Statistical Analysis Plan

Targeting Dopaminergic Mechanisms of Slowing to Improve Late-Life Depression

IRB #7733

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Overview: All variables at all time points will be examined for illegitimate values, outliers, and inconsistencies. The distribution of demographic variables and baseline clinical characteristics will be examined and described across the two randomized patient groups (N=45 each) in terms of means, standard deviations, proportions, and 95% confidence intervals. Indications of inequality between groups in specific features (despite randomization) will trigger examination of whether differences in primary outcome measures can be attributed to an imbalance in group assignment. Intent-to-treat will be used for analyses including all participants who are randomized and have at least one post-baseline HRSD score. Tests will be two-sided and statistical significance determined at p-value < 0.05.

Missing data: We will make every effort to obtain all data. The longitudinal mixed modeling described below is valid if missing data are missing at random (MAR). MAR assumptions cannot be verified. A 2010 national expert panel (166) recommended sensitivity analyses for the impact of missing data via pattern mixture models (167), which we will conduct (e.g., by investigating robustness of results to perturbations of assumed values for missing data within clinically plausibly ranges).

Analyses for Aim 3: Aim 3.1: To determine whether L-DOPA administration results in greater improvements in depressive symptoms on the HRSD, a longitudinal mixed effects model will be used to analyze group differences using SAS Proc Mixed Version 9.3. The change in 24-item HRSD from baseline will be analyzed as a function of time, treatment group, the interaction between time and treatment, and baseline HRSD. Contrasts of mean difference in HRSD at each week will be formed and tested. *Aim 3.2:* To determine whether greater increases in processing and gait speed are associated with greater HRSD improvement, change scores from baseline to 8 weeks will be calculated for both processing and gait speed. Pearson correlation among all change scores, including change in HRSD will be examined, and two-sample t-tests will be used to assess treatment group differences. Multivariate linear regression models will be fit with change in HRSD as the outcome predicted by treatment, processing and gait speed change scores, and baseline values of processing and gait speed.

Exploratory aims: Inflammatory markers and COMT genotype will be tested as moderators of the L-DOPA effect on HRSD change by including their interactions with treatment in the Aim 3 analyses.

Power analysis: Aim 3.1: With N=45 per treatment group, and assuming a drop out of 15%, using two-sided test with α=0.05, we have >80% power to detect treatment group differences with ES = 0.60 or greater. Given expected SD=5 points based on similar previously conducted studies in the LLDRC, this ES would correspond to a change in HRSD of 3 points, which is smaller than the 4 point change considered meaningful. *Aim 3.2:* With N=90, assuming a drop out of 15%, we would be able to detect correlations >0.31. Thus, we have adequate power to detect a moderate to large correlations between change in HRSD and change in processing and gait speed.