Precision Mental Health: Evaluating Biotype-guided Interventions for Depression

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Statistical Analysis Plan

Primary Outcome
We will evaluate the primary cognitive control circuit measure by testing the effect of 8 weeks of guanfacine immediate release (GIR) using a general linear model (GLM). This model will include a within-subjects factor for treatment (pre- vs. post-treatment sessions) and a within-subjects repeated measures factor for cognitive control circuit function, comprising five measures: task-evoked activation of the dorsal anterior cingulate cortex (dACC), left dorsolateral prefrontal cortex (dLPFC), right dLPFC, and connectivity between these regions. The analysis will assess the main effect of treatment and, secondarily, the interaction between treatment and circuit measure. Planned paired t-tests will evaluate the effect of GIR on changes in individual circuit measures.

Secondary Outcomes
For secondary outcomes, GLMs will include treatment as a within-subjects factor and a repeated measures factor for variables with multiple observations. Cognitive behavioral performance will comprise six test measures of cognitive control (Maze, Digit Span, Verbal Interference Color and Word, Switching of Attention, and GoNoGo), and quality of life, four domains (physical health, psychological health, social relationships, and environment) as measured by the by the World Health Organization Quality of Life – Brief (WHOQOL-BREF) Scale. Planned paired t-test contrasts will test for the effect of GIR on change in each set of individual secondary measures in each general linear model. The secondary measures of depression symptom severity (measured by the 17-item Hamilton Depression Rating Scale and Quick Inventory of Depressive Symptoms-Self Report), global satisfaction with life (assessed using the Satisfaction With Life Scale), and suicidality (measured by the Columbia-Suicide Severity Rating Scale Ideation Score) are exceptions that do not have repeated measures.

Significance, Multiple Test Correction, and Handling Missing Data
A two-sided significance level of 0.05 will be applied to each analysis within each modality for both primary and secondary outcomes. Corrections for multiple testing across modalities will not be applied, as each outcome targets a distinct hypothesis about the effect of GIR on cognitive, behavioral, symptom, and functional measures. Effect sizes (Cohen's d) will be reported for each outcome, along with 95% confidence intervals, to aid interpretation of clinical meaningfulness. Missing data will be handled using listwise deletion.