# Efficacy and Safety of the Melanocortin Activator Bupropion in Treating Binge Drinking

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# ***Protocol Version 3.1***

## ***Efficacy and Safety of the Melanocortin Activator Bupropion in Treating Binge Drinking***

**Overall Concept:** The current proposal represents an innovative pharmacological approach to the treatment of binge drinking that derives from preclinical findings from the laboratory of Dr. Todd Thiele, one of the proposal's consultants. Dr. Thiele found that a melanocortin agonist, melanoton II, potently suppresses binge drinking (Navarro et al, 2015) in a mouse model of binge drinking. Because the antidepressant bupropion has been shown to activate melanocortin systems in brain (Greenway et al, 2009) Dr. Thiele's lab also studied the effect of bupropion on binge-drinking in their model and showed that bupropion significantly reduced binge-drinking at doses that were lower than those that suppress appetite (unpublished data). Because bupropion is a clinically available and FDA approved medication Dr. Thiele initiated a discussion with our group to consider a clinical trial of bupropion for binge drinking. Navarro et al (2015) found evidence that using a melanocortin agonist with an opioid antagonist enhanced the potency of the opioid antagonist to suppress binge drinking. In addition to a direct effect on binge drinking, Dr. Thiele's lab has proposed that modulating the melanocortin system and counteracting binge drinking may have value in *preventing* progression of alcohol use from binge drinking to dependent level drinking (Thiele, 2012; Navarro et al, 2015)—potentially, a very important finding for clinical care.

The current proposal uses this preclinical and clinical data to design a groundbreaking translational placebo-controlled, Phase IIa clinical trial to 1) assess for an efficacy signal of the melanocortin activator bupropion in binge drinking individuals who have not developed physical dependence on alcohol and 2) to assess for a modulating effect of coexisting nicotine dependence on possible bupropion response. The current proposal is highly novel as it tests the efficacy of activating the melanocortin system in an understudied population (binge drinkers without physical dependence on alcohol.

**General Background**: Binge drinking is a major public health problem in the United States. The Center for Disease Control (CDC) places alcohol as the number three cause of preventable deaths following nicotine use and overweight (Mokdad et al, 2004). Binge drinking, generally defined as the consumption of five or more standard drinks for a man or four or more drinks for a woman in about a two hour period (see Courtney and Polich 2009), is a major component of excessive alcohol use and a serious problem for the United States. The CDC (2012) report indicated that 17.1% of the adult U.S. population reported one binge drinking episode in the past 30 days in 2010--men (23.2%) vs. women (11.4%) with peak ages 18-24 years (28.2%), 25-34 years (27.9%), and 35-44 years (19.2%). Men reported an average of 5 binge drinking episodes/month with a mean of 9.0 drinks/episode and women 3.2 binge drinking episodes/month at 5.9 drinks/episode. Binge drinking leads to multiple problems, e.g. accidental injury (Gmel et al, 2006), aggressive and violent behavior (Shepard et al, 2006), and high blood pressure (Fan et al, 2008). Additionally, there is increased risk for developing alcohol dependence in individuals that binge drink frequently (Hingson et al, 2006). Overall, binge drinking contributes to more than half of all deaths attributed to alcohol and to three quarters of the economic cost of excessive alcohol use—*binge drinking is a serious public health problem and one that may exceed traditionally defined alcohol dependence in its overall cost to society*.

Binge drinking is a complex construct as it is both a stand-alone phenomenon and also a component of alcohol use disorders. We are focusing on the behavior to allow greater fidelity to the preclinical data where the key behavior was consumption of an intoxicating amount of alcohol in a two hour period, a non-dependent

model (Navarro et al, 2015). The majority of binge drinkers do not have physical dependence (see Woerle et al, 2007), and we are particularly interested in this "developmental" phase towards overt physical dependence as the preclinical literature suggests this phase may be a key time for clinical intervention (Thiele 2012).

***Treatment of Binge Drinking with or without Co-Occurring Alcohol Use Disorders***

Despite the significant economic and personal costs associated with binge drinking, efforts to improve recognition and treatment of binge drinking have received less attention than efforts directed towards DSM-IV defined alcohol dependence though this is beginning to change (Siqueira and Smith, 2015). A recent assessment of screening and brief intervention for patients with risky drinking (where many binge drinkers are categorized) and related alcohol-use problems in the primary care setting revealed that a variety of brief intervention techniques, e.g. brief advice, motivational interviews, can reduce heavy drinking episodes (12% more individuals with no heavy drinking, 95% CI 7-16%) (Jonas et al, 2012). Unfortunately, the improvements were modest and health impacts were unclear highlighting the need for additional approaches such as pharmacotherapy. As noted by Hester (2015) "…they [non-dependent drinkers] are an underserved patient population associated with significant and growing health care costs." The availability of medication options for binge drinking would increase medical clinicians' interest in identifying and treating this significant problem.

*Pharmacotherapy approaches to treat binge drinking*: Few clinical trials for binge drinking per se have been completed. O'Malley et al (2015) studied 128 young adult college students with heavy drinking (≥ 4 heavy drinking days in 4 weeks; ~60% DSM-IV alcohol dependent but without physical dependence) and compared 25 mg daily + 25 mg targeted naltrexone to be taken in anticipation of a heavy drinking episode to placebo. They did not find evidence for an effect on %heavy drinking or %abstinence but naltrexone led to a reduction in drinks/drinking day. They noted, "…the risk-benefit ratio favors offering young adult drinkers naltrexone to reduce the amount of alcohol they drink." Three trials have been conducted for older heavy drinkers or problem drinkers, mean age late 40's, using the opioid antagonists naltrexone (Kranzler et al 2003, 2009) or nalmefene (Karhuvaara et al, 2007). These trials sought individuals who were problem drinkers or heavy drinkers rather than physically dependent on alcohol, though 84-95% met criteria for DSM-IV alcohol dependence. These trials excluded individuals with evidence of more severe alcohol dependence, i.e. >4 DSM-IV criteria for dependence or having a history of alcohol withdrawal. All three trials found evidence for modest benefit. Taken together, these studies indicate that medications can be effective in the treatment of the milder end of the spectrum of alcohol use disorders where many binge drinkers are categorized. Pharmacotherapy for binge drinking is clearly in its infancy, perhaps in a similar state to pharmacotherapy for traditionally defined alcohol dependence 20 years ago when naltrexone was first discovered.

The current proposal will conduct the first human trial to test the novel preclinical finding that activating melanocortin systems in brain with/without opioid blockade potently reduces binge drinking. Identification of a potential efficacy signal would be significant as it would not only demonstrate that activation of melanocortin systems with/without opioid blockade has potential for therapeutic application for binge drinking in humans but would increase awareness of a biomedical component of binge drinking which could positively affect medical clinicians' attitudes and potentially increase identification and treatment efforts.

**Nicotine as a potential moderator of bupropion response**: Two recent reports have suggested that comorbid nicotine dependence may be associated with a reduction in drinking with pharmacotherapy (naltrexone) in alcohol use disorders (Fucito et al, 2012; Anton et al, Abstract, Research Society Alcoholism, 2016). The reasons for this are unclear though Fucito et al (2012) have noted that co-existing nicotine use may be associated with more severe alcohol use disorders that are more responsive to pharmacotherapy perhaps because of differences in neurobiology. Given that bupropion has been shown to treat nicotine

dependence and has been approved by the FDA for this purpose there is an interest in whether co-existing nicotine dependence has any impact on possible drinking responses to bupropion. Accordingly, we will stratify by nicotine dependence, attempt to recruit about 50% of subjects with nicotine dependence and will monitor for changes in nicotine use.

***Innovation***

The present application is innovative in two major areas: *1) it represents the first clinical test of the exciting preclinical finding that activating melanocortin systems potently counteracts binge drinking and 2) it represents one of the first clinical trials to investigate the efficacy of pharmacotherapy for binge drinking*. These innovations have the potential to affect clinical practice for the binge drinking patient.

*Innovation 1. First proof of concept trial to translate to humans the preclinical finding that activation of melanocortin systems with/without μ-opioid receptor antagonism reduces binge drinking*

Navarro et al (2015) recently demonstrated that activating melanocortin systems with/without opioid receptor antagonism in brain produced a powerful effect to reduce binge drinking in a mouse model. The rationale to test these systems derived from evidence that activation at the melanocortin receptor blunts ethanol intake in animals and that melanocortin peptides and the endogenous opioid β-endorphin share a common protein precursor and functional relationships (See Navarro et al, 2015).

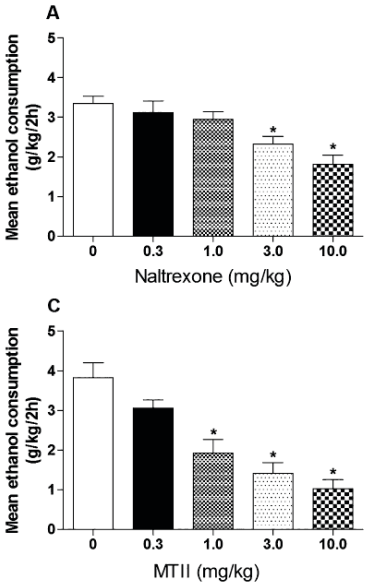


Figure 1: Effects of MT-II compared to naltrexone on binge drinking in mice (Navarro et al, 2015).

In their study, Navarro et al (2015) used melanotan II (MT-II) to activate the melanocortin receptor and naltrexone for opioid blockade. MT-II reduced bring drinking with MT-II being more potent and overall more effective than naltrexone (72% decrease in ethanol consumption vs 47% decrease), Figure 1. Furthermore, MT-II increased the effectiveness of naltrexone in a synergistic manner. A key aspect of this study was that it investigated effects on binge-drinking rather than dependent level drinking, as the authors note "*…our results specifically speak to the possibility that these targets could be useful for curbing excessive binge drinking, an approach that may be useful for preventing the transition to dependence*."

Advantageously, for human trials, Bupropion (Wellbutrin®), an FDA approved antidepressant and anti-nicotine agent, activates the melanocortin system through proopiomelanocortin neurons likely via norepinephrine and dopamine reuptake inhibition (Greenway et al, 2010; Hasegawa et al, 2005). Thus, we now have access to a pharmacological approach approved in humans to test the hypothesis that activation of melanocortin systems will significantly reduce binge-drinking-- a true translational trial.

*Innovation 2: One of the first clinical trials to investigate the efficacy of pharmacotherapy for binge drinking.*

As noted earlier, there has been very limited effort towards identifying pharmacological agents that help with binge drinking, particularly in younger populations. The O'Malley et al (2015) trial may be the first placebo-controlled trial in young (18-25 years), heavy drinkers and it did find evidence that naltrexone reduced drinks/drinking day. Given that the prevalence of binge drinking peaks in the 18-34 year age range and is commonly not associated with physical dependence it is important to conduct clinical trials in populations with these characteristics. The current proposal will therefore focus on subjects ages 21-44 years and will exclude those with overt physical dependence on alcohol.

Targeting the binge drinking population moves the field towards the concept of using pharmacotherapy to treat early phases of alcohol use disorders and potentially reduce the likelihood of individuals progressing from binge-drinking to overt physical dependence. While still a theoretical concept this is a highly innovative idea and one that could have profound implications for clinical management, see Thiele (2012).

**Research Approach**

The proposed clinical trial will be the first randomized, double-blind, placebo-controlled Phase IIa trial examining the efficacy and tolerability of the melanocortin activator bupropion along with Medical Management for binge drinking with or without mild/moderate alcohol use disorder. The trial will include 12 weeks of medication administration and a 30-day (safety) and a 90 day (durability) follow-up to assess for delayed adverse events and post-medication drinking behavior.

For this proof of concept trial, it is important to use doses of bupropion that are known to be effective and safe for humans. For bupropion we have selected a 300 mg/d dose of the extended release formulation. The 300 mg dose of bupropion is approved by the FDA for depression and for nicotine dependence. The extended release 300 mg formulation has a lower estimated risk of seizures (0.1%) compared to the 0.4% rate for the immediate release formulation. The 0.1% risk of seizures is comparable to the risk reported with other antidepressants such as sertraline and fluoxetine (FDA labels) and with acamprosate (FDA label), which is approved for alcohol dependence. Furthermore, we will be studying a binge drinking population without evidence of physical dependence, a history of seizures, or a reported history of cocaine use so seizure risk is minimized which has been raised as a concern based on animal studies (Silverstone et al, 2008).

**Participants:** 50 men and women between the ages of 18 and 44 years of age will be recruited from social media, e-mail list serve to UNC students and staff, and local newspaper/radio advertisements. **Key Inclusion criteria**: 1) A minimum of 5/3 (men/women) or more binge drinking episodes per month over the past three months (mean population values, CDC (2012)). A binge drinking episode is defined as the consumption of 5/4 (men/women) standard drinks (~12 gms ethanol) in about a two-hour period. Requiring multiple episodes of binge drinking over several months is important to identifying subjects with a consistent pattern of binge-drinking as shorter time frames may give misleading information (see Courtney and Polich, 2009). Subjects may meet DSM-V criteria for mild or moderate alcohol use disorder; 2) BMI ≥18.5 (normal weight or above); 3) express a desire to achieve abstinence or to reduce alcohol consumption. **Exclusion criteria:** 1) Presence of physical dependence on alcohol as assessed by clear tolerance to alcohol or alcohol withdrawal symptoms based on SCID interview or a Severe Alcohol Use Disorder (>5 SCID DSM-V symptoms); 2) a history of bulimia or a seizure disorder; 3) clinically significant medical disease that might interfere with the evaluation of the study medication or present a safety concern (e.g., renal insufficiency, cirrhosis, unstable hypertension, diabetes mellitus); 4) clinically significant psychiatric illness including any psychotic disorder, bipolar disorder, anorexia/bulimia, severe depression, or suicidal ideation; 5) other substance abuse or dependence disorder other than nicotine or occasional cannabis use ; 6) Concurrent use of anticonvulsants, varenicline, MAOIs, any anti-alcohol medication or any psychotropic medication with the exception of stable doses of antidepressants for one month; prior history of adverse reaction to bupropion or naltrexone; 7) AST or ALT > 3.5 times ULN or bilirubin > 1.5 X ULN; 8) positive urine toxicology screen with the exception of cannabis. Individuals with positive cannabis screens will be excluded only if they have a history of a cannabis use disorder; 9) pregnancy or breastfeeding.

**Trial Design**: The design is a 1:1 random assignment to placebo or bupropion XL (300mg/d). Dr. Robert Gallop, the study biostatistician, will prepare the randomization schedule and include blocking by gender. Randomization will be based on a stratified block design, with gender and nicotine dependence as the

stratification variable given some evidence of a moderating effect of nicotine dependence on response to alcohol pharmacotherapy (Fucito et al, 2012).

Bupropion XL will be initiated at 150 mg/d on Days 1-4 and increased to 300 mg/d for Days 5-84. Medication is reduced to 150mg/day for 3 days before being stopped at Week 12 UNC Hospital's Investigational Drug Services (IDS) will prepare opaque capsules containing bupropion XL 150/300 mg and matching placebo. Capsules will be inserted into blister packs with each pack containing 1 week of medication. The IDS will receive the randomization schedule from our statistician Dr. Gallop and prepare the blister packs according to the blocked schedule with blocking for gender

**Recruitment, Telephone Screen, and Full Eligibility Screening:** Subjects will initially be prescreened by phone and then at full screening read and sign the informed consent. A breathalyzer test will be administered (must be 0.00 gms/dl to give informed consent), height, weight and BMI recorded and a medical history and examination completed. Over-the-counter and prescription medication use will be recorded and nicotine use documented (Heatherton et al, 1991). CBC with differential; serum bilirubin, AST, ALT, GGT, sodium, potassium, chloride, blood urea nitrogen, creatinine, glucose; and urinalysis and urine toxicology completed. Women will be given a urine pregnancy test (Uβ-HCG) at screening and at weeks 4, 8, and 12 and at the initial treatment visit if it is more than 10 days from the screening visit. Trained interviewers will conduct the psychiatric screening interview using the M.I.N.I. (Sheehan et al., 1998). The SCID Substance Use Disorders Module to establish DSM-V criteria for alcohol use disorders (First et al, 2016) will be administered by either Dr. Garbutt o another doctor listed on the IRB protocol. The study coordinator will conduct the pretreatment 90-day Timeline Followback (TLFB) interview to identify amount of alcohol consumed and timeframe of consumption (Sobell et al, 1988 and personal communication). *A binge drinking episode requires a minimum of 5/4 (men/women) standard drinks consumed over about a two hour period, i.e. consuming a bottle of wine over five hours would not be coded as a binge drinking day*. The Penn Alcohol Craving Scale (PACS) (Flannery et al, 1999) and the University of Rhode Island Change Assessment (URICA) (Diclimente and Hughes, 1990) will be completed and treatment goal—abstinence vs. reduction— recorded.

**Initial Treatment Visit (within 21 days screening):** Eligible individuals will *not be required to abstain from drinking alcohol* prior to randomization. The study coordinator will administer a breathalyzer test (BAC must be ≤0.04 gms/d) and complete assessments as outlined in Table 1, Protection of Human Subjects. A salivary sample for cotinine to be assayed at UNC will be taken. A 1-week blister pack of bupropion-XL or placebo with written instructions will be dispensed from the Investigational Drug Services according to the randomization block. A 1-week back-up blister pack will dispensed once the participant reaches the maintenance dose in case of delayed appointments or lost doses. Bupropion-XL will be titrated with 150 mg given daily for 4 days followed by 300 mg/d. Participants will be given a calendar style diary to track pill taking, drinking quantity/timing, intoxication and any side effects. Finally, participants will receive Medical Management from a trained clinician.

**Subsequent Treatment Visits:** See Table 1 in Protection of Human Subjects for a summary of procedures and assessments. Salivary cotinine samples will be obtained at weeks 4, 8 and 12. TLFB and PACS are gathered each visit. Medical monitoring will be conducted by study physicians and will consist of review of vital signs, concomitant medication use, and general inquiries into side effects. Blood pressure readings of >100mm Diastolic or >160mm Systolic will be automatically rechecked. If a participant has sustained, recurrent blood pressure readings above this limit, their medication will be tapered and stopped. The physician may recommend that medication be held or reduced for a period of time to deal with an adverse event, e.g. nausea. The Visit Window is defined as +/-3 days for weekly visits and +/-7 days for visits that occur every 2 weeks.

Missed Visits are expected. Participants can remain in the study as long as they do not miss more than 2 consecutive visits. If a missed visit has a safety lab test, every effort will be made to schedule the subject as soon as possible to obtain the sample. One month and three months following the last visit subjects will be contacted to update drinking (TLFB), adverse effects and medications.

**Medical Management Intervention:** The psychosocial support for the study will be Medical Management (MM) (Pettinati et al, 2005). Drs. Kampov, Jordan, Pedersen and Garbutt will conduct MM. Drs. Kampov and Garbutt have been trained in MM by Dr. William Dundon and again by Ms. Gail Kaemf of the University of Pennsylvania where Dr. Pedersen was trained as well. Dr. Jordan has been trained in MM by Dr. Garbutt. MM sessions average 10-15 minutes and focus on three main areas: (1) feedback on consequences of drinking; (2) encouraging compliance with medication/addressing compliance problems and (3) encouraging progress towards drinking goal— reduction or abstinence are acceptable. 10% of sessions will be audiotaped and reviewed to enhance fidelity.

**Medication Compliance Monitoring:** Participants will record their pill taking in calendar-style diaries that will be provided and collected at each visit. Pills will be distributed in blister packs that will be returned to the study coordinator to reconcile any unused medication from the returned blister packs with participants' diary records.

## Statistical Plan and Data Analysis

**Outcome Variables:** Key outcome variables include frequency of binge drinking, intensity of binge drinking, treatment response, and GGT levels. Frequency is assessed as number of binge episodes/time in trial controlling for missing data (see Statistical Analysis). Intensity of binge drinking is the number of drinks/binge drinking day. Response is defined as no binge drinking in final 6 weeks. Consequences of binge drinking and craving for alcohol will be examined.

**Sample Size per Group:** In the assessment of feasibility, we need sufficient size to fit our respective models and ensure adequate coverage of our confidence intervals. VanVoorhis and Morgan (2007) provide guidance with respect to minimal sample size needed for differences between groups. They recommend that the groups be no lower than 7 per cell. Our aim is on the effectiveness of bupropion versus placebo in addition to the examination of a potential moderation effect attributable to nicotine use. Assuming a 2:1 ratio between nicotine usage, a sample size of 30 per arm should ensure at least 7-10 per treatment arm as a function of nicotine use. Additionally, our proposed sample size of 30 per treatment arm is in agreement with Sugden et al. (2002) minimum sample size to ensure adequate coverage of nominal 95% confidence intervals, which require n> 28 under minimal skew.

**Statistical Analysis:** Study participants will first be characterized on baseline measures with appropriate methods. We will derive weekly summary scores from the TLFB quantifying the %Binge Drinking Days and the average drinks per binge drinking day per week. Descriptives and exploratory graphing will be used to assess the presence of skew and/or outliers with appropriate transformation implemented as needed. As stated above, our sample sizes are set to assess feasibility and implementation; therefore, the respective analyses, are exploratory, and therefore, not powered, but analyzed in accordance with the methods and recommendations per Kianifard & Islam (2011) for this proof-of-concept study. Per recommendation 4 of Kianfiard & Islam (2011) who describe caution when interpreting analyses from small trials, we will implement

an analytical procedure which maximizes the statistical power. The Institute of Medicine recommends several approaches, including clustered models, to maximize information from small trials and increase statistical power (Institute of Medicine, 2001). Using the full sample (N=50), we will fit a Mixed Effects Model (MEM) (Schwarz, 1993)) on: %Binge Drinking Days, drinks/binge drinking day, GGT outcomes with the focus on the linear contrasts within the MEM framework examining the superiority of bupropion to placebo. Our modeling will not focus on statistical significance but rather derive confidence intervals for the respective contrasts within the MEM framework examining the superiority of bupropion to placebo MEM accommodates the within-subject correlation of the repeated assessments (weekly for TLFB measures). MEM allows for the inclusion of potential predictors and covariates such as cotinine levels, medication compliance, demographics, and baseline clinical measures such as motivation. Pattern-mixture models (Hedeker & Gibbons, 1997 & 2006) will be used within the MEM structure to assess whether linear contrasts are dependent on attrition/missing data patterns. The pattern-mixture model is dependent on the number of distinct missing data patterns. With this limited sizes study, we will define the patterns as completers vs non-completers as was done by Hedeker & Gibbons (1997,2006). An assessment of significance will not be made but rather we will derive effect sizes of the respective bupropion and placebo contrast for both completers and dropout. With the limited sample and therefore, limited sample per pattern, we realize the respective confidence intervals will be wide. An additional benefit of the MEM is, it will allow us to assess for possible moderators. A moderator is a baseline measure or prerandomization characteristic that has a differential effect on outcome across intervention condition (Kraemer et al., 2002). Moderators are typically defined as variables that significantly interact with condition (Baron & Kenny, 1986; Holmbeck, 1997). The particular moderator of interest is use of nicotine. Assessment of moderation will be made by augmenting our MEM outcome analyses to include the interaction of the effect of assignment (bupropion vs placebo) intervention with the use of nicotine. In a sufficiently sized study, we will have a significant moderator of the assignment effect if the interaction term is significant (Kraemer et al., 2002), where statistically significant interactions would be interpreted by plotting simple regression lines for use versus non-use of nicotine (Holmbeck, 1997; Aiken & West, 1991). With the small sample, we will derive a confidence interval for the respective interaction effect, namely the difference of the differences (the difference between buproprion versus placebo for nicotine users versus the difference between buproprion versus placebo for the nicotine abstainers). Subsequently, we will perform a corroborative set of analyses, in accordance with Kianfiard & Islam (2011), where summary measures over the entire TLFB period are derived. Simple ANOVA/ANCOVA models will be used to perform the above analyses with the model structure producing confidence intervals for both the buproprion versus placebo contrast, as well as the moderation assessment.

Response, i.e. no binge drinking days in final 6 weeks of medication, tolerability measured via retention time, and number of adverse events reported will be examined with Logistic regression, Cox-Regression , and Ordinal-regression models, respectively with the same contrast comparisons as above focused on the derivation of confidence intervals for the respective contrasts. Moderation of nicotine use will follow the procedure as discussed earlier, where the respective models will be augmented to include the interaction of nicotine use with assignment, with the derivation of the confidence interval for the difference of the differences as described above.

DATA MANGEMENT PLAN

The Database will be configured in Microsoft Access or Excel. Discrepancies will be examined and additional data checks completed as indicated. A closed and password-protected data entry system will be used and only

certified study personnel will be able to enter or edit data. Data and user stamping are used to create an audit trail. Range checks, review screens, and error trapping routines are built into the system as quality control procedures. Hardcopy data summaries will be available to the investigators for data analyses. As a final check on data integrity, the investigators and study coordinator will check these outputs against the raw data and resolve any discrepancies. We will be asking subjects to fill out self-ratings on a tablet mobile device. The ratings will be in the form of Qualtrics surveys. No identifying data will be entered into the tablet, just a subject ID number.