Detailed Protocol

Title: Effects of cannabidiol on responses to emotional stimuli ("Effects of drugs on mood and behavior" on the consent form)

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Objectives: To study the effects of cannabidiol (CBD), a constituent of marijuana, on responses to emotional stimuli in healthy young adults.

Aim 1. We will assess the effects of CBD on subjective and psychophysiological responses to images with positive (rewarding) vs. negative (aversive) emotional content. Our working hypothesis is that CBD will reduce subjective and psychophysiological responses to negative images without affecting responses to positive images.

Aim 2. We will examine the effect of CBD on responses to the socially rewarding and aversive information conveyed by emotional facial expressions. We will measure speed of identification for positive (rewarding) and negative (aversive) emotional expressions as they dynamically develop, psychophysiological reactions to emotional expressions and direction of attention to emotional expressions. Our working hypothesis is that CBD will slow identification of negative expressions, reduce psychophysiological responses to negative expressions, and reduce direction of attention to negative expressions without affecting responses to positive expressions.

Aim 3**.** We will examine the effect of cannabidiol on a controlled social interaction with a research assistant. Our working hypothesis is that the reduction in responses to negative emotional and social stimuli produced by CBD will result in greater talkativeness in a controlled social interaction.

Exploratory Aim. We will additionally measure the effects of CBD on subjective mood, including anxiety, euphoria and sedation, to determine whether the CBD's effects on responses to emotional stimuli are mediated by effects on subjective mood, or occur above and beyond CBD-induced changes in mood.

Significance

The purpose of this project is to investigate the effects of cannabidol (CBD) on responses to emotional stimuli in humans. CBD is one of the primary constituents in whole plant marijuana (Ashton 2001). Such cannabinoid compounds are of interest for two reasons. First, understanding the effects of these compounds may shed light on the phenomena of marijuana use and abuse. Second, studying the effects of cannabinoids may be informative about the purposes and functioning of the brain's endocannabinoid

system. This system has recently been the focus of much therapeutic interest due to its involvement in stress and eating disorders (Felder 2006). Most research on cannabinoids has focused on delta-9-tetrahydrocannabidiol, the primary psychoactive ingredient in marijuana and the chemical that appears to be most responsible for the typical subjective effects of marijuana (Ilan et al. 2005). However, cannabidiol has recently become a focus of interest for two reasons. First, it appears to dampen some of the anxiogenic effects of THC, which may contribute to the reinforcing effects of whole plant marijuana (Zuardi et al. 1982). Second, cannabidiol may have anxiolytic effects in and of itself (Bergamaschi et al. 2011b; Crippa et al. 2011; Fusar-Poli P and et al. 2009; Zuardi et al. 1993). At this point, the neural mechanisms by which cannbidiol produces these effects are unknown. Cannabidiol does not appear to have direct actions at either of the endocannabinoid receptors, although it can antagonize the effects of cannabinoid agonists. It may act as an antagonist at the putative new cannabinoid receptor, GPR55, and it may act as a 5-HT_{1A} receptor agonist as well as a modulator at opioid receptor sites (Pertwee 2008).

Our primary interest here is in the potential anxiolytic properties of CBD. In animals, CBD increases exploratory behavior in the elevated plus maze, and reduces freezing in a conditioned environment and in response to exposure to a predator, suggesting anxiolysis (Schier et al. 2012). These effects were comparable to those of diazepam, a benzodiazepine and known anxiolytic, but were mediated by different neurochemical mechanisms (Schier et al. 2012). In humans, CBD reduced anxiety in responses to public speaking in both healthy volunteers and individual with social anxiety disorder (Bergamaschi et al. 2011b; Zuardi et al. 1993), reduced amygdala responses to fearful faces (Bhattacharyya et al. 2009; Fusar-Poli P and et al. 2009), and reduced subjective anxiety in response to a stressful imaging procedure (Crippa et al. 2003). Importantly, CBD also produced less sedation when compared to the traditional anxiolytic diazepam (Zuardi et al. 1993). Together, these findings suggest CBD has anxiolytic properties that may be comparable to those of traditional drugs, but that are mediated through different neural mechanisms and potentially produce fewer sedative side-effects.

In the current study we intend to examine the effect of CBD on responses to both positive and negative emotional and social stimuli. We will characterize both subjective responses and subtle psychophysiological responses to these stimuli. These measures of emotional response have been used to characterize many other drugs, including traditional anxiolytics like diazepam (Bitsios et al. 1999; Murphy et al. 2008; Patrick et al. 1996) and drugs of abuse such as amphetamine and THC (Ballard et al. 2012; Wardle and de Wit 2012). This investigation will allow us to determine whether cannabidiol dampens responses to aversive stimuli in a manner comparable to traditional anxiolytics (Patrick et al. 1996). Importantly, in contrast to previous studies that have examined only anxiety-provoking stimuli, we can also examine whether CBD affects responses to positive stimuli. Ideally, to consider CBD as a novel anxiolytic, CBD should produce a decrease in negative responses without affecting positive responses. If CBD dampens responses to positive stimuli also, this might suggest general sedation (Grillon and Baas 2003). In contrast, enhancement of responses to positive stimuli might suggest CBD contributes to the rewarding and potentially addictive effects of whole plant marijuana

(e.g. Wardle and de Wit 2012). In addition, we will examine the relationship between effects on responses to emotional stimuli and social behavior in a controlled talking task. It has been suggested that CBD may be an effective treatment for social anxiety, and this will provide a model of how CBD's effects may contribute to changes in actual social behavior. If CBD does dampen responses to negative stimuli without interfering with positive responses, and these changes contribute to measurable changes in actual social behavior, this would contribute to mounting evidence that CBD should be considered as a novel treatment for anxiety disorders (Schier et al. 2012).

Finally, we will examine on an exploratory basis the extent to which any changes in responses to emotional stimuli and social behavior are accounted for by CBD's subjective effects. Specifically, we will examine the extent to which observed effects of CBD on responses to emotional stimuli and behavior can be accounted for by changes in subjective anxiety, sedation and euphoria. A growing literature suggests that both abused and therapeutic drugs may produce subtle changes in perception and responses to emotional stimuli that are independent of more commonly measured subjective changes (Harmer 2008; Harmer et al. 2003; Harmer et al. 2008; Wardle and de Wit 2012).

In a four-session within-subjects study we will compare a placebo control to 300, 600 and 900mg of cannabidiol. In Aim 1 we will explore how cannabidiol affects reactions to rewarding vs. aversive pictures. Participants will view pleasant pictures (e.g. of parties, pets, sunsets), neutral pictures (e.g. of household objects, neutral landscapes) and unpleasant pictures (e.g. medical imagery, war scenes and disgusting objects) drawn from the standardized International Affective Picture Set (IAPS) while we measure subjective responses to these pictures using self-reports. We predict that cannabidiol will reduce subjective and psychophysiological responses to negative pictures without affecting responses to positive pictures. In Aim 2 we will examine responses to emotional facial expressions, which are an ecologically relevant category of rewarding and aversive stimuli. We will measure how quickly individuals are able to perceive happy vs. negative facial expressions using dynamically developing expressions of happiness, fear, anger and sadness. We predict that cannabidiol will blunt perception of, psychphysiological responses to and attentional bias towards negative facial expressions without affecting responses to positive facial expressions. In Aim 3 we will examine the relationship of responses to emotional stimuli with talkativeness in a controlled social interaction. We predict that cannabidiol will increase talkativeness, and this effect will be mediated by the decreased responses to negative social and emotional stimuli measured in the previous aims. Finally, on an exploratory basis we will measure the subjective effects of cannabadiol, and specifically the its effects on anxiety, sedation and euphoria, with the aim of determining whether CBD's effects on responses to emotional stimuli are related to, or independent of, its subjective effects.

Methods:

Design: The study will use a 4-session within-subjects double-blind design in which participants will receive three doses (300, 600mg and 900mg oral) of cannabidol and a placebo in randomized order. All screening, orientation, and study session procedures

will take place in the Human Behavioral Pharmacology Laboratory suite in the L4 wing of 5841 S. Maryland Ave.

Subjects: We will recruit 50 healthy volunteers, with the expectation (based on previous retention rates) that 36 healthy volunteers (18 male, 18 female; age range 18-35 years) will complete all experimental procedures. All participants will be recruited without regard to race, religion or ethnicity through posters, advertisements and word-of-mouth referrals. Candidates will be screened in accordance with our general screening protocol, approved by the IRB under Protocol #13681B, which includes a physical, EKG, psychiatric screening interview and detailed drug use history questionnaire. Because CBD will be administered as part of the study, the following populations are excluded for safety reasons: Individuals with a medical condition contraindicating study participation, as determined by our physician, individuals regularly using any medications aside from hormonal contraception in women, individuals with a current (active in the past year) DSM-IV Axis I mood, anxiety, eating, or substance dependence disorder or a lifetime history of a psychotic disorder or mania; women who are pregnant, nursing, or planning to become pregnant in the next 3 months; anyone reporting a known or suspected allergy to cannabinoids. The self-report questionnaires we use require fluency in English, and have not been translated and validated in other languages, thus individuals with less than a high-school education or those not fluent in English will be excluded, as lack of English familiarity at a high school level may compromise our ability to interpret their self-reports. Individuals with a BMI below 19 or above 30 will also be excluded, as this would change dosing requirements. Last, for scientific reasons, we will include only individuals who report using marijuana < 100 times in their lifetime, to reduce variation in possible developed tolerance to CBD.

Drug and Doses: We will administer placebo, 300mg, 600mg and 900mg CBD in counterbalanced order under double-blind conditions. Plasma levels peak approximately 1 - 4 hr after oral administration, with mean peak concentration at 90min, and remain elevated up to 12 hr after an acute dose. The 300mg, 600mg and 900mg doses have been effective doses for reducing anxiety in previous studies (Bergamaschi et al. 2011b; Fusar-Poli P and et al. 2009; Zuardi et al. 1993). Using three doses will help establish a dose-response curve for any effects. Doses will be separated by at least 7 days

CBD will be obtained in pure form from GW Pharmaceuticals (GW Pharmaceuticals 2012). Our IND has been approved (IND 125302). CBD is currently in Phase II studies for several indications including MS neuropathic pain and spasticity, and a 1:1 ratio combined CBD and THC oral spray is approved in several countries in Europe and in Canada for MS related spasticity (GW Pharmaceuticals 2012). Preclinical toxicity data suggest a good safety margin between the clinical dose proposed and a toxic dose, and doses of up to 1500mg CBD per day in humans are reported to be well-tolerated (Zuardi et al. 2006). Adverse effects of CBD/THC combined products have been subject to greater study that CBD alone, and these include dizziness, nausea, fatigue, dry mouth, somnolence, anxiety, mood changes, transient hypotension or tachycardia, delusional ideas, disorientation, and hallucinations. Most of these effects are likely attributable to the THC present in these combinations (GW Pharmaceuticals 2012). Indeed, one review

of the safety and side-effects of CBD alone noted no adverse effects across several studies (Bergamaschi et al. 2011a). However, we will take precautions against these possible adverse effects in our CBD alone study. See "Risks" for complete safety precautions. CBD alone may produce mild sedation, but does not appear to produce subjective intoxication, marked negative effects on mood or changes in cardiovascular functioning (GW Pharmaceuticals 2012).

Study Tasks:

1. International Affective Picture System (IAPS) – (Lang et al. 1999) Participants will view standardized positive, negative and neutral pictures from the IAPS. The negative and positive images will be matched on degree of valence and arousal. We will record psychophysiological facial EMG responses during a 1s baseline recording period will precede each picture, and during the 6s presentation of each (see "Psychophysiological Measures"). An Evaluative Space Grid rating will follow each picture to collect subjective reactions (see "Subjective Measures").
2. Dynamic Emotion Identification Task (DEIT) – In a task created for use in our laboratory (Wardle et al. 2012a), participants will view dynamically developing facial expressions composed of 2% morphs between a neutral face and a 100% expression of an emotion presented sequentially. The emotions will be happiness, sadness, anger, fear and disgust. Participants will be instructed to respond as soon as they believe they can correctly identify the emotion expressed. In this way both sensitivity (% of emotion expressed at time of identification) can be measured. Accuracy is usually near ceiling with this paradigm, and thus is not a primary dependent variable. EMG measurements will also be taken while participants view the facial expressions to examine psychophysiological reactions to the expressions (see "Psychophysiological Measures").
3. Attentional Bias Task (ABT) – In a task adapted from Garner and colleagues (Garner et al. 2006) participants will be presented with pairs of faces, one on each side of a computer screen. Each pair will contain one neutral face and one 100% emotional expression taken using the same actor. The emotional expressions used will be from the standardized Karolinska set (Goeleven et al. 2008). Participants will be shown a central fixation cross for 1,000 ms, then the pairs of faces side by side for 500 ms. To distract participant attention from the primary purpose of the task, and reduce response bias, a probe (either an up arrow or a down arrow) will be presented in the same location as one of the previous pictures after each trial. Participants must respond to the direction the arrow is pointing by pressing a key. After a response, or after 10s have elapsed with no response, an intertrial interval of 750 to 1,250 ms will begin, followed by the presentation of another trial.
4. Interpersonal Speech Task (IST) – This is a controlled interaction task previously validated in our lab (Wardle et al. 2011) The IST is a semi-structured dialog task designed to model certain aspects of the psychotherapeutic encounter. During the IST, participants will be asked to describe a significant person in their life. They will be given 5 minutes to speak about this person with the research assistant, who will be trained in basic active listening skills (Sommers-Flanagan and Sommers-Flanagan 2009). Transcription and textual analysis by the Linguistic Word Count and Inquiry

Program will be used to examine the total number of words as an index of social activity, and the amount of positivity and the amount of negativity expressed in each speech task, as a behavioral index of affect (Pennebaker et al. 2007).

Subjective Measures:

1. Profile of Mood States – POMS (McNair et al. 1971). The POMS is a validated measure consisting of 72 adjectives commonly used to describe momentary mood states. The POMS is highly sensitive to the effects of drugs in similar samples of healthy volunteers (de Wit & Griffiths, 1991; Johanson & Uhlenhuth, 1980), and will be used to assess mood effects of the drug during the study sessions.
2. Drug Effects Questionnaire – DEQ (Fischman and Foltin 1991). The DEQ is a validated measure consisting of questions on a visual analog scale about the subjective effects of drugs. Subjects are asked to rate the extent they feel a drug effect, whether they like or dislike the drug effect, and if given a choice would they want to take more of the drug. This is also be used to assess the pharmcodynamics of the drug effect during the study
3. The Addiction Centre Research Inventory – ARCI (Martin et al. 1971). The ARCI is a true-false questionnaire that consists of empirically derived scales sensitive to the effects of a variety of classes of psychoactive drugs (Haertzen 1966). We used a 53-item version, which yields scores for six scales that include: sedation (Pentobarbital-Chlorpromazine Group; PCAG), stimulant-like effects (Amphetamine; A, and Benzedrine Group; BG), somatic and dysphoric effects (Lysergic Acid; LSD), euphoria (Morphine-Benzedrine Group; MBG), and marijuana-like effects (M).
4. The Evaluative Space Grid – ESG (Larsen et al. 2009). The Evaluative Space Grid is validated measure consisting of a two dimensional grid that provides a single item measure of positivity and negativity. This will be used to measure subjective reactions to the IAPS pictures.

Psychophysiological Measures:

1. Cardiovascular measures – Blood pressure and heart rate will be periodically monitored using portable blood pressure cuffs, to track the cardiovascular effects of the drug, and ensure participant safety.

Procedure:

Orientation: Participants who meet criteria will first be scheduled for an orientation session. During this session, subjects will be informed that the capsules used in the study may contain a placebo, a stimulant drug (e.g. amphetamine, methylphenidate), a sedative drug (e.g. diazepam, alprazolam), or a cannabinoid drug, which is a component of marijuana (e.g. THC or cannabidiol). In previous studies we have found this procedure reduces expectancy effects. Participants will be given an oral description of the study procedures and the written consent form. After the experimenter reviews this information and the consent form with the subject, and answers any questions he/she may have, subjects will answer questions confirming their understanding of the study, and sign the

informed consent document. The subject will then practice completing the tasks and questionnaires to be used in the study. This will help reduce practice effects across the study sessions.

Study Session: Please see below for a full timeline of the study session. Participants will be asked to fast overnight. On study session days, participants will arrive at 9am, and consume a standardized snack. Participants will then complete a urine and breath screening for recent alcohol and drug use, and a pregnancy test (for women). We will then take Time 1 measures of subjective mood, drug effects and cardiovascular variables. We will continue to take these same measures periodically throughout the study (see below). Participants will be administered the drug or placebo at 1:30pm. While waiting for the drug effect to reach peak, participants will be allowed to relax and watch a movie or read a book, but will not be allowed to do work. At 2:15 pm, 3 pm, 3:45 pm, we will reassess mood. The task portion of the study will begin approximately 90min after administration of the drug, and will last for approximately 1 hour, to coincide with the peak effect of the drug. The IAPS, DEIT, ABT tasks will be presented in a counterbalanced order. The psychophysiological equipment will then be disconnected and the IST task will be completed. Participants will then remain in the lab completing subjective measures of the drug effect every half-hour until at least 5:45 pm (when we expect drug effects will be decreased sufficiently to permit participants to leave safely), or until drug effects decrease sufficiently to permit participants to leave safely (as measured by both subjective report and cardiovascular variables). Some drug effects may persist for up to 12hrs after the end of the study session, but based on the literature on CBD given chronically to an ambulatory population, these should be mild and non-impairing (Cunha et al. 1980). Sessions will be separated by at least 5 days.

Timeline

1:00pm	- Arrival, snack, breath and urine tests
1:15pm	- Mood (POMS), drug effect (DEQ, ARCI) and cardiovascular measures
1:30pm	- Capsule administered
2:15pm	- Mood (POMS), drug effect (DEQ, ARCI) and cardiovascular measures
3:00pm	- Mood (POMS), drug effect (DEQ, ARCI) and cardiovascular measures
3:45pm	- Mood (POMS), drug effect (DEQ, ARCI) and cardiovascular measures
4:00pm	- IAPS, DEIT, ABT tasks, counterbalanced
4:45pm	- IST task
5:00pm	- Mood (POMS), drug effect (DEQ, ARCI) and cardiovascular measures
5:45pm	- Mood (POMS), drug effect (DEQ, ARCI) and cardiovascular measures
5:50pm	- Leave laboratory

Debriefing: Participants will return to the lab for a final session at which they will complete a final DEQ rating of how much they liked each study drug and how much they would want to take each study session drug again. Participants will also be asked to report which type or types of drugs they think they received at each session. Finally, participants will be fully debriefed with regard to the study hypotheses, methods and the types of drugs that they received, and will be given a chance to ask any final questions.

Data Analysis

IAPS: We hypothesize that participants will react less to negative pictures while taking CBD, while reactions to positive and neutral slides will be unchanged. We will conduct a Mixed Linear Model analysis in R using lme4 on each dependent variable (subjective ratings, corrugator and startle responses) using Drug (0, 300, 600 and 900mg) and picture type (positive, neutral, negative) as independent variables, and including random variables for Subject and Drug.

DEIT: We hypothesize that participants will show decreased sensitivity to negative facial expressions (anger, sadness and fear) on CBD, as measured by a greater intensity of expression required to identify negative facial expressions, but unchanged intensity for happy facial expressions. We also hypothesize that CBD will reduce negative psychophysiological responses to negative facial expressions, but not happiness. We will conduct a Mixed Linear Model analysis in R using lme4 on each dependent variable (expression intensity and corrugator responses) using Drug (0, 300, 600 and 900mg) and expression type (happy, angry, fearful, sad) as independent variables, and including random variables for Subject, Drug and Actor.

ABT: We hypothesize that participants will show reduced attentional bias to negative facial expressions (anger, sadness and fear) on CBD, as measured by increased reaction times for probe response for negative faces, without any change in responses to happy faces. We will conduct a Generalized Mixed Linear Model analysis in R using lme4 on the binomial variable of initial gaze direction with Drug (0, 300, 600 and 900mg) and expression type (happy, angry, fearful, sad) as independent variables, and including random variables for Subject and Drug. We will conduct a Mixed Linear Model analysis in R using lme4 on total dwell time on each face, using Drug (0, 300, 600 and 900mg) and expression type (happy, angry, fearful, sad) as independent variables, and including random variables for Subject and Drug.

IST: We hypothesize that participants will show increased talkativeness on the IST, as measured by total word count and further, that this increased talkativeness will be mediated by reduced negative responses to negative emotional and social cues (as measured in the IAPS, DEIT and ABT). We will first derive per-participant estimates of the effect of drug on responses to negative stimuli from the Mixed Linear Model analyses described above. We will then conduct a Mixed Linear Model analysis in R using lme4 on total word count with Drug (0, 300, 600 and 900mg) as an independent variable, and including random variables for Subject and Drug (per Wardle et al. 2012b). Following criteria for within-subject mediation (Judd et al. 2001), we will first establish whether drug has the hypothesized effect on talkativeness. We will then include the per-participant estimates of the effect of drug on responses to negative stimuli as covariates, and examine 1. Whether changes in responses to negative stimuli account for a significant proportion of changes in talkativeness, and 2. Whether the effect of drug on talkativeness is still significant after inclusion of the changes in responses to negative stimuli. If the effect of drug on effort is wholly mediated by changes in responses to negative stimuli, we would expect the effect of drug on talkativeness to no longer be

significant after including drug-induced changes in responses to negative stimuli as a covariate (see Wardle and de Wit 2012 for an example of this type of analysis).

Exploratory Analysis of Relationship to Mood: We will conduct similar within-subject mediational Mixed Linear Model analyses in R using lme4 on our primary outcomes of responses to negative stimuli, using subjective measures of anxiety (from the POMS), sedation (from the ARCI) and euphoria (from the POMS, ARCI and DEQ) as covariates. Following the procedure described above, we will determine whether the effects of the drug on responses to negative stimuli are partially or wholly mediated by its effects on subjective mood.

Human Subjects Information

Recruiting methods: We will place print ads in newspapers and on online job search sites such as craigslist.org, and flyer in the Chicago area. Healthy volunteers who respond to our ads are screened using our standard screening protocol for all studies in the Human Behavioral Psychopharmacology Laboratory, which is separately approved by the IRB under Protocol #13681B.

Obtaining consent: Written informed consent for the screening session only is obtained at the screening according to procedures outlined in Protocol #13681B. Written informed consent for the study procedures is obtained at the orientation session, after a verbal explanation of study procedures, check of comprehension, and an opportunity for the participant to ask any questions they may have. Consent is verbally re-verified at the beginning of each study session.

Risk to subjects:

1. Diagnostic procedures and questionnaires: Some of the questions asked during the screening may be considered sensitive information, including drug use history and psychiatric history. We have rigorous procedures in place to ensure confidentiality of data, including locked cabinets for confidential files, subject coding, secure computer systems, and rigorous training of personnel. Please see screening protocol #13681B for full information on steps taken to protect information gathered as part of the screening.

2. Study drug: The possible side effects of CBD include: dizziness, nausea, fatigue, dry mouth, somnolence, anxiety, mood changes, transient hypotension or tachycardia, delusional ideas, disorientation, and hallucinations. This list of effects is derived from study of CBD/THC combined medicines, and most of these effects are likely attributable to the THC present in these combinations. However, we will still take precautions to minimize these possible effects in our CBD-alone study. Subjects are carefully screened to exclude those who are physically or psychiatrically at risk for these side effects (e.g., any Axis I disorders or history of psychosis, high blood pressure or cardiovascular risk factors). The studies are conducted in a hospital, where emergency assistance, including the psychiatry resident on-call, and the psychiatrist connected with the study are close at hand. A research assistant will be present throughout the

procedures and will monitor heart rate and blood pressure throughout the sessions. In addition, on-call physicians will be available in the case of medical emergencies. Subjects will be told not to drive following the sessions and, if necessary, will be reimbursed for public transportation costs. Subjects will be told that small amounts of the drugs or their metabolites will be detectable in the body for several weeks and to advise the experimenter if they intend to undergo a drug screening within one month of participating in the study. There have been no clinical reports of drug-drug interactions (GW Pharmaceuticals 2012), but participants regularly taking medication aside from birth control will be excluded, and participants will also be told to refrain from using any other recreational or medical drugs (aside from birth control) for at least 12 hours after the study to minimize any chance of interaction effects with other drugs. Because CBD is contraindicated in pregnant or nursing women, women must not be pregnant or planning to become pregnant within three months of the study. They will be tested for pregnancy at each session. Last, we will exclude any individuals reporting a known or suspected allergy to cannabinoids.

Because the subjects are normal healthy adults participating voluntarily, there are no alternative treatments to the study drug. They will be fully debriefed following the study.

3. Tasks: Some of the tasks (emotional pictures, pictures of facial expressions) employ stimuli that are designed to elicit short-term positive and negative emotional reactions. Although the pictures used are designed to elicit emotional reactions, these reactions are typically brief, and similar methods to have previously been used in a wide range of studies without evidence of any long-term adverse reactions. Further, participants are screened for any psychiatric conditions that might make them vulnerable to experiencing adverse reactions to brief alterations in mood. Any participants who are unduly distressed will be counseled by a trained staff member.

Benefits to subjects: There is no direct benefit to the participants, although we hope that the information learned from this study will contribute to our knowledge of factors influencing drug use. Additionally, participating in research may be an educational experience for participants, and we attempt to facilitate this by providing a thorough debriefing including an explanation of study hypotheses and procedures at the conclusion of participation.

Subject time commitment and compensation: The screening portion of the study takes approximately 2 hours. The orientation typically takes approximately 1 hour. The study sessions are estimated to last 5 hrs each, and the debriefing is .5 hours, for a total of 21.5 hours spent in study sessions. Participants are compensated $35 for each study session, with a bonus of $110 for completion of all study sessions, giving a total of $250.

Data and Safety Monitoring: The PI will monitor data collection and safety at weekly staff meetings. During these meetings, the PI will review and respond appropriately to

(1) data collection and storage practices and (2) any adverse or unexpected effects from the study drugs. Both the study physician and PI will monitor the safety of study participants on an ongoing basis. The physician connected with this study will be on call during the experimental sessions and for 24 hours after sessions. Subjects will be given telephone numbers for the study physician and investigators in case they experience unpleasant effects after leaving the laboratory.

If an unanticipated problem were to occur, the staff member most closely involved with the subject at that time or the physician would notify the PI immediately. The PI would then submit written notification of the problem to the problem to the IRB using the "Unanticipated Problem" report within 10 working days. The PI would then determine, in collaboration with the IRB whether the problem requires further reporting to the federal funding agency or FDA. If a life-threatening adverse event were to occur, the PI would communicate the event to the IRB chair immediately, and halt further study sessions and participant enrollment.

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