIES

As this study investigates the effect of progesterone for cannabis withdrawal in women, only women will be included. The most recent data (2012) provided by the Drug, Alcohol, and Other Drug Abuse Services (DAODAS) of South Carolina indicates that approximately 32% of individuals presenting for cannabis use disorder treatment at state supported treatment facilities were female and 68% were male. In our previous studies, without targeted recruitment efforts, women have constituted 25-30% of the samples. If there does not appear to be adequate recruitment of women into the study, measures that could be taken to improve recruitment include media advertisement and inservices detailing the study at womens' groups. In South Carolina, African Americans comprise approximately 25% of the population, with other minority representation being negligible. In our previous cannabis treatment trials, minorities have constituted 27% of the samples (25% African American and 2% Asian American). If there does not appear to be adequate recruitment of minorities into the study, measures that could be taken to improve recruitment include media advertisement and inservices detailing the study to minority interest groups.

7. INCLUSION OF CHILDREN

As per the current NIH definition that "children" refers to all subjects under the age of 18, children will not be included in the study. Children under the age of 18 will not be included because insufficient data on progesterone administration in these individuals makes the risk/benefit ratio of including this population unacceptable.

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