Cognitive-enhancing DA Medications for Cocaine Dependence

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STATISTICAL ANALYSIS PLAN (SAP)

Data will be entered by research assistants into an existing, relational database (i.e. Microsoft Access). Data integrity will be maintained by restricting allowable input values on standardized Access entry forms. Double entry of a random subset of 10% of the observations will be used to identify problematic data entry issues. Preliminary data analyses evaluating group differences on demographic and baseline variables will use contingency tables with chi-square testing, ANOVA's, and examination of correlations between baseline variables and specified outcomes. Baseline or demographic variables, on which group differences are detected and which are correlated with outcomes, meet the definition of confounders and will result in two sets of analyses: one in which the relevant variable is included as a covariate and one in which it is not. This will permit determination of the degree to which any group differences might confound conclusions regarding treatment.

Broadly, the data analytic strategy will use generalized linear modeling and mixed effects models. Longitudinal analyses will be conducted using generalized linear mixed modeling (Proc GLIMMIX; SAS 9.2) for both continuous and discrete outcomes. Count, dichotomous and time to event data will be evaluated using Poisson (Proc GENMOD; SAS 9.2), logistic (Proc GENMOD; SAS 9.2), and proportional hazards regression (Proc PHREG; SAS 9.2) respectively. Distributional assumptions will be evaluated via inspection of residual plots and, where possible, by formal statistical tests. Violation of assumptions will be addressed, depending upon statistical technique, through the use of transformations, robust estimators, scaling coefficients, and stratification. Sample size approximations are obtained through empirical data simulation using SAS v.9.2.

PRIMARY HYPOTHESIS TESTING: **To evaluate the efficacy of combination levodopa/carbidopa-ropinirole therapy in treatment of cocaine dependence**. **H1. The combination of levodopa/carbidopa and ropinirole will reduce cocaine use and increase treatment retention. H2. There will be a dose-response relationship such that [levodopa/carbidopa + 4 mg/d ropinirole] > [levodopa/carbidopa + 2 mg/d ropinirole] > [levodopa/carbidopa + placebo] > [placebo + placebo]**. H1 will test for differential change over time as a function of treatment. H2 will test the ordinal relations of treatment effects as a follow-up analysis. As defined above (see Sect. B.3.2.5.ii) cocaine use will be measured by urine benzoylecgonine and by the SPRHK1 approach. Generalized linear mixed models will evaluate the probability of cocaine use as a function of time, treatment and their interaction. Logistic regression will evaluate retention, defined by completion of 12 weeks of treatment, as function of intervention condition. Proportional hazards regression will evaluate time to drop-out as a function of treatment. If differential attrition raises concerns regarding non-ignorable missingness, evaluation of cocaine use will implement pattern-mixture modeling. To evaluate the relative efficacy of the treatment conditions we will follow up the omnibus test with ordinal contrasts.