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Study: **NT-814: EVALUATION OF ITS ABILITY TO ALTER THE ABUSE LIABILITY OF OXYCODONE IN AN EXPLORATORY CLINICAL STUDY**

Statistical Analysis Date: **February 18, 2016**

IV. Statistical Analyses

HYPOTHESIS 1: Active medication will be superior to placebo medication in reducing drug-taking behavior, positive subjective effects, and withdrawal.

Three primary measures will be considered for each study: drug-taking behavior measured by average percentage of drug choices during *Choice Sessions* and progressive-ratio breakpoint values (our measure of relapse) generated during *PR Choice Sessions*; positive subjective responses, measured by visual analog scales during *Drug Exposure* and *Exp Ad Sessions*; and withdrawal measured by SOWS and COWS questionnaires during *Withdrawal* weeks. These data will be analyzed using repeated-measures ANOVAs with planned contrasts with medication dose (2 levels) as the first factor. The time course data for average percentage of drug choices across the 4 Choice days will be analyzed within each arm of the studies and treated as repeated measures. Differences in choice as a function of self-administered dose (placebo vs. oxycodone) will be evaluated under each medication dose. We will conduct two sequences of planned comparisons: 1) effects of peak measures averaged across participants, and 2) time course of drug effects (all time points compared). Both sets of analyses will be accomplished by repeated measures ANOVA's.

HYPOTHESIS 2: Active medication will be superior to placebo medication in reducing drug craving, as well as physiological and subjective reactivity to drug cues.

The secondary measures of interest for this study are for craving, specifically, ratings of "I want opioids," as well as scores on the Opioid Craving Questionnaire. Physiological response, including galvanic skin response, skin temperature, and heart rate, will be evaluated. As above, these measures will be analyzed using repeated-measures ANOVAs with planned contrasts using medication dose (2 levels: placebo and active) and available self-administered dose (2 levels: placebo and active oxycodone) as factors. Other dependent measures (cognitive and physiological effects) will be analyzed in a manner similar to the subjective ratings. That is, peak (or trough) and time course analyses will be conducted on these measures.

POWER ANALYSES

Power analyses were conducted using nQuery Advisor®, Statistical Solutions. Estimates for our primary measure of drug-taking behavior were obtained from a recently completed trial using similar verbal choice procedures. A total sample size of 12 completers per study will provide 90% power to detect a 26% difference in average percentage of drug choices in a 19-trial choice procedure (i.e., an average difference of 4.9 choices between drug and money), which is a Cohen's *d* effect size of 0.92. This assumes a standard deviation (SD) of 28%. Estimates for our primary measure of relapse (progressive-ratio breakpoint values) were based on our study of the reinforcing effects of heroin in buprenorphine/naloxone-maintained heroin abusers (Comer et al., 2005). A sample size of 12 completers will provide 86% power to detect a 500-point difference in progressive ratio breakpoint values. Our calculated effect size of 0.84 assumes a SD of 594 points.

Twelve completers will provide 83% power to detect a 20-mm difference in positive subjective effects, e.g. "Liking" on a 100-mm VAS scale. This analysis assumes a SD of 25 mm (effect size of 0.80). These values were generated from ratings by individuals who received a dose of heroin that produced a magnitude of effects similar to those expected for the oxycodone dose proposed in the present project. Thus, with regard to detection of differences in subjective effects, these calculations suggest that this study is suitably powered.

Twelve completers will provide 84% power to detect a 10.6-point difference in withdrawal, e.g. SOWS sum score (range: 0-64). Our estimated effect size of 0.81 was based upon a SD of 11.1 and differences in SOWS scores from detoxified heroin users one week after low and high dose depot naltrexone (Comer et al., 2002).

We are under-powered to detect sex differences in our endpoints for individual studies in **Project 3**, but we will combine data across studies under the placebo maintenance conditions in the medication alone studies to determine whether men and women differ in their propensity to relapse, respond to cues, etc.

To control for possible Type 1 errors due to the multiple comparisons, *P* values < 0.01 will be used to indicate statistical significance. Data from participants who do not complete the studies or are missing more than 5% of data points will not be included in the analyses. Self-administration data will not be imputed. If a baseline data point is missing for other dependent measures, the first data point that is collected will be used as the baseline value. If data points are missing from a continuous variable from a series of administrations, an average of the points from both sides of the missing value will be imputed. The conservative implementation of these data handling guidelines for our missing data will assist us in drawing appropriate conclusions.