STATISTICAL ANALYSIS PLAN

for

Improving Therapeutic Learning in Depression: Proof of Concept
NCT02376257
Date of Document: November 15, 2013

Otto et al. DCS, Modafinil, PBO: Data Analysis

Analyses for outliers, non-normal distributions, nonlinear relations, and influence statistics will be conducted; data transformations will be considered where appropriate. We will perform repeated-measures ANOVAs using mixed-effects regression models (MRMs) in SPSS 20.0 to analyze the data. The MRM approach to repeated measures ANCOVA allows inclusion of all participants regardless of missing data (which improves power and generalizability), can model the covariance matrix of the repeated measures more flexibly than ANCOVA, and is the recommended method for longitudinal data analysis (Hamer & Simpson, 2009). The ANCOVA will consist of 3 levels of the between-subjects IV (Treatment Condition) and 2 (or 3) levels of the within-subjects IV (Time). For delayed recall memory, Time will represent weeks 3 and 4, when recall for information presented at the previous session will be assessed. Three separate analyses will be performed, one for each of the 3 measures of delayed recall memory; retention of 1) cognitive therapy principles, 2) emotional narrative, and 3) WMS Story B *(exploratory analyses will also examine cognitive therapy skill use, following this analytic approach)*. For immediate memory, Time will represent weeks 2 & 3, the time points of primary interest for the immediate memory tests (digit span, HVLT, ICAT). Scores on the baseline memory assessments (week 1) and baseline antidepressant use will be included as covariates in all analyses. Since the relation between the covariates and outcome may be different among treatment conditions (e.g., the relation between baseline memory and drug influenced memory may be lower for 250 DCS and 100 modafinil compared to placebo), interaction terms will allow these relations to vary across treatment conditions. Similarly, because the relation between the covariates and the DVs may be lower at weeks 2 and 3 (with drug ingestion) compared to week 4 (no drug ingestion), interaction terms will also allow these relations to vary across Time. Non-significant interaction terms will be dropped.

Aim 1. A significant main effect for Treatment Condition for "delayed memory" would indicate differences between conditions in delayed memory. In particular, we expect that pairwise comparisons among the 3 treatment conditions (using the Sidak correction for multiple comparisons [this correction is available in SPSS's mixed effects routine]) will show that 250 DCS and 100 modafinil significantly enhance delayed memory compared to placebo.

Aim 2: A significant interaction between Treatment Condition and Time will indicate that differences between delayed recall in the "drug context" (week 3) vs. "no-drug context" (week 4) are different for different treatment conditions. Dummy variable coding for treatment condition, comparing modafinil to each of the 2 other treatment conditions, is expected to show significantly greater reduction of recall memory between weeks 3 and 4 for those taking modafinil compared to other conditions due to the change in drug context in week 4.

Aim 3: We hypothesize a Treatment Condition main effect for immediate memory, such that pairwise comparisons among the 3 conditions (using the Sidak correction for multiple comparisons) will show that 250 DCS and 100 modafinil will significantly enhance immediate memory compared to placebo.

Exploratory Analyses: We will examine whether baseline antidepressant use, mood (BDI-II), fatigue (FSS), attentional/executive function (COWAT,TMT-B), HVLT total score, and/or digits backward performance moderates active study drug effects relative to the placebo condition. Examination of associations between performance on immediate memory scores and delayed recall (including ICAT performance at Weeks 2-4) will also be examined in each study drug condition to help clarify the nature of in-session memory augmentation vs. retention effects across the weeks of testing. The effect of treatment condition on BDI will also be examined using the same analysis as Aim 1 (including pairwise comparisons among the groups). We expect BDI to be enhanced in 100 Modafinil, and explore whether it will also be enhanced in 250 DCS. We will also examine if improved memory mediates the changes in BDI.

Power Analysis. We used PinT 2.12 (a program to calculate effect sizes in mixed models) to calculate the smallest N necessary to detect a medium effect size (d=.5) with .80 power for the

specific hypothesized comparisons in Aims 1, 2, and 3. We conservatively assumed that 15 covariates (including interaction terms between covariates and both Treatment Condition and Time) will be included as additional predictors in each analysis (the power is greater if no interaction terms are necessary). We also assumed 10% attrition by week 4, although the mixed effects models include all participants regardless of missing data. Since there are multiple comparison tests, we used the conservative Bonferroni correction and set the p level at .05/3=.0167. **Aim 1:** A total sample size of 77 is necessary to detect a medium effect with .80 power. **Aim 2:** A sample size of 59 is necessary to detect a medium effect size for the interaction between time and individual treatment contrasts. **Aim 3:** Since the analysis in Aim 3 is identical to that in Aim1, 77 participants are required for Aim 3. Thus, a total sample size of 77 will give us at least .