Neuroimaging predictors of relapse during treatment for Opiate dependence
NCT: 02696096
June 22, 2017

C**1. Brief Description of Subjects**

The study sample will consist of 72 opiate dependent persons, 21-50 years old, who want to initiate buprenorphine treatment.

C**2. Study Design**

Participation for all individuals will last 4 months. Assessments will occur at baseline, and weeks 1, 4, 8, and 12. FMRI scans will occur on the initial study day (consent and BL assessment are also completed on this day) or within a week of the initial study day, and approximately 2-3 days later. Buprenorphine induction will begin at the completion of the second scan; follow-up medical visits will align with study assessments on weeks 1, 4, 8 and 12. All participants will receive 16 weeks of buprenorphine (the final 4 of these 16 weeks will include a taper).

C**3. Specific Procedures or Treatments**

Assessments: Participants will meet with the Research Assistant (RA) at the baseline visit, during the scanning sessions, and prior to the medical visit at weeks 1, 4, 8, and 12 after beginning buprenorphine. The goal of the follow-up contacts will be to assess drug and buprenorphine use using the TLFB, dispense buprenorphine, and biochemically confirm acute abstinence with urine toxicological analysis.

During the baseline (first study visit) day, participants will be cabbed to Butler Hospital to complete informed consent, meet with the study physician to confirm study eligibility, and complete the baseline assessment. If their FMRI is the same day, they will then be cabbed to the FMRI facility, where they will meet with a second research staff member and complete the FMRI session. At the conclusion of this first day, they will be cabbed home. If their FMRI is on a separate day from the BL appointment, they will be cabbed home from the BL appointment, then cabbed back and forth to the FMRI facility for the first FMRI. For all participants, for the second FMRI day, they will be cabbed directly to and from the FMRI facility. For the study visits during weeks 1-12, which all take place only at Butler Hospital, they will be asked to provide their own transportation.

Assessments will include the following measures: general demographic information, social support (Duke Social Support Index[78]), self-efficacy (Thoughts About Abstinence Scale[79]), other drug use (Addiction Severity Index section on drug use[80], self-report by TLFB, and urine toxicology), alcohol use, craving[81] (Brief Substance Craving Scale[82]), withdrawal symptoms (Clinical Opiate Withdrawal Scale[83]), delayed discounting (paper version), and service utilization (The Treatment Services Review which quantifies types of treatment services received by participants[84] during treatment, including the number of 12-step groups attended).

This study will use Care New England's instance of REDCap for the collection and storage of data. The study will not collect or store any actual data within REDCap until the project has been moved into REDCap's production environment.

REDCap is a secure, web-based application developed by Vanderbilt University for building and managing surveys and databases. It is primarily designed to support online or offline data capture for research studies, quality improvement, and operations. REDCap provides easy data manipulation (with audit trails for reporting, monitoring and querying patient records), real-time data entry validation, and an automated export mechanism to common statistical packages.

Care New England's instance of REDCap is hosted within the Care New England data center in Warwick, RI. This REDCap instance is role-based and is fully integrated with CNE's Active Directory structure. It enjoys 24/7/365 enterprise-level support and security inherit to CNE's HIPAA-compliant data center. Network transmissions (data entry, survey submission, and web browsing) to and from REDCap are protected via TLS 1.2 encryption. REDCap's data is stored on encrypted servers within CNE's data center.

The REDCap Consortium is composed of thousands of active institutional partners in over one hundred countries who utilize and support REDCap. REDCap was developed specifically around HIPAA-Security guidelines, and more information about the consortium and system security can be found at http://www.projectredcap.org/.

Buprenorphine: The participant will meet with the study physician (Dr. Stein) at the first study visit at Butler Hospital, prior to buprenorphine induction. During this visit, he will take a medical history, confirm the participant's eligibility for buprenorphine and explain how to use the buprenorphine medication. Participants will be told at this first visit that they need to be in mild to moderate opiate withdrawal when they complete the second FMRI scan at the upcoming study visit (2-3 days later) in order to be eligible to receive their initial buprenorphine dose. At the conclusion of this second scan, research staff at the FMRI facility will complete the COWS to confirm withdrawal symptoms, remind the participant how to self-dose the buprenorphine, and provide the participant with enough buprenorphine to last until the next study visit in about a week.

As their initial buprenorphine dose, the participant will receive four milligrams of buprenorphine (with 1 mg of naloxone) sublingually[14]. Following this protocol, which Dr. Stein has used in multiple prior studies[14,15], additional buprenorphine will be taken home for use later in the day, with the usual first day dose of 16 milligrams (with 4mg naloxone), and 16 mg administered daily throughout the 12 weeks of maintenance for standardization. Participants will be seen and dosed by Dr. Stein thereafter with only enough buprenorphine provided at each study visit to reach the next scheduled medical visit. Buprenorphine dosing will be done with the understanding that a total of 16 weeks of treatment will be offered. Thus, at the week 12 visit, a buprenorphine taper will begin, with a reduction of half the week 12 dose during week 12-14, and the remaining taper during weeks 14-16. Upon request, participants will be provided with a complete list of buprenorphine providers in the area to continue buprenorphine assisted therapy (maintenance) if participants wish to continue treatment beyond the study period. For those participants continuing buprenorphine assisted therapy with a buprenorphine provider arranged post-study, a stable dose of buprenorphine will be provided during weeks 12-16 in lieu of taper. If the participant's appointment with this outside buprenorphine provider is after, but within approximately 10 days of, the 4-month study date, when the study medication is completed, the participant can be eligible to receive a "bridge prescription" to maintain continuity of medication between the end of the study and the start of outside care. Urine toxicology will be performed at each medical visit. No participant will be discharged for use of illicit opiates. Thus, the incentive to misrepresent opiate use behavior at follow-up assessments is relatively low since use does not result in discontinuation of buprenorphine or from the study, or loss of monetary compensation for assessment.

FMRI: For FMRI session 1, research staff will be certain that participants are not in opiate withdrawal (scoring <7 on the Clinical Opiate Withdrawal Scale[83]). For FMRI session 2,

participants will be instructed to stop using opiates 12-24 hours prior to the session so they arrive at the Brown University FMRI facility at the time of their scan in a state of mild opiate withdrawal, scoring 7-12 on the Clinical Opiate Withdrawal Scale (COWS)[83]. This COWS score range will allow standardization of withdrawal symptoms across opiate types (e.g., heroin, oxycodone). If they appear at the FMRI appointment and are not in withdrawal, participants will need to reschedule their scan. Participants will remain in withdrawal throughout the FMRI session 2 procedures, and after this FMRI will receive their first dose of buprenorphine. This plan is in keeping with the fact that withdrawal symptoms are essential for buprenorphine to be initiated.

After administration of pre-scan measures, participants will be "trained" to perform each of the three FMRI tasks, that is, made aware of what they will see and be asked to do when in the FMRI scanner. This training takes 15 minutes. Despite training, performance below chance level on the WM task and invalid responses on the DD task are expected in a small minority of participants, making the data from these individuals unusable. Resting state scans are not based on performance levels or subjective responses and therefore (unless data are lost to movement) always analytically adequate. Based on our experience administering these paradigms and the careful participant screening procedures that we have developed, we expect that analytic exclusions based on head movement and the inability of the participants to complete any particular FMRI portion of the study will be *approximately 20%.*

Participants will then apply earplugs and FMRI-compatible vision correction, if needed, and lie on the MR scanner table. Stimuli will be back-projected with a LCD projector onto a screen that the participant will view through mirrors fixed to the scanner. High-resolution T1 scans will be acquired before FMRI. During FMRI, participants will respond using a response box. The FMRI scan process will last approximately 60 minutes.

During both FMRI sessions, we will administer three FMRI behavioral challenges and a resting scan during the 60-minute protocol (see Table 1). Research staff will be overseen by co-Investigator Dr. Jerskey, who will be responsible for administering the paradigms during FMRI data acquisition.

Table 1. FMRI Paradigms and domains challenged

Paradigm	Relapse Risk Domain(s)	Time	Bilateral ROIs
Delay Discounting (DD)	Reward, Impulsivity, Restraint	16 min	MFG, anterior insula, ACC, PCC, MedFG
Working Memory (WM)	WM, WM Cognitive Persistence	8 min	MFG, IPL, SMA
Inhibitory Control (IC)	Inhibitory Control	12 min	
Rest	Default Network	6 min	PCC, MedFG

Abbreviations: Middle frontal gyrus (MFG), anterior insula (AI), anterior cingulate (ACC), posterior cingulate (PCC), medial frontal gyrus (MedFG), inferior parietal lobule (IPL), supplementary motor area (SMA), ventral striatum (VS).

Delay Discounting Paradigm. This paradigm will be presented to examine decision-making for smaller immediate rewards versus larger delayed rewards. Thus, this task will assay impulsive choice preferences and the relative activity of both motivational drive and inhibitory control prior to entering buprenorphine treatment. Using an event-related design, participants make choices between smaller immediate rewards or larger delayed rewards over 72 trials (e.g., "Would you rather have $25 today or $35 in 29 days"). Each item has a temporal discounting function and the overall array of responses permits calculation of an individuals' discounting level.

Working Memory Paradigm. The 2-Back version of the n-Back has been widely used in FMRI experiments as a WM challenge (i.e., a construct that refers to the process of short-term storage and management of information). This task challenges persistence during a sustained cognitive set since information is constantly maintained and updated over six 45s blocks of time. During the 2-Back WM challenge a series of 15 consonants are presented visually, one every 3000 ms. Participants make a yes/no response following each consonant - whether it is the same as, or different from, the consonant presented two earlier. Each consonant block contains 33% stimulus-target consonants pairs, which randomly overlap (e.g., F, N, B, ***N***, ***B***, K, ***B***, ***K***, N…). The *0-Back task* (a control task for the 2-Back) will include nine consonants presented at the standard 3000 ms rate. Subjects respond "yes" when a predetermined target consonant appears and "no" for other consonants. In total, there will be two runs of six 2-Back blocks each, requiring 4.8 minutes to complete (including control blocks). Three blocks of the 0-Back and three blocks of the rest will be included in each run. Accuracy and reaction time will be used as dependent measures of cognitive performance.

Go/No-Go: The Go/No-Go is an inhibitory control task. The version used in this study is similar to the version used previously by Kiehl and colleagues (2000), except that the Go stimuli are randomly selected letters other than "X". Specifically, letters will be presented for 100 ms each, with an interstimulus interval of 900 ms. A total of 240 letters will be presented consisting of 80% "Go" stimuli (all letters other than "X") and 20% "no-go" stimuli ("X"). Participants will be instructed to press a button for each "Go" stimulus in order to establish a pre-potent response, and inhibit their response when an "X" appears on the screen. Total percentage correct, percentage of false alarms (commission errors), and reaction times for correct go stimuli will be used as behavioral measures of performance.