Cover Page: ECT Current Amplitude and medial temporal lobe engagement (MH111826)

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Study Protocol and Statistical Analysis

*Study Protocol*

All subjects started the ECT series with right unilateral (d'Elia) electrode placement (28). Subjects were randomized and blinded to 600, 700, and 800 mA prior to the first ECT treatment. Subject randomization was completed with a random number generator prior to study initiation with a 1:1:1 ratio for each study arm. As determined by our preliminary data, 500 mA pulse amplitudes compromised efficacy. Subjects received clinical, neuropsychological, and imaging assessments pre- (V1), mid- (after the sixth ECT treatment, V2) and post-ECT (within one week of finishing the ECT series, V3). If subjects were non-responsive to the assigned pulse amplitude (< 25% reduction in from baseline $HDRS_{24}$ at the second visit), subjects then received bitemporal (BT) electrode placement (800 mA, 1.0 milliseconds (ms) pulse width) for the remainder of the ECT series (29).

Subjects received ultrabrief pulse width (0.3 ms) until a planned interim data analysis (n = 47) to ensure that the experimental arms were equipoise with the active comparator. The analysis demonstrated a trend towards the lower efficacy of the 600 mA arm. We subsequently increased the pulse width from ultrabrief (0.3 ms) to brief (1.0 ms) all treatment arms for the remainder of the study (n = 15). The rationale for the increased pulse width, as approved by the National Institutes of Health (NIH) and the study Data Safety Monitoring Board (DSMB), was to improve the efficacy of the lower amplitude arm. The strength-duration curve established that lower pulse amplitudes required longer pulse widths to elicit neuronal activation potential (30, 31). Thus, we reasoned that the increased pulse width may improve the neuronal activation potential and the antidepressant efficacy of the 600 mA arm.

The first ECT session determined individual seizure thresholds with subsequent treatments provided at six times the seizure threshold with similar adjustments to pulse train duration and frequency across all amplitude arms (32). Further adjustments to charge were permitted to ensure adequate seizure morphology and duration based on clinical judgment. Motor, electroencephalographic, and heart rate parameters were recorded for each treatment. The treating anesthesiologist determined the appropriate dose of methohexital, a general anesthetic, and succinylcholine, a depolarizing neuromuscular blocker.

*Statistical Analyses*

Clinical and demographic variables were assessed with chi-square or one-way analysis of variance. For the primary outcomes (change in $HDRS_{24}$ and HVLT-R retention raw score), we performed a full longitudinal model with an unstructured repeated measures covariance matrix on subjects who completed the study in the assigned treatment arm. Missing values for the depression and cognitive variables (14% of values) were imputed using regression multiple imputation with five iterations (33). We completed imputation for seven subjects that did not complete the final post-ECT assessment and for sparse missing cognitive values. When a subject had all their values imputed for a variable, then that subject was removed from the analysis of that variable. In addition, we performed a separate analysis with subjects receiving bitemporal electrode placement between V2 and V3. For depression outcomes, the dependent variable was HDRS at each visit and the independent variables included progress (time within the ECT series: pre-, mid-, and post-ECT), amplitude, age, sex, pulse width and the following interactions: progress/amplitude, progress/sex, and progress/pulse width. For primary cognitive outcomes, the dependent variable was HVLT-R retention scores at each visit with the same model plus the Test of Premorbid Functioning Standard Scores as an additional covariate. In addition to our primary cognitive outcome, we assessed secondary outcomes for the additional cognitive measures using the same cognitive statistical model. Follow-up contrasts included the following: 1) longitudinal changes within each amplitude (e.g., $HDRS_{24}$ differences in 600 mA subjects between V1 and V2); 2) amplitude contrasts during the mid- and post-ECT assessments (e.g., $HDRS_{24}$ differences 600 and 700 mA at V2); 3) sex differences; and 4) pulse width differences. The amplitude contrasts were averaged for sex and pulse width with Tukey's method for multiple pairwise comparisons.