Detailed Protocol

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

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Objectives: To study the effects of buprenorphine, a partial mu-opioid agonist, on emotional responses to social stimuli in healthy young adults with a range of depressed and anxious mood.

Aim 1. We will assess the effects of buprenorphine on subjective and psychophysiological responses to images and sounds with positive (rewarding), negative (aversive), social, and non-social content. We hypothesize that buprenorphine will selectively reduce responses to negative social stimuli.

Aim 2. We will examine the effect of buprenorphine on responses to information conveyed by emotional facial expressions. We will measure automatic direction of attention towards emotional expressions (EOG). We hypothesize that buprenorphine will selectively reduce sensitivity and attention to negative emotions.

Aim 3. We will examine the effect of buprenorphine on responses to simulated experiences of social rejection and responses to social and nonsocial touch. We hypothesize that buprenorphine will reduce responses to both physical and social pain.

Aim 4. We will investigate the effect of buprenorphine on motivation to socialize. During the sessions, participants will be given the opportunity to spend 10 minutes waiting alone or 10 minutes waiting with another person. We hypothesize that buprenorphine will reduce the desire to socialize with other individuals.

Background:

The purpose of this study is to investigate the role of opioid signaling in mediating responses to social stimuli in humans. There is strong evidence in support of the role of endogenous opioids and opiates in mediating social behavior in humans and other animals. Studies in humans have shown that reduced opioid transmission underlies stronger responses to social rejection and social loss or "social pain", and that the same neural systems that underlie perception of physical pain may underlie the perception of social pain (Eisenberger and Lieberman, 2004). The minor allele of the mu opioid receptor gene (OPRM1 A118G), which leads to reduced mu opioid transmission, is associated with increased social rejection sensitivity (Way, Taylor, & Eisenberger, 2009). In line with this study, PET imaging has shown that women recalling recent losses of relationships exhibit reduced mu opioid-mediated neurotransmission

(Zubieta et al., 2003). These studies suggest that social pain may have overlapping circuitry with physical pain, and that reduced opioid neurotransmission is associated with heightened responses to negative social stimuli such as social pain. By seeking to correlate the analgesic effects of buprenorphine (via the cold pressor task) with its effects on perception of social pain, we can better understand the relationship between these phenomena.

In addition to the evidence implicating reduced endogenous opioid signaling in intensified responses to negative social input, studies in animals have shown that exogenously administered opiate agonists can have the opposite effect, reducing reactivity to such stimuli. It has been shown that opioid agonists reduce distress calls in response to social isolation in rodents (Panksepp, Najam, & Soares, 1979), chicks (Warnick, McCurdy, & Sufka, 2005), and non-human primates (Kalin, Shelton, & Barksdale, 1988). The "brain opioid hypothesis of social attachment" suggests that reduced opioid neurotransmission increases desire for attachment (Fabre-Nys, Meller, & Keverne, 1982), whereas increases in opioid signaling act as a proxy for social reward, thereby reducing the need for social interaction (Stein, van Honk, Ipser, Solms, & Panksepp, 2007; Herman & Panksepp, 1978; Panksepp et al., 1979). While there is a great deal of evidence in the animal literature that exogenous opiates act to blunt responses to negative social stimuli, this question has not been fully addressed in humans. An exception to this is one recent study, in which the investigators administered buprenorphine to healthy volunteers and found that the drug reduced participants' ability to recognize fearful facial expressions (Ipser et al., 2013). Additionally, a handful of small studies have shown that buprenorphine is effective in treating treatment-resistant depression (Bodkin et al., 1995; Emrich et al., 1982; Nyhuis et al., 2008). In the study proposed here, we seek to determine the effect of an opioid agonist on a battery of tasks assessing an array of social behaviors in an effort to more thoroughly understand the role of opioids in mediating responses to social stimuli. Further, we plan to recruit subjects with a range of scores for depressed and anxious mood, in an effort to determine whether the drug is more effective in individuals scoring higher on this measure.

Determining the effect of an opioid agonist on responses to social stimuli in humans is important for several reasons. First, there has been a recent increase in the number of individuals abusing opiate drugs, particularly teenagers and young adults. It has been argued that opiate abusers are "self-medicating", or using the drugs to alleviate some particularly painful psychological state (Khantzian, 1997), and it has been suggested that opiates may reduce unpleasant subjective responses to negative social stimuli. However, this idea has never been tested in humans in a laboratory setting. This project seeks to address these questions for the first time. Second, this would significantly extend our knowledge about the role of the opioid system in human social behavior. This study would expand findings from the animal literature to humans. This is important to understanding the neurobiology underlying conditions that involve responses to negative social stimuli, such as social anxiety disorder and other conditions with a social component, such as depression.

Based on the literature reviewed above, our central hypothesis is that buprenorphine, a mu partial agonist and kappa antagonist, will selectively reduce responses to negative social stimuli. In Aim 1 we will explore how buprenorphine affects reactions to positive (i.e., rewarding) vs. negative (i.e., aversive) social and nonsocial visual stimuli. The stimuli will consist of 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). We will measure subjective responses to these pictures using self-reports of liking and physiological hedonic responses using subtle electromyographic (EMG)

measurements of facial muscles associated with positive and negative emotions. We predict that buprenorphine will specifically reduce subjective and psychophysiological responses to negative social pictures. In Aim 2 we will examine attentional biases towards positive vs. negative expressions using eyetracking. We predict that buprenorphine selectively will blunt perception of attentional bias towards - negative as compared to positive facial expressions. In Aim 3 we will simulate experiences of social rejection and acceptance, combined with the same EMG measures of responses to reward used in Aims 1 and 2, in addition to testing the effects of buprenorphine on responses to social touch. We predict that buprenorphine will ameliorate subjective and psychophysiological responses to social pain (rejection) and physical pain. In Aim 4 we will measure participants' desire to socialize by giving them the opportunity to spend 10 minutes with another person or to wait alone. We hypothesize that buprenorphine will reduce their desire to socialize. Finally, we hypothesize that buprenorphine will reduce negative processing biases seen in participants with depressed mood.

Methods:

Design: The study will use a 2-session within-subjects double-blind design in which participants will receive single doses of buprenorphine (0 or 0.2 mg sublingual) 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: 86 healthy volunteers (18 male, 18 female; age range 18-35 years) will participate in the experiment. Based on our previous rates of participants completing two-session drug studies, to recruit 86 complete subjects we will need to consent 120 participants. Participants with a range of scores on the Beck Depression Inventory (BDI-II; Beck et al., 1996) and State-Trait Anxiety Inventory (STAI; Spielberger et al. 1983) will participate in the experiment. The BDI-II contains 21 questions, each scored from 0 to 3. Higher total scores indicate more severe depressive symptoms. The standardized cutoffs are: 0–13: minimal depression, 14–19: mild depression, 20–28: moderate depression and 29–63: severe depression. We will aim to recruit approximately half the participants in the 0-13 range, and half in the 14-28 range. Candidates who meet criteria for Major Depressive Disorder will be excluded and referred for treatment. 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 buprenorphine 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 (e.g. liver or kidney disease), individuals regularly using any contraindicated medications (e.g. opioid pain-killers), individuals with current or past opioid abuse or dependence, individuals with past dependence on other drugs, individuals with a DSM-IV Axis I mood, anxiety, eating, or psychotic disorder, individuals with a previous bad reaction to buprenorphine, women who are pregnant, nursing, or planning to become pregnant in the next 3 months. 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.

Women not on hormonal birth control will be scheduled only in the follicular phase of the menstrual cycle, as hormonal fluctuations may change responses to the drug (Roche, Childs, Epstein, & King, 2010).

Drug and Doses: We will administer placebo and 0.2 mg buprenorphine (Temgesic) via sublingual tablet in counterbalanced order under double-blind conditions. These tablets dissolve within 5-8 minutes. This drug has been approved for treatment of severe pain. The onset of action after sublingual administration is 30 minutes, with a peak plasma concentration at 1/5-2 hours and a half-life of 5 hours. These doses of buprenorphine is very low, and the average maintenance dose for opioid abusers is 8 mg. Doses will be separated by at least 72 hours. See "Risks" for complete safety information.

Study Tasks:

1. International Affective Picture System (IAPS) – (Lang, Bradley, & Cuthbert, 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 preceding each picture, and during the 6s presentation of each (see "Psychophysiological Measures"). Valence-matched sounds from the Oxford Vocal Sound Database (OxVoc) will also be presented. An Evaluative Space Grid rating will follow each picture or sound to collect subjective reactions (see "Subjective Measures").
2. Attentional Bias Task (ABT) – In a task adapted from Garner and colleagues (Garner, Mogg, & Bradley, 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, De Raedt, Leyman, & Verschuere, 2008). Participants will be shown a central fixation cross for 1,000 ms, then the pairs of faces side by side for 2,000 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. Electrooculograms (see "Psychophysiological Measures") will be used to quantify which face is initially fixated on in each trial, and overall dwell time per face on each trial as indicators of attentional bias.
3. Social Touch Task: This task, introduced as "an experimental light touch method" (Björnsdotter and Olausson, 2011) is designed to measure affective responses to light or social touch mediated via C-tactile fibers. Participants will be stroked with a painter's brush at varying velocities as facial EMG recordings of the corrugator and zygomatic muscles are obtained. Velocities will include those for which C-tactile fibers are optimally activated (i.e. 30 cm/s) as well as non-optimal velocities (i.e. 3 cm/s). The participants will also rate the intensity and pleasantness of the stroking. EMG measures will also be collected during this task.
4. Social Feedback Task (Hsu et al., 2013): This task will be presented to participants as a "hypothetical profile rating task." During the orientation session, participants will provide

basic personal information (e.g. hobbies) and provide a digital picture of themselves. Participants will also log on to a web-based survey and rate profiles of other "participants," which are created by the experimenter. Subjects answer questions about each profile. This survey will determine which profiles are the most likeable to each participant. This method has advantages over other social feedback paradigms because the task is tailored to each subject. During each experimental session, subjects will be presented with their own picture, and a picture of the profiles that they had previously rated, and receive feedback on how that person rated them. Subjects will be given questionnaires before and after the task to monitor changes in emotion.

Subjective Measures:

1. Beck Depression Inventory (BDI-II: Beck et al., 1996) The BDI-II is a validated questionnaire to assess depressed mood.
2. The State-Trait Anxiety Inventory (STAI; Speilberger et al. 1983) is a validated questionnaire consisting of 40 questions assessing anxiety levels.
3. Profile of Mood States – (POMS:McNair, Lorr, & Droppleman, 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.
4. Drug Effects Questionnaire - (DEQ:Fischman & 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 will also be used to assess the pharmacodynamics of the drug effect during the study.
5. Visual Analogue Scale (VAS) – This includes adjectives assessing common side effects of buprenorphine, such as dizziness and nausea. During the cold pressor task, a VAS including adjectives such as pain intensity and unpleasantness will be presented.
6. The Addiction Centre Research Inventory (ARCI: Haertzen,1970) is a true-false questionnaire that consists of empirically derived scales sensitive to the effects of a variety of classes of psychoactive drugs. 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), and euphoria (Morphine-Benzedrine Group; MBG).
7. The Evaluative Space Grid - (ESG:Larsen, Norris, McGraw, Hawkley, & Cacioppo, 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 and OxVoc sounds.
8. Motivation to socialize – Drug effects on the motivation to socialize will be measured by giving the participants the opportunity to wait alone for 10 minutes, or with another person (a trained experimenter).

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. Additional cardiovascular effects will be measured using EKG electrodes during the Cyberball task and cold pressor task to provide information about autonomic reactivity to physical and social pain. We will use disposable self-adhesive electrodes arranged in the standard Lead II configuration. These signals will be amplified and processed by an integrated Mindware Bionex system (Mindware Technologies, Gahanna, OH). We will analyze the ECG waveform with Heart Rate Variability Analysis Software 2.51, also by Mindware Technologies. The software will prepare the interbeat interval (IBI) series for spectral analysis as follows: each IBI series will be interpolated and sampled at 4 Hz to ensure adequate resolution of the appropriate frequencies and equal intervals between samples, and then de-trended with a quadratic function to ensure stationarity (full details of this procedure in (Berntson, Hart, & Sarter, 1997). This signal will be brought into the frequency domain using a fast Fourier transform, and integrating the power over the respiratory frequency band (0.12 to 0.40 Hz) will give us the measurement we will report as RSA. Values will be obtained at baseline and at peak drug effect for each sixty-second segment of a five-minute recording period, and for each sixty-second segment of a three-minute recording period during the Cyberball games and then ensemble averaged. To ensure that participants were aware of their social condition before we measure RSA, we will allow 90 s game time to elapse before taking 3 min of cardiovascular data.

2. Corrugator supercilii and zygomaticus major electromyography (EMG) – Muscle activity in the corrugator (frown) and zygomatic (smile) muscles is sensitive to the presentation of pleasant and unpleasant images and faces (Larsen, Norris, & Cacioppo, 2003). Corrugator activity is potentiated by negative images and reduced by positive images, while zygomatic activity is potentiated by positive images. This activity is measurable using psychophysiological recording techniques even when it is not large enough to produce a visible facial expression. There is some evidence that EMG may be sensitive even to emotional impulses that do not reach the level of conscious expression (Dimberg, Thunberg, & Elmehed, 2000). We have previously demonstrated that facial EMG activity to similar stimuli can be altered by pharamacological manipulations (Wardle & de Wit, 2012). EMG will be recorded using 4 standard 4mm silver/silver chloride electrodes (2 at each site on the right side of the face), plus one ground electrode. Data will be relayed to a Biopac (Biopac Systems, Inc, Santa Barbara CA) EMG100C amplifier, which will amplify signals 5,000x, and band pass filter signals below 10 Hz and above 500 Hz. Signals will be digitized at 5000 Hz by a Biopac MP150 system and recorded using Acqknowledge, Biopac's recording and analysis software. If needed, data will be submitted offline to a 15-Hz high pass filter to reduce movement and blink artifact, and a 50/60 Hz notch filter to reduce line noise, the need for which will be decided during the pilot test period. EMG in each case will be quantified as the difference between mean activity during a 1,000 ms period before the onset of the stimuli, compared to mean activity during the presentation of the stimulus.

3. Eyetracking – To examine attentional biases for one type of emotional expression over another, electrooculogram (EOG) eyetracking equipment will be used to measure horizontal eye movement during the attentional bias task, during which two pictures are presented side by side. A 4mm Ag/AgCl electrode filled with electrolyte (Biopac System Inc.) will be attached 1.5 cm from the outer canthus of each eye, using the same ground as the EMG signal. The EOG signal will be amplified using an EOG100C (Biopac Sysems, Goleta.CA),

digitized using a Biopac MP150 system and sampled at 1000 Hz throughout the task using AcqKnowledge software. Picture stimuli will be presented using E-Prime and a 17" VGA monitor. The EOG signal will be filtered using a low pass filter 20 Hz. Fixations to each picture will be identified as changes in EOG trace reflecting a shift in gaze towards one of the pictures. Criteria for identifying an initial shift in gaze on each trial will be as follows: (a) participants are fixated in the central region before picture onset, (b) eye movements occur at least 100 ms after picture onset and before picture offset, (c) gaze is directed to either picture (left or right) rather than remaining at the central position during the picture presentation.

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 used to treat ADHD (e.g. methylphenidate), a sedative drug used to treat sleep disorders (e.g. diazepam), or an opiate drug used to treat drug used to treat pain (e.g., buprenorphine). 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, including providing a photo for their profile for the social feedback task and rating of other profiles. This will help reduce practice effects across the study sessions. Abstention from recent drug and alcohol use will verified by breathalyzer and urine drug tests. Women will also be urine tested for pregnancy.

Study Session: Please see below for a full timeline of the study session. On study session days, participants will arrive at 1pmm, 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:pm and 2:30pm we will reassess mood. The task portion of the study will begin 1.5 hrs after administration of the drug, and will last for approximately 1.5 hours, to coincide with the peak effect of the drug. Participants will first have the areas for the psychophysiological electrodes for EMG and EOG prepped by cleaning with a rubbing alcohol and an exfoliant. Psychophysiological electrodes will be attached, and impedance checks will be done on the EMG pairs. If impedance across each EMG pair is not below 5 KΩ, the cleaning and application procedure for that pair will be repeated. EkG electrodes will also be placed. All tasks involving psychophysiology will take place with the participant seated in a comfortable chair with a headrest, placed a pre-determined distance from the computer monitor. The IAPS, DEIT, ABT, social touch, and social feedback tasks will be presented in a counterbalanced order. The psychophysiological equipment will then be disconnected. Participants will remain in the lab completing subjective measures of the drug effect every half-hour until at least 5:15pm (when we expect drug effects will end), or until

effects of the drug return to baseline (as measured by both subjective report and cardiovascular variables). Sessions will be separated by at least 72 hours.

Timeline
9:00am – Arrival, snack, breath and urine tests
9:15am – Mood (POMS), drug effect (DEQ) and cardiovascular measures
9:30am – Tablet administered
10:00am - Mood (POMS), drug effect (DEQ) and cardiovascular measures
10:30am - Mood (POMS), drug effect (DEQ) and cardiovascular measures
10:45am – Social Choice Task, Psychophysiology sensors applied
11:00am – IAPS, ABT, social feedback, social touch task counterbalanced
12:30pm –Mood (POMS), drug effect (DEQ) and cardiovascular measures
1:00pm - Mood (POMS), drug effect (DEQ) and cardiovascular measures
1:15pm – Leave Laboratory

Debriefing: Participants will be emailed 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 in person, via phone, or via email.

Data Analysis

The subjective effects of the drug will be assessed using three-way repeated measures analysis of variance (ANOVA), with group (high vs. low BDI scores) as the between-group factor and dose and time as within-subjects factors. We hypothesize buprenorphine will dose-dependently reduce depressed mood in those individuals with high scores on the BDI. Our primary mood measure will be scores on the Depression scale of the POMS.

Behavioral Tasks:

IAPS: We hypothesize that participants will react less negatively to unpleasant social pictures while taking buprenorphine, 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 zygomatic responses) using Drug (0, .2mg) and picture type (positive, neutral, negative) as independent variables, and including random variables for Subject and Drug.

ABT: We hypothesize that participants will show reduced attentional bias to negative facial expressions on buprenorphine, as measured by reduced initial fixations and overall dwell times on 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, .2mg) and expression type (happy, angry, fearful, sad) as independent variables, and including random variables for Subject and Drug (per Wardle et al.). We will conduct a Mixed Linear Model analysis in R using lme4 on total dwell time on each face, using Drug (0, .2mg) and expression type (happy, angry, fearful,

sad) as independent variables, and including random variables for Subject and Drug (per Wardle et al.).

Social feedback and social touch tasks: We hypothesize that participants will be less sensitive to both social rejection and the positive effects of social touch. We will conduct a Generalized Mixed Linear Model analysis in R using lme4 on each dependent variable (ratings of rejection and pleasantness) using drug as the independent variable (0, .2mg), and including random variables for Subject and Drug (per (Wardle et al.)).

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 buprenorphine include: fatigue, nausea, vomiting, sweating, lightheadedness, miosis, orthostatic hypotension, respiratory depression, and a sensation of heat. However, the risk of these effects is low at the doses used in this study. The risk of nausea is reduced by asking participants to each breakfast before the sessions. In addition, to protect against, or minimize any possible risks with buprenorphine, subjects are carefully screened to exclude those who are physically or psychiatrically at risk (e.g., any history of AXIS I disorders or history of psychosis). 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, blood pressure, and respiratory rate 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.

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.

4. Electrical equipment: We will monitor cardiovascular and psychophysiological responses to the drug and tasks using conductive electrodes attached to the skin of participants using an adhesive. There may be mild discomfort or irritation to the participant's skin as a result of cleaning the sites to apply the sensors, but this should be transient. All equipment will be appropriately grounded and shielded, and stimulus equipment will be optically isolated from the participant making any electrical hazard to the participant extremely unlikely.

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 orientation typically takes approximately one hour. The study sessions are estimated to last 4.25hrs each, for a total of 9.5 hours spent in study sessions. Participants are compensated $10 for the orientation, $30 for each study session, with a bonus of $80 for completion of all study sessions, giving a total of $150.

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 a serious or unexpected adverse event 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 take appropriate action and communicate with all necessary offices within the University and the FDA.

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