Statistical Analysis Plan
Pharmacologically-augmented Cognitive Therapies (PACTs) for Schizophrenia
NCT02634684
5R01MH059803-15
Latest IRB approval date: July 9, 2020
IRB expiration date: July 8, 2021

The primary statistical considerations for these data are those required to test the primary hypotheses that amphetamine (AMPH) would enhance: 1) computerized targeted cognitive training (TCT) performance and 2) sensorimotor gating, in biomarker-identified schizophrenia (SZ) patients. The operational measure of TCT performance was the change in auditory processing speed (APS) after 1 hour of a frequency modulation auditory discrimination task. The operational measure of sensorimotor gating was prepulse inhibition of startle (PPI), and specifically %PPI at a 60 ms prepulse interval. Neurocognition was tested using the MATRICS Comprehensive Cognitive Battery (NMCCB). The primary hypotheses were tested by repeated-measure ANOVA of APS change (TCT) or %PPI with AMPH dose and prepulse interval (PPI: 10, 20, 30, 60 or 120 ms) as within subject factors.

Specific analyses for primary hypotheses:

1. PPI: For statistical analyses of PPI, repeated measure ANOVAs identified the main and interaction effects of diagnosis (HS vs SZ) and dose (placebo vs 10 mg) on the dependent measures. These ANOVAs (main effects and two- and three-way interactions) were used to test the primary hypotheses (eg, amphetamine will enhance 60 ms PPI and MCCB performance in patients). Startle magnitude, latency, and %PPI were averaged across right and left eyes, treated as continuous measures, and analyzed with repeated measure analyses of variance (ANOVAs) with appropriate post hoc comparisons. Startle measures were analyzed only in startle 'responders', ie, subjects for whom mean startle magnitude on pulse-alone trials was $\geqslant$10 units (1.31 μV/unit; Swerdlow et al, 2006a, 2014, 2017). Based on known sex differences in PPI (Swerdlow et al, 1993), sex was included as a between factor in all primary analyses of PPI. Post hoc analyses assessed specific effects of variables (eg, COMT genotype) on the primary outcomes. Once ANOVAs detected significant effects of amphetamine on PPI, post hoc exploratory correlations were assessed among changes in PPI and neurocognition, and subjective and autonomic drug responses and clinical variables. MCCB T-scores were also analyzed via ANOVAs, with diagnosis as a between- and drug, test order and cognitive domain as within factors. Based on known effects of amphetamine on attention, a priori post hoc analyses of amphetamine effects on the MCCB attention/vigilance domain were pursued.

To assess the subjective effects of amphetamine, visual analogue scale (VAS) scores in mm were first reduced by subtracting pre-pill values from the value at each post-pill time point. To calculate the magnitude of the amphetamine effect, a difference score (amphetamine minus placebo values) was then calculated for each post-pill time point, and treated as a continuous measure for regression analyses. Data for the subjective and autonomic effects of amphetamine from the majority (n=60) of the present subjects were previously reported (Swerdlow et al, 2016b). Alpha for planned comparisons and empirical findings was set at 0.05 and 0.01, respectively.

2. TCT "learning": Repeated measure ANOVAs identified main and interaction effects of diagnosis, dose (placebo vs 10 mg), and in some cases genotype (AA vs GG) on the dependent measures. These ANOVAs (main effects and 2- and 3-way interactions) were used to test the primary hypotheses (eg, amphetamine will enhance APS learning in patients). Post hoc analyses assessed specific effects of variables (eg, age) on the primary outcomes and evaluated more complex explanations for the findings (eg, state-dependent learning). Once ANOVAs detected significant effects of amphetamine on APS learning, post hoc exploratory correlations

were assessed among a measure of APS amphetamine sensitivity and baseline (screening) measures of event-related potentials (ERPs), PPI and neurocognition, and subjective and autonomic drug responses and clinical variables. TCT day 2 post-assessment data were lost from 1 HS due to computer failure. In addition, for 1 patient, placebo-day learning exceeded levels in the patient group or the inclusive group of all subjects, by 4.73 SD and 6.35 SD, respectively; this “outlier” value did not alter main statistical effects (main effect of drug on APS) but did impact correlations, and thus all APS data from this subject were omitted. To test primary hypotheses, alpha was .05. To test secondary hypotheses (5 predictive biomarkers), alpha was adjusted to .05/5 = .01.