SCOR Grant:

Project 4

Sex Differences and Progesterone:

Association with Impulsivity and Marijuana Reduction in Co-Users of Marijuana and Nicotine Cigarettes

Short Title: Hormones & Reduction in Co-Users

Principal Investigator:

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Study Protocol

Version:
6.0

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Significance

Marijuana is one of the most commonly used, behaviorally addictive, substances in the world, surpassed only by caffeine, alcohol and nicotine. Marijuana use has gradually risen over the last several decades and with increasing legalization, relaxing of restrictions, and no firm regulation this trend is likely to continue. Approximately 1 in 10 users develop an addiction to marijuana, and this fraction is even higher for adolescents (Hall, 2009). Adolescents are particularly at risk since marijuana use contributes to more adverse long-term outcomes with earlier use and has potential effects on brain adolescent development (Volkow, 2014). In 2012, overall use among 12th graders was > 30%, lower than alcohol use (about 40%), but greater than tobacco use (approximately 18%) (Johnston, 2012). Further in all age groups (12-65) from 2007 to 2012 marijuana use has increased with >300 days/year of use occurring at a rate of approximately 5% and >20 days/month of use occurring at approximately 7%.

Sex hormone research to date indicates that estrogen is associated with the facilitation of drug-abuse behaviors, whereas progesterone is associated with reduction of these behaviors (Carroll & Anker, 2010; Lynch & Sofuoglu, 2010). While the clinical literature is mixed, our work offers additional support for this theory as the luteal phase (high progesterone) of the female menstrual cycle appears to be associated with decreased smoking-related symptomatology (Allen et al 2009b) and improved smoking cessation outcomes (Allen et al 2008; Allen et al 2009c) relative to the follicular phase (low progesterone).

Illicit drug users appear to be more impulsive than non-users (Bickel et al 2001) and sex differences have been observed in this association such that females are more susceptible to the effects of impulsivity than men (Nieva et al 2011). Preliminary evidence suggests sex hormones may play a role as females who have recently quit smoking have less impulsive behavior while in the luteal phase than in the follicular phase (Allen et al 2009a). Further, within the animal literature, delivery of exogenous progesterone has been shown to decrease impulsive behavior (Llaneza & Frye, 2009).

Taken together, these data suggest that progesterone may improve marijuana use outcomes perhaps by reducing impulsive behavior. However, the clinical literature on this topic is lacking. Therefore, in this pilot study, we are proposing a double-blind randomized controlled trial to assess the role of exogenous progesterone on impulsivity and change in marijuana use in a sample of males and females who are co-users of marijuana and nicotine cigarettes.In the first 3 years of our P50 SCOR entitled “Sex Differences and Progesterone: Effects on Impulsivity, Smoking and Cocaine Abuse” (P50 DA033942, Carroll PI) we have noted an immediate opportunity to follow an interesting and potentially important finding. In Project 1 entitled “Sex Differences and Progesterone: Effects on Impulsivity and Smoking Cessation” we have found that a large percentage of subjects screened have marijuana use concurrent with their nicotine dependence (23% of 1704 screening phone calls), and were therefore ineligible for the nicotine study. With IRB approval, we have already been collecting additional screening data on these concurrent nicotine and marijuana users to prepare for a future application on the efficacy of progesterone as treatment for marijuana addiction.

As the number of marijuana users has continued to grow in Minnesota, with approximately 8% of the population reporting to have used marijuana within the last year, we have an excellent opportunity in our demographic area, and it would be informative to carry out a pilot study on the effects of progesterone (vs placebo) on this population that are co-users of marijuana and nicotine and to compare them to the nicotine group currently being studied.

Marijuana abuse is growing in the age group we are studying (20-60 years) and may continue to increase as other states in addition to Washington and Colorado legalize marijuana. There is a high rate of co-use with nicotine and given we are successfully recruiting nicotine dependent subjects we feel that we have an exceptional opportunity to capture this comorbid population and examine effects of progesterone treatment for cessation of marijuana.

Specific Aims

This study will be similar to the ongoing double-blind clinical trial of Progesterone (PRO) vs. placebo (PBO) for cigarette smoking cessation which is successfully being conducted (currently in year 4 of 5). We will enroll a parallel participant group of marijuana smokers who are co-using nicotine cigarettes, randomized 1:1 to PRO vs. PBO in a pilot double-blind trial, adjusting the protocol to address our time constraints. Our aims are:

Primary Aim: To estimate the association between PRO vs. PBO and percent reduction of marijuana use in

males and females who are co-users of cigarettes.

Hypothesis 1a. Males and females randomized to exogenous PRO will have greater percent reduction in marijuana use compared to those randomized to placebo.

Hypothesis 1b. Males compared to females, regardless of randomization, will have greater percent reduction of marijuana use.

Hypothesis 1c. Males and females, regardless of randomization, with higher levels of serum progesterone, will have a greater percent reduction in marijuana use.

Exploratory Aim: To estimate the association between impulsivity and percent reduction in marijuana use in males and females who are co-users of cigarettes.

Hypothesis 2a. Males and females with lower impulsivity at baseline will have greater reductions in marijuana use.

Hypothesis 2b. Higher serum levels of progesterone in males and females are predicted to reduce impulsivity and marijuana use.

Methods

Study Design, Recruitment and Subject Sample

Study Design. This double-blind, randomized pilot clinical trial will prescreen an estimated 250 potential subjects, consent and further evaluate approximately 100 potential subjects, and ultimately enroll 70 subjects to ensure 40 subjects will provide a primary marijuana reduction outcome measure at four weeks post quit date. Subjects will be stratified by sex then randomized to one of two treatment groups (n=20 per drug group, 50% female): progesterone (PRO; 200mg 2x/day) or Placebo (PBO). They will take the medication for 5 weeks and will attend weekly clinic visits (see Visit Sequence & Procedure below for more information).

Setting: This project will be conducted at the Delaware Clinical Research Unit (DCRU). The DCRU has both inpatient and outpatient resources for the spectrum of biomedical research including special capabilities that were developed for study of substance use disorders. The Clinical and Translational Sciences Institute (CTSI), runs the DCRU and functions parallel to and supports the activities of the NIH funded CTSI, which it predated. The DCRU includes: reception area, examination rooms, meeting rooms, clinical interview rooms, testing rooms for computer based performance tasks, a wet lab for handling bloods and other specimens, freezers (to -80°C), all essential staff offices, each with multiple telephone and computer lines through the University of Minnesota servers, locked limited access protocol, equipment and medication rooms, as well as secure cabinets for study files and essential supply and support areas and services.

Recruitment: To meet recruitment goals, we aim to enroll a total of 70 subjects (~6 subjects/month) to ensure a final sample size of 20 females and 20 males completing the study. Our primary recruitment method will be advertising in the mainstream media. While this type of recruitment can be challenging, our team has been successful with this form of recruitment. For example, our current study (PRO for smoking cessation) has had success with Facebook, Craigslist, TV, and radio advertising. Specifically, over the past seven months, we have received an estimated 300 phone calls from interested participants which resulted in the enrollment of 30 subjects (~8 subjects/month).

Study Sample. This study will enroll males (n=35) and females (n=35) who self-report use marijuana ≥4days per week and are interested in changing their marijuana use. Specific eligibility criteria are as follows:

Inclusion: Males 18-60 years old, females 18-50 years old, stable physical and mental health, self-report Timeline Follow-Back (TLFB) indicating current marijuana use ≥4 days/week for ≥1 year, positive urine THC dipstick test (> 50ng/mL; indicating marijuana use in the past 48-72 hours), motivated to change their marijuana use (≥1 on a 10-point Likert-type scale), regular or sporadic use of nicotine cigarettes (> 1 cigarettes in the past 30 days) , self-report of regular menstrual cycles ≥6 months (female only), willing to use double-barrier contraception if sexually active and not surgically sterilized (female only), ability to comply with study procedures, ability to provide informed consent.

Exclusion: Current breastfeeding (females only), current or planned pregnancy within the next three months (females only), DSM-IV diagnoses for psychotic disorders, bipolar disorder, ADHD, major depressive

disorder within the last 3 months, substance dependence within the last 3 months with the exception of nicotine and marijuana dependence, unstable psychotropic medications (<3 months), current use of exogenous hormones, finasteroid (propecia), efavirenz, red clover, ketoconazole and other drugs that are CYP3A4 inhibitors, conditions contraindicated to progesterone treatment (including, but not limited to, thrombophlebitis, deep vein thrombosis, pulmonary embolus, clotting or bleeding disorders, heart disease, diabetes, history of stroke, allergy to peanuts, hypersensitive to progesterone and liver dysfunction).

Visit Sequence & Procedures

Screening Visits (Visits 1 and 2): Candidates completing the consent process will be screened in a two-visit process (with the option of completing visits 1 and 2 simultaneously). For males, this two-visit process will be scheduled within two weeks of completion of the phone interview. For females, this two-visit process will be scheduled during the follicular phase of their menstrual cycle (in order to avoid any potential menstrual phase effects on marijuana use or mood measures, as well as to limit wait time for initial study procedures) (details below). Therefore, after the phone screen females will be told to contact the study coordinator with the first day of their next period, and then the two-part screening visits will be scheduled during days 1-7 (where Day 1 is the onset of menses) of the menstrual cycle.

At the first of two screening visits (*Screening Visit 1*), the study will be described in detail to candidates by the study coordinator, and informed consent will be obtained. Subjects agreeing to participate will undergo medical, psychiatric and other evaluation to determine eligibility. The medical evaluation will include: brief physical exam (height, weight, blood pressure, heart rate, and medical history interview), psychiatric interview, carbon monoxide level and a blood draw (for measurement of serum hormone levels and liver function via ALT and AST measurement), a urine pregnancy test (females only) and a drug screening for marijuana (see *THC Urine Dipstick Test* for more information). Trained staff will conduct all interviews including the Structured Clinical Interview for DSM-IV (SCID; First, 1995) and instrument administration. Self-report instruments measuring impulsivity, personality characteristics, stress, caffeine use, tobacco use, marijuana use, craving and behavior will be completed. At the second screening visit (*Screening Visit 2*; scheduled within two days of Screening Visit 1), impulsivity tasks will be completed. The investigators will review the data to determine eligibility. Subjects meeting eligibility criteria will be given instructions on when to come back for their Baseline Visit (details below).

Baseline Visit (Visit 3): Female subjects will be instructed to come into the clinic within three days of the start of their Luteal Phase for their baseline visit and to start medication (PRO or PBO). Female subjects will self-report menstrual cycle length at their screening visit and staff will determine when their Luteal Phase will most likely begin. Male subjects will be instructed to come into the clinic according to their assigned delay (per randomization list generated by the Statistical Analysis Core). This visit will occur seven days prior to quit date. At this visit, subjects will be randomized to PRO or PBO within strata defined by sex. The Statistical Analysis Core (SAC) will generate the randomization tables (one for each sex, 1:1 allocation using randomly permuted blocks of size 2 and 4), and the Clinical Trials Research Pharmacy will use it to determine randomization assignment. Randomization assignment will be stored in a secure file in a secure location at the Clinical Trials Research Pharmacy, to be shared only with the SAC. All other project staff including PI and study coordinator, as well as the participant, will remain blinded to the randomization assignment. At the baseline visit subjects will provide a blood sample (for hormone assessment), urine sample for THC, breath sample (to confirm smoking status via carbon monoxide breathalyzer), have their vital signs (blood pressure, heart rate, weight) measured, be informed of their quit date, and receive brief behavioral counseling to prepare for their quit date. At the end of this visit subjects will be compensated for their time, given study medication along with instructions for taking the medication (beginning at 8PM that day), as well as a clinic visit schedule for the remaining clinic visits. This visit will take approximately one hour to complete.

Marijuana Change Date Assignment: Change date (Week 0) will be set for 7 days following the Baseline Visit. Since this entails a delay of variable duration from Screening Visit 2 to Baseline Visit (thus impacting timing of medication initiation) across female subjects, each male subject will be matched to a female subject for a similar delay so that, across the male and female groups, study procedures will be follow a similar chronology.

- *Weeks 0-5 (Visits 4-9):* The Week 0 clinic visit will occur on the assigned “Marijuana Change Date”. Subjects will attend clinic visits on a weekly basis thereafter for 5 weeks. At weeks 0, 2, 4, and 5, blood samples will be collected and stored for the analysis of hormones. Urine samples will be collected at each

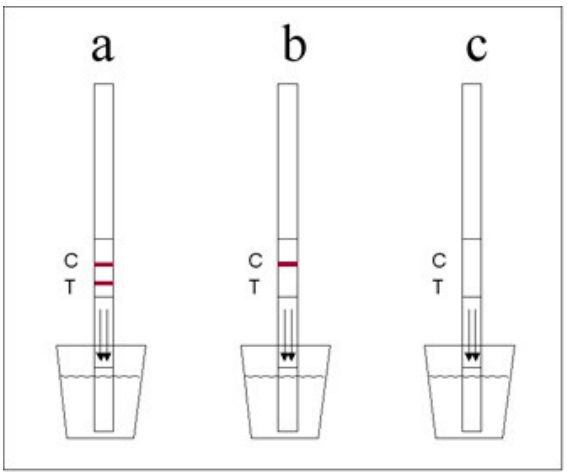
clinic visit for the visual inspection of riboflavin (assessing medication compliance), biochemical confirmation of THC, and for a pregnancy test (females only). Urine will be saved and stored on Weeks 0, 2, 4, and 5 for cotinine analysis.

Subjects will also complete several forms and questionnaires (described below). Subjects will return the medication bottle and unused medication, be given a new one-week supply and adverse events will be assessed. At Week 4, subjects will complete impulsivity tasks and study medication will be discontinued. Finally, subjects will receive brief, behavioral counseling at each clinic visit. At the end of each visit subjects will be paid for their time. These visits will take approximately 30-45 minutes to complete.

Study Adherence: To encourage compliance the following will occur: (1) at the Baseline Visit, subjects will be given a schedule of all remaining appointments; (2) at each visit the subjects will be given an appointment reminder card for the next visit; (3) reminder calls, texts and/or emails (per subject's preference) will be placed or sent the day before each visit; (4) subjects will be routinely reminded that regardless of their marijuana use that their data are valuable and important; and (5) regardless of marijuana use, subjects will be compensated at each visit (described below). If a subject misses a visit, study staff will try to reach him/her by phone that day to reschedule for one to three days later. If that does not work, staff will contact the subject's designated 'contact person' (i.e., someone who does not live with the subject but knows how to get in touch). If a subject does not attend any visits after the screening visits, he/she will be labeled as a "*drop*" and replaced. If the subject discontinues from the study after randomization but before the final follow-up visit, he/she will be labeled an "*incomplete*" but not replaced. If a subject does not quit on their assigned quit date or relapses later, she/he will be encouraged to stay in the study and make another quit attempt; such that we will follow them for the length of the study regardless of marijuana use. Subjects who complete the weekly follow-up period after quit date, regardless of marijuana use, will be labeled a "*completer*" for the primary outcome and not replaced.

THC Urine Dipstick Test: The THC Urine Dipstick Test is a one-step immunoassay that qualitatively detects delta-9-tetrahydrocannabinol in urine. The results obtained are of a preliminary nature and is for screening purposes only. THC, psychoactive component of marijuana, is a central system stimulant relaxant. THC in marijuana is strongly absorbed by fatty tissues in various organs and a metabolite form of THC, delta-9-tetrahydrocannabinol, is present in urine 48-72 hours after a smoking-section. This is what denotes a marijuana user.

Figure 2. Dipstick Test Results



The THC Urine Dipstick Test is an immunochromatography device based on the principle of competitive immunoassay. The nitrocellulose membrane of the dipstick is immobilized with THC-protein conjugate on the test zone (see Figure 2). Antibodies against THC, which have been conjugated with colloidal gold, are impregnated on a porous pad overlapping the bottom end of the membrane. When the sample pad of the dipstick is dipped into the urine sample to perform the test, by capillary attraction, the urine will flow through the porous pad towards the other end of the assay strip. The antibody-gold conjugate dissolved by the urine sample will flow with the liquid front-end. In the absence of THC, the antibody-gold conjugate will bind to the immobilized drug conjugate causing a visible red band to appear at the test zone. However, when a sufficient concentration of THC (>50 ng/mL) is present in the urine sample, the THC in urine will bind with the antibody and saturate the binding capacity of the antibody-gold conjugate, thus, no visible band will appear at the test zone.

Possible Results: NEGATIVE: If there is no THC present in urine, there will be a rose-color bands appearing on both the control and the test section. POSITIVE: A positive result is observed when there is a control line and no test line and indicates a minimum THC concentration of 50 ng/mL. At concentrations less than 50 ng/mL, there may be weak signal appearing at the test line area. INVALID: If there is no rose-color band visible in the control window, then the test result is invalid. (Source: Acro Biotech Inc., Rancho Cucamonga, CA, www.acrobiotec.com)

Subject Compensation

Subjects will receive compensation at each clinic visit for their time and effort. Subjects will be paid $25 for Screening Visit 1 and $25 for Screening Visit 2. For each follow-up visit they attend, they will be compensated $20 for their time, for completing study procedures and to cover transportation costs. Subjects will also complete the Balloon Analogue Risk Task (BART) twice during the study. The average compensation a subject can earn from this task is $35. The subject will also be eligible for a study bonus upon study completion: $30 for attending W5 and $50 for missing no more than 1 follow-up clinic visit (must not be Week 4). Therefore, subjects will receive approximately $340 ($25 Screening Visits x 2 visits + $20 follow-up visits x 7 visits + $80 in bonus payments + an average of $70 in BART payments).

Study Medication

Subjects will be stratified by sex and then randomly assigned to PRO or PBO, as described above. All medication (active and placebo) will be prepared by the University of Minnesota Clinical Trials Research Pharmacy, which is a specialized facility that prepares medication for clinical trials including our ongoing research. The research pharmacist (D Luke Pharm D) will provide medications. There will be oversight and monitoring with regular audits by local regulatory boards including the IRB and DSMB. This study requires double-blind procedures, therefore progesterone will be over encapsulated and be identical to the placebo capsules. Medications will be discontinued at the Week 4 clinic visit. Adverse events will be assessed at each clinic visit.

Progesterone: The progesterone will be given in the form of an active or placebo micronized natural progesterone (generic Prometrium). All subjects will take 200 mg twice daily (approximately 8am and 8pm) for five weeks starting seven days prior to the assigned change date. The dosage was selected to ensure that serum progesterone levels will be consistent with those observed in the natural Luteal phase of the menstrual cycle (6-14 ng/mL) since that phase has been shown to be favorable for smoking cessation (Allen et al 2008). We expect the following serum progesterone levels by group (Figure 5):0 (1) females + PRO 9-13 ng/mL; (2) males + PRO 6-7 ng/mL; (3) females + PBO, varies by menstrual phase from 1-14 ng/mL; and (4) males + PBO 0-1 ng/mL (Goletiani et al 2007; Reed et al 2010; Yen et al 1999). Delivery of exogenous progesterone has been successfully used in other studies and is generally well tolerated (Sofouglu et al 2001; Sofouglu, et al 2004; Goletaini et al 2007; Reed et al 2010). The most common adverse effect in males and females is sedation. Less common effects include breakthrough bleeding (females), nausea (females and males) and breast tenderness (females) (de Lignieres, 1999; Goletaini et al 2007). While it is possible that progestins may contribute to risk for thromboembolism, we will be using natural micronized progesterone instead of synthetic progestins. Natural micronized progesterone is not known to be associated with thromboembolic risk (PDR, 2002; Goletaini et al 2007), and consequently is a safer choice. Micronized progesterone is not a form of birth control. Therefore, all female subjects will be educated on the importance of using a double-barrier method to protect against pregnancy.

Study Measures

We will assess marijuana use using two methods (self-report, biochemical confirmation). *First*, at each clinic visit the TimeLine Follow-Back (TLFB) method will be completed. The TLFB is a validated retrospective data capture technique (Sobell et al 1996). *Second*, at each clinic visit we will measure urinary THC levels (see table 1for all study measures and when they are collected).

Impulsivity Measures: Subjects will complete *three self-report measures* that have been computerized at each clinic visit beginning at Screening Visit 2. These measures will assess the characteristics of impulsivity, inhibition, planfulness, and cognitive impairments, key areas of focus in this grant.

- *Behavioral Inhibition/Activation scales (BIS/BAS):* 20-item form is commonly used to study externalizing tendencies (Carver and White, 1994). Investigators in Project II have used this instrument with success.
- *Barratt Impulsiveness Scale (BIS)*: 30-item self-report measure of self-control (Patton et al 1995). Doran and colleagues (2004) demonstrated that impulsivity, as measured with this item, was a predictor of smoking relapse.
- *Brief Self Control Scale (BSCS)***:** This item consists of 13 questions rated on a 4-point scale from “very true” to “very false” on items reflecting the ability to control problematic behaviors (Tangney et al 2004).

The *Impulsivity Tasks* represent two forms of impulsivity, 1) impaired cognitive inhibitory mechanisms, and 2)

deficits in motor inhibitory mechanisms. “Delay discounting” entails higher-level cognitive inhibitory processes that may characterize the behavior of individuals who are drug dependent (Bickel and Marsch, 2001) tobacco users (Baker et al. 2003), cocaine users (Monterosso et al, 2001), other drug users (e.g. Vuchinich and Simpson, 1998; Kollins, 2003) and pathological gamblers (Dixon et al, 2003). The following items will be completed at Screening Visit 2 and Week 4.

- *Delay Discounting Task*: Developed by de Wit and colleagues (Richards et al, 1999), delay discounting refers to the reduction in value of a reward over time relative to its immediate worth. One’s discount rate, also known as a time preference, is a measurable individual difference and involves a series of choices (e.g. Petry and Casarella, 1999): one option is an immediate payment (e.g. $1); the second option is a larger payment (e.g. $50) after a delay (e.g. 6 hours to 25 years). Titrating the payment amounts at each delay interval allows the identification of points of indifference (the point at which the subject switches from choosing the immediate to the larger reward at a given delay interval). We additionally included a probability discounting condition to measure risk aversion in addition to time preference (Richards et al, 1999).
- *GoStop Task***:** This task measures response inhibition. A series of five-digit numbers are presented on a computer monitor at a rate of 500ms for ever two seconds. Subjects are instructed to click the mouse button when the number they see is identical to the previous number. Half of the numbers change color from black to red at 50, 150, 250 and 350. Subjects are instructed to respond to the matching number only when the displayed number is black. The primary outcome of this task is the percent of inhibition failures for the 150ms delay (Dougherty et al 2008). This item has been successfully used to assess tobacco dependence and smoking behavior (Billieux et al 2010).
- *Balloon Analogue Risk Task (BART):* This task, with 30 replications/session, is a measure of risk-taking. It involves displaying a small balloon on a computer screen. Each “pump” to inflate the balloon accumulates five cents, with each pump potentially breaking the balloon. The average pumps to the breaking point is 64. To ensure attentive responding, subjects will receive the actual amount of money accrued on this task. The primary outcome on this task was the number of exploded balloons divided by the number of trials (Lejuez et al, 2002).
- *Immediate Memory Task / Delayed Memory Task (IMT/DMT):* This task is a continuous performance task that has two phases. First, the IMT displays a series of five-digit numbers in on a computer monitor for 500 ms followed by a blank screen 500 ms. Subjects click the mouse button whenever an identical number is displayed. Next, the DMT requires the subject to remember a five-digit number and compare it to another that is presented 3.5 seconds later. During the 3.5 interval subjects are presented with a distracter (12345) and told to ignore it. The primary outcome of this task is the IMT/DMT ratio which is defined as the proportion of commission errors to correct detections (Mathias et al 2002). This item is included as it we have used it in prior studies to identify menstrual phase differences in impulsivity and attention (see Preliminary Studies B.2.1.), and therefore is expected to be sensitive to the group differences in sex and progesterone.

Independent Measures (sex, randomization, and serum progesterone):

Sex will be collected via self-report on the Demographics form completed at Screening Visit 1.

Randomization, assignment (PRO vs. placebo) will be known as of the Baseline Visit to the SAC and Clinical Trials Research Pharmacy, but not will be known to other staff or participants until after completion of all measurements. Participants will be informed on their randomization assignment in a letter mailed within six months of the study’s completion; this letter will also briefly summarize the study’s findings.

Measurement of serum progesterone will be measured by collecting a blood sample at Screening, Bassline and Weeks 0, 2, 4, and 5.. Blood (20cc) will be drawn then centrifuged. The serum stored at -20°C in sealed storage tubes to prevent evaporation. Approximately two mL of serum will be analyzed by the University of Minnesota Laboratories for progesterone sample. The remaining serum (approximately two to four mL) will be used for estradiol measurement (described below) and/or stored as back-up to be used in the event that problems occur during analyses.

Other Covariates: Information on potential covariates is collected at the clinic visits, including:

- *Cannabis Use Disorder ID test* (CUDIT-R, Adamson et al 2010): This item is 8 questions that screens for

problematic cannabis use. The domains captured in this questionnaire are consumption, abuse, dependence and psychological features. This screening test has been shown to have 91% sensitivity and 90% specificity. This item will be completed at Screening Visit 1.

- *Marijuana Craving Questionnaire* (MCQ-SF; Heishman et al 2008): This item includes 12 questions that assess 4 characteristics of craving, compulsivity, emotionality, expectancy and purposefulness. This item will be completed at Screening Visit 1. This item will be completed at each clinic visit thereafter.
- *Cannabis Withdrawal Scale* (CWS; Allsop et al 2011): This item measures the intensity of cannabis withdrawal symptoms and the distress or functional impairment caused by each symptom using a 10-point Likert scale. This item will be completed at Screening Visit 1. This item will be completed at each clinic visit thereafter.
- *Severity of Dependence Scale Cannabis* (SDS-C; Swift et al 2000): This 5 item questionnaire is sensitive to the severity of cannabis dependence. This item will be completed at Screening Visit 1.
- *Reasons for Quitting Marijuana Questionnaire* (Stephens et al 1995): This item is 29 questions that assess participant's reasons the quit marijuana. This item will be completed at the Baseline visit.
- *Self-Efficacy Questionnaire* (Stephens et al 1995): This item is 20 questions that assess a participant's self-efficacy for quitting marijuana. This item will be completed at the Baseline visit.
- *Cigarette Smoking Behavior*: Specifically, number of cigarettes smoked per day during ad libitum smoking, self-reported number of past quit attempts, past longest quit attempt, motivation to quit smoking, and social influences such as partner smoking. This item will be completed at Screening Visit 1 only.
- *Fagerström Test for Nicotine Dependence* (FTND; Heatherton et al 1991): This item will be administered during the first screening session to assess level of nicotine dependence. The FTND is a 6-item self-report measure derived from the Fagerström Tolerance Questionnaire. This item will be completed at Screening Visit 1 only.
- *Minnesota Nicotine Withdrawal Scale* (MNWS; Hughes & Hatsukami, 1998): This item includes measurement of: irritability, anger, anxiety, difficulty concentrating, restlessness, depressed or sad mood, and hunger. MNWS scores are calculated without the item of craving. We have changed the wording of the craving item to 'desire to smoke,' and its mean scores are analyzed separately in light of evidence suggesting distinct patterns of craving from other withdrawal symptoms (Hughes & Hatsukami 1998). This item will only be completed once during the screening process. This item will be completed at Screening Visit 1. This item will be completed at each clinic visit thereafter.
- *Questionnaire for Smoking Urges* (QSU-brief; Cox et al. 2001): This item is the shortened version of the QSU (Tiffany & Drobes, 1991) and will assess smoking urges. It includes 10 items clustered into two factors similar to those assessed by the longer version of QSU. Factor 1 includes items that indicate a strong desire and intention to smoke. Factor 2 includes items indicating expectation of a relief from negative affect with an urgent desire to smoke (Cox et al, 2001). This item will only be completed once during the screening process. This item will be completed at Screening Visit 1. This item will be completed at each clinic visit thereafter.
- *Cigarette Smoking Stage of Change Questionnaire* (SOC; Prochaska et al, 1993) This 3-item questionnaire will be used to assess readiness to quit smoking cigarettes. It will classify the sample into two groups - those who are 1) in the "active/preparation" stage of quitting and those who are in the 2) "contemplation/pre-contemplation" stage.
- *Profile of Mood States* (POMS; McNair et al, 1971): On this 72-item form subjects use a 5-point Likert-type scale, to indicate 10 subscales (Evans et al 1998) including positive mood, arousal, vigor, elation, friendly, fatigue, tension-anxiety, depression-dejection, confusion, and anger-hostility. This item will only be completed once during the screening process. This item will be completed at Screening Visit 1. This item will be completed at each clinic visit thereafter.
- *Beck Depression Inventory-II* (BDI-II, Beck et al, 1996): This is the most commonly used screening measure for adults and will be used to assess depressive symptoms. This item will only be completed once during the screening process. This item will be completed at Screening Visit 1. This item will be

completed at each clinic visit thereafter.

- *Perceived Stress Scale* (PSS; Roberti et al, 2006): This ten item questionnaire will measure perceived stress. The items are rated on a 5-point scale, ranging from 0 (never) to 4 (very often), and they focus on events during the last week. The scale has adequate reliability and validity. This item will only be completed once during the screening process. This item will be completed at Screening Visit 1. This item will be completed at each clinic visit thereafter.
- *Columbia-Suicide Severity Rating Scale:* This questionnaire (C-SSRS; Posner et al, 2009) will be completed at each clinic visit to assess suicidal ideation, given this is listed as an SAE on the Prometrium label. If any item of suicidality is endorsed referrals to the appropriate mental health care will be made.
- *Sociodemographic Variable*s: At the first screening visit we will collect information on age, race/ethnicity, education, income and other related variables. This item will be completed at Screening Visit 1 only.
- *Serum Estradiol*: Blood samples will be collected at Screening, Baseline and Weeks 0, 2, 4, and 5 to allow for the measurement of serum estradiol. Following identical procedures described above for serum progesterone, approximately two mL of serum will be analyzed by University of Minnesota Laboratories.
- *Leisure Time Exercise Questionnaire* (LTEQ): This questionnaire has four-items to assess strenuous, moderate and mild exercise completed during leisure time and has high reliability (r=0.83, 0.85; Gordin & Shepard, 1985). This item will be completed at Screening Visit 2. This item will be completed at each clinic visit thereafter.
- *Life Event Occurrence* Survey (LEOS; McKee et al, 2005): This item will assess and account for the presence of current or recent significant life events. This measure includes 38 yes/no questions assessing various events that may have happened in the last six months including aspects of work, social life, family and finances. The measure includes instructions on how to rate the level of disruption the event caused in the subjects life from none too severe disruption. This measure will be administered at screening visit 1 and the final visit W5.
- *Caffeine Use:* Caffeine use will be collected via self-report at each clinic visit using the TimeLine FollowBack methods in which participants will report the total number of ounces of caffeinated beverages drank per day for each of the last 7 days.
- *Tobacco Use:* Tobacco use will be collected via self-report at each clinic visit using the TimeLine FollowBack methods in which participants will report the total number of cigarette smoked per day for each of the last 7 days.
- *Adverse Childhood Experience (ACE):* Participants will complete this form at the SC2 visit.

Debriefing Questionnaire: At end of study participation or Week 4, whichever is later, participants will complete a questionnaire to indicate which study medication (active or placebo) they thought they were on.

Table 1. Study Measures at Each Time Point

	SC1	SC2	BL	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5
Intake Form: Demographics, baseline characteristics	INTAKE								
Medical History: Assess inclusion/exclusion criteria	MH								
Structured Clinical Interview for DSM Disorders	SCID								
MN Impulsive Disorders Interview: Buying, stealing, hair pulling, anger, gambling, sex, binge eating	MIDI								

Randomization: Progesterone or Placebo			RAND						
Cannabis Use Disorder Identification Test: Disorder	CUDIT-R								
Severity of Dependence Scale-Cannabis: Dependence	SDS-C								SDS-C
Cannabis Withdrawal Scale: Withdrawal	CWS		CWS	CWS	CWS	CWS	CWS	CWS	CWS
Marijuana Craving Questionnaire: Craving	MCQ-SF		MCQ-SF	MCQ-SF	MCQ-SF	MCQ-SF	MCQ-SF	MCQ-SF	MCQ-SF
Reasons for Quitting Questionnaire: Marijuana	RFQ		RFQ			RFQ		RFQ	
Self-Efficacy Questionnaire: Confidence to resist marijuana	SE		SE			SE		SE	
Fagerström Test for Nicotine Dependence: Nicotine dependence	FTND								
Minnesota Nicotine Withdrawal Scale: Withdrawal, craving	MNWS		MNWS	MNWS	MNWS	MNWS	MNWS	MNWS	MNWS
Questionnaire for Smoking Urges: Intention to smoke, anticipation of relief from negative affect	QSU		QSU	QSU	QSU	QSU	QSU	QSU	QSU
Cigarette Smoking Stage of Change Questionnaire: Readiness to quit smoking cigarettes	SOC		SOC			SOC		SOC	SOC
Columbia-Suicide Severity Rating Scale: Suicidal ideation	C-SSRS		C-SSRS	C-SSRS	C-SSRS	C-SSRS	C-SSRS	C-SSRS	C-SSRS
Adverse Events: Since you last visit…			AE	AE	AE	AE	AE	AE	AE
Perceived Stress Scale: Perceived stress		PSS	PSS	PSS	PSS	PSS	PSS	PSS	PSS
Profile of Mood States: Positive mood, arousal, vigor, elation, friendly, fatigue, tension-anxiety, depression-dejection, etc.		POMS	POMS	POMS				POMS	
Beck Depression Inventory-II: Depressive symptoms		BDI-II	BDI-II	BDI-II	BDI-II	BDI-II	BDI-II	BDI-II	BDI-II
Adverse Childhood Experiences: childhood maltreatment		ACE							
Life Event Occurrence Survey: Significant life events		LEOS-R							LEOS-R
Leisure Time Exercise Questionnaire: Strenuous, moderate and mild exercise		LTEQ	LTEQ	LTEQ	LTEQ	LTEQ	LTEQ	LTEQ	LTEQ
Behavioral Inhibition/Activation scales: Motivational systems (appetitive & avoidance)		BIS/BAS	BIS/BAS	BIS/BAS	BIS/BAS	BIS/BAS	BIS/BAS	BIS/BAS	BIS/BAS
Barratt Impulsiveness Scale: Impulsivity and self-control		BIS	BIS	BIS	BIS	BIS	BIS	BIS	BIS
Brief Self Control Scale: Ability to control problematic behaviors		BSCS	BSCS	BSCS	BSCS	BSCS	BSCS	BSCS	BSCS
Delay Discounting Task: Evaluates discount rates for rewards, impulsivity		DD						DD	
Debriefing Questionnaire: Perception of rand. assignment (PRO/PBO)								DQ	
Study Satisfaction Survey: Taking meds, working with staff, etc.									SS
Time-Line Follow-Backs:									
Marijuana: Since you last visit... (TPD - Times per day)		MJ	MJ	MJ	MJ	MJ	MJ	MJ	MJ
Cigarettes: Since you last visit… (CPD)		CPD	CPD	CPD	CPD	CPD	CPD	CPD	CPD
Caffeine: Since you last visit... (ozs.)		CAFF	CAFF	CAFF	CAFF	CAFF	CAFF	CAFF	CAFF
Computer Tasks:									
Immediate/Delayed Memory Task: Impulsivity & attention		IMT DMT						IMT DMT	
GoStop Computer Task: Response inhibition		GoStop						GoStop	
Balloon Analogue Risk Task: Risk-taking		BART						BART	
Biological Specimen Collection:									
Blood (plasma/serum): Hormones	BLOOD		BLOOD	BLOOD		BLOOD		BLOOD	BLOOD
Urine: THC and Cotinine		URINE	URINE	URINE	URINE	URINE	URINE	URINE	URINE

Analysis Plan

Our primary outcome is change in marijuana use as defined by the TLFB at the week 4 visit relative to the baseline visit. This is a pilot study to generate data to potentially motivate and justify a future fully-powered study of PRO and marijuana cessation, so the intent of these analyses is to estimate magnitude and direction of treatment effects and associations with impulsivity (sex-specific and overall). While we expect baseline covariates to be balanced across treatment groups due to the randomization, this pilot study is small so both unadjusted and adjusted assessments of effects will be carried out by including the randomized treatment assignment and pre-specified adjusting covariates such as age, baseline progesterone, estradiol, baseline

impulsivity measures, etc. This pre-specified list will be determined by the study team during the finalization of the protocol, prior to the first study enrollment. We expect these analyses to be somewhat conservative, since they do not explicitly account for the randomized permuted blocking (Matts and Lachin, 1988). An analysis that accounts for the blocking (such as a stratified Mantel-Haenzel test) cannot be generalized to include the adjustment for impulsivity measures, for example, which are a focus of this proposal. All persons randomized and with a measured primary outcome at the week 4 visit will be included in this analysis, regardless of whether or not they ever took any of their assigned treatment (intent-to-treat analysis); persons with missed visits are discussed below.

Addressing Hypothesis 1a: An unadjusted assessment of the treatment effect will come from a linear model of percent reduction in marijuana use on randomized treatment assignment, separately by sex. ***Hypothesis 1b:*** A linear model including both males and females will be used to estimate the overall gender effect on percent reduction in marijuana use. ***Hypothesis 1c:*** A linear model including both males and females will be used to estimate the association of serum progesterone with percent reduction in marijuana use; we will separately consider baseline progesterone, cumulative progesterone (summed over weeks 0-4), and week 4 progesterone.

Addressing Hypothesis 2a: A linear model including both males and females will be used to estimate the association of impulsivity with percent reduction in marijuana use. ***Hypothesis 2b:*** A linear model including both males and females will be used to estimate the interaction between baseline impulsivity and baseline serum progesterone on percent reduction in marijuana use.

Missing data plan: Quality assurance plans are described below. The primary outcome analysis will be carried out using two parallel models: one model will exclude subjects for whom we were unable to obtain a week 4 TLFB or urine THC. Since 'missing at random' is a strong statistical assumption to make, we will also carry out a parallel model that uses multiple imputation of the week 4 TLFB and urine THC based on an individual's previous visits' TLFB and urine THC levels. We will also examine whether persons missing their week 4 visit differed in their baseline characteristics or treatment assignment from persons not missing their week 4 visit.

Power: This is a pilot study to generate data to potentially motivate and justify a future fully-powered study of PRO and marijuana use. This study will estimate magnitude and direction of treatment effects and associations with impulsivity (sex-specific and overall). Hence, no power calculations are provided.

Data Safety and Monitoring Plan, Board, and Administration.

The Admin Core Director (Carroll) and the Statistical Analysis Core Director (Eberly) of the P50 will jointly organize review by the Data Safety and Monitoring Board (DSMB). The Project PI (S. Allen) will administratively oversee complying with reporting requirements. The DSMB will meet annually and will, post meeting, provide a summary of discussion, which will be conveyed to NIDA. This report will include subject demographics, expected versus actual recruitment rates, summary of any quality assurance or regulatory issues, summary of adverse events (AEs) or serious adverse events (SAEs) which may have occurred, and any changes in the protocol as a result of these issues. The DSMB will receive current data and blinded data unless a specific request or cause to view un-blinded data is evident. The final report will be complete and inclusive with the unblended data set.

The Project Coordinator (N. Tosun) and PI (S. Allen) will meet on a weekly basis to review the study's progress. The team will meet regularly and as needed regarding data and project safety. Additionally, all key personnel will meet regularly regarding overall progress, specific problems and problem resolution. The daily monitoring of subjects will be the coordinator's responsibility.

Participants will be closely monitored throughout the trial. A summary of all data, with the exception of information that entails breaking the blind, will be provided to the DSMB at annual meetings. SAE's will be reported to the head of the DSMB when they have been identified and characterized. The chair of the DSMB may request a special meeting of the panel as needed. The Board will consist of Drs. Frances Levin (Chair), Dr. Joy Schmitz, Dr. Paul Pentel, and an expert in marijuana abuse (TBN). These individuals will serve to monitor all the SCOR projects involving human subjects, including this project.

The group will meet on an annual basis and review data including recruitment, progress, safety, adverse events, and serious adverse events associated with the study. The DSMB meeting will include open, closed and executive sessions. The Principal Investigator, co-investigators, statisticians, and study coordinators will attend the open session and present during the meeting. The purpose of the open session is to provide relevant information to the Board about general aspects of the trial. The open session will focus on the background of the study, the protocol, status of the study, problems with accrual and follow-up, baseline demographic data, compliance issues, frequency of adverse events, documentation of endpoints, data quality issues, flow of forms, data based protocol modification issues, and any other issue regarding the studies under review that can be discussed without reference to interim comparative results.

Following the open session, a closed session will be held if deemed appropriate and necessary by the DSMB Chair. During the closed session, the chairperson (Frances R Levin MD) will conduct the review of all issues and puts each issue to a vote. This session will be attended by the DSMB members and if necessary the statistician and principal investigator. During the closed session, the discussions will focus on the treatment safety, requesting and reviewing additional information if needed and updating the Board on actions taken related to their actions and recommendations of the previous meeting.

Following the closed session, an executive meeting may be held, at the discretion of the DSMB Chair. The executive meeting will be restricted to DSMB members. During these sessions, the Board may discuss any sensitive issues surrounding the clinical trials under review.

The Board Chairperson will prepare a draft report of the meeting along with minutes for inclusion in the final DSMB report. The report will outline and summarize discussion during the open and closed sessions of the meeting. Recommendations and action items will be clearly marked within the body of the report. If the DSMB conducts an executive session, a statement will be included in the Minutes of the Meeting stating that an executive session was conducted, but content of the discussion will be retained by the chair and not included in the report. The draft report shall be reviewed and edited by all Board members prior to issuance of the final report.

If deemed necessary, the DSMB can request to know whether or not the participant received active medication or placebo. If they believe that termination of the trial is warranted, the blind of all study participants will be broken. DSMB recommendations will be communicated to the NIDA Project Officer soon after the DSMB meetings.

Affiliation and contact information for the DSMB members are listed below (additional marijuana expert member TBN):

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Data Management

Data Acquisition and Transmission. Data collection at study visits will take the form of subjective measures (forms), blood and urine samples, and will be identified with a four-digit identification number. Samples will be collected and stored with the subject ID code only. The coordinator will keep the code that links the subject ID with the identity of the subject in a database protected by two-levels of security, stored separately from the data.

Data Entry Methods. All self-report data collection items throughout the study will be self-administered per direction of study staff via a computer program (REDCap; http://project-redcap.org/) to improve the quality of data (by avoiding missing data, illegible data, etc) and limit the time spent on data entry and cleaning. Any data not entered directly into a computer system (i.e. height, weight, blood pressure) will be double entered on our password protected server by trained data entry personnel at the Tobacco Research Programs using the REDCap data entry programs. The study coordinator will be available to monitor the data and correct any discrepancies based on source documents.

Quality Assurance

Data collected via computer programs (REDCap) will be monitored by the study coordinator by random inspection of completed forms, and any problems detected will be discussed with the PI. The SAC (Eberly, Director) will analyze the data using the SAS program. In addition, the SAC will provide support in developing data entry programs. Data analyses will be completed at the end of the study. For missing data: Persons who do not attend a week 4 visit, assessment of the primary outcome is not directly possible. During their week 5, study staff will attempt to contact them in order to collect by phone and/or email a self-reported recall of marijuana use as of week 4; outcomes collected in this way will be denoted separately in the study database.

Trial Safety

*Potential Risks and Benefits for Participants***.** The potential risks for study subjects are minimal to moderate. To help protect subject privacy, we will obtain a Certificate of Confidentiality from the National Institutes of Health. The researchers can use this Certificate to legally refuse to disclose information that may identify a subject in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify a subject, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

Subjects will be told that a Certificate of Confidentiality does not prevent them or a member of their family from voluntarily releasing information about themselves or their involvement in this research. If an insurer, employer, or other person obtains their written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Medical histories for all subjects will be reviewed prior to entry into the study and all subjects will be under medical supervision while in the study. Urine and breath samples will be obtained and should not present risk to the subjects. Blood samples will be obtained by trained phlebotomists. A minimal amount of blood will be collected (20cc) per collection. Blood drawing may result in slight discomfort, bruising, or there may be some soreness at the puncture site. In some cases there may be dizziness or fainting.

Progesterone is generally well tolerated. The most common adverse effect is sedation. Other less common adverse effects include menstrual irregularity (spotting or breakthrough bleeding; females only) dizziness, cramps, nausea, fatigue, headache and breast tenderness (de Lignieres, 1999; Simon, 1995, Sofuglu, 2009). Other side effects attributed to synthetic progesterone including depression, fluid retention, pruritus, jaundice, rash and thrombotic disorders, are unlikely to occur. Recently there have been reports of increased risk of stroke, coronary artery disease, venous thromboembolism and breast cancer in postmenopausal females who have been on long-term hormone replacement treatment with estradiol and progestin (medroxyprogesterone) combination (Anonymous, 2002; 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 (Anonymous, 2002). 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, natural progesterone is not known to cause thromboembolism (PDR, 2002). However, as a safety measure for these serious adverse events, we will exclude subjects with history of thrombophlebitis, deep vein thrombosis, pulmonary embolus, clotting or bleeding disorders, heart disease, diabetes or history of stroke. Possible adverse events from Progesterone will be assessed weekly by the research nurse (Schulz, NP) in consultation with the study physician (Allen, MD). If the side effects cannot be tolerated the medication dosage will be decreased to 200 mg once/day for those on the active medication.

Although uncomfortable, marijuana withdrawal symptoms do not pose significant health risks. Subjects who participate in this study will be asked to quit or reduce their marijuana use on an assigned quit date. This may result in increased irritability, anxiety, tension, decreased appetite or sleeplessness.

Adverse Events: An adverse event is any unwanted experience or event occurring during the course of a clinical trial. At each visit, research assistants will collect pertinent information on any AE's and meet with the Nurse Practitioner (NP) at least once per week. The NP will decide if the AE was related to the study medication and give recommendations for follow-up. In cases where the NP is unavailable or if the AE needs immediate attention, it will be escaladed to the PI immediately for acknowledgment and recommendations. The study investigators will follow all AEs to the point of a satisfactory resolution. A study subject may be withdrawn from the study if the PI determines it is the best decision for protection of the safety of the subject. All AEs will be assessed to determine if they meet criteria for an SAE. AEs will be quantified separately by sex and treatment groups and compared across treatment groups with Fisher's exact test (for binary events) or with chi-square test (for counts of events or event rates). The event will be documented as to whether there is 1) no relationship between the study drug and the adverse event, 2) the adverse event is unlikely related to administration of the study drug, 3) the adverse event is possibly related to study drug administration, or 4) the adverse event is probably related to the administration of the study drug.

Serious Adverse Events (SAE): A serious adverse event is defined as an outcome that is 1) fatal or life-threatening, 2) significantly or permanently disabling or incapacitating, 3) requires or prolongs inpatient hospitalization, or 4) results in a congenital anomaly. *SAE's,* whether or not related to study medication, will be reported to the IRB and NIDA. All drug related adverse events of a non-serious nature are reported to the University of Minnesota's IRB on an annual basis. Serious adverse events will be reported by telephone to the IRB, and to NIDA and the FDA within the three days of our receipt of information regarding the event and written reports will be submitted within ten days. If a subject either withdraws from the study or the investigator decides to discontinue a subject due to SAE, the subject will have appropriate follow-up medical monitoring. Monitoring will continue until the problem requiring hospitalization was resolved or stabilized with no further change expected, is clearly unrelated to study medication, or results in death. Outcome of SAEs will be periodically reported to NIDA. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NIDA. Finally, the PI will ensure that serious adverse events are reported to NIDA via the serious adverse event tracking and reporting system at https://saetrs.nida.nih.gov/.

The Principal Investigator will then take appropriate action (including study modification) as agreed upon by these monitoring groups including the DSMB when needed. The Principal Investigator will determine whether the seriousness of the event warrants removal of the participant from the study. Appropriate diagnostic and therapeutic interventions will be initiated and the participant will be medically followed and kept under observation as long as medically indicated. After the review of the data, the DSMB report will make recommendations about whether the trial should continue with or without modifications, or be terminated. Any potential conflict of interest in the Data and Safety Monitoring Board will be disclosed.

Protection against Risk. Subjects will be told the potential risks involved in this study. Although risks to subjects in the proposed study are minimal, the following actions will be taken to minimize these risks. We will exclude subjects with health conditions that may be exacerbated by their participation. Subjects will be monitored regularly by medical personnel employed by the study. Dr. Sharon Allen (PI) will be available for emergency phone calls 24 hours/day and for office visits in case of problems. Blood will be collected by trained phlebotomists to reduce the risks involved with blood draws.

During Progesterone administration, the first dose of the study medication will be taken at 8 PM to minimize possible sedation from initiation of progesterone treatment. Subjects will be warned about using caution when driving a motor vehicle or operating machinery. Subjects will also be warned about the side effects associated with Progesterone. Further, although unlikely, the study physician (Dr. Allen, PI) will be alert to the earliest

manifestations of thrombotic disorders including thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis (PDR, 2002). If any of these occur or are suspected, the study medication will be discontinued immediately and medical treatment will be sought.

Potential Benefits of the Proposed Research to the Subjects and Others

Whereas no assurance can be made to an individual subject that he/she will personally benefit from such research, the experience should be beneficial. Subjects will have the opportunity to learn about their marijuana use behavior and receive behavioral counseling. Society may benefit from a better understanding of the role of sex hormones on marijuana use and impulsivity. A better understanding of this relationship will help improve treatment strategies for marijuana use. The risks in relation to the potential benefits are minimal to the individual research subject and virtually nonexistent to society in general.

Trial Efficacy

No interim analyses of efficacy are planned for the proposed study.

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Protocol Changes:

Version 2.0 (IRB approved 01/29/2016)

- Expanded on the significance of sex hormones on drug abuse and impulsivity.
- Inclusion criteria: decreased the cut-off for motivation to quit using marijuana (from a ≥7 on a Likert-type scale to ≥1)
  Inclusion criteria: decreased the cut-off for minimum cigarette use (from ≥4 days per week to ≥1 days per month)
- Provided more information on the THC urine dipstick used to verify marijuana status.
- Provided more information on the study drug: progesterone 200mg.

Version 3.0 (IRB approved 03/25/2016)

- Removed Figure 1 as it was causing confusion with IDS pharmacy. Further description and clarification regarding the medication schedule was added.
- Relaxed the criteria for receiving participation bonus from not missing any visits to allowing subjects to miss one visit and still collect the bonus payment.

Version 4.0 (IRB approved 07/18/2016)

- A discrepancy was found between the ICF and protocol. The ICF stated that blood draws would only be collected at SC, BL, W0, W2, W4 and W5. The protocol stated that blood draws would be collected at each clinic visit. The protocol was amended to match the ICF.

Version 5.0 (IRB approved 11/15/2016)

- RA's collection information on AE's

Version 6.0 (IRB Approved 02/13/2017)

- Increased subject compensation