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Electroconvulsive Therapy Pulse Amplitude and Clinical Outcomes

Christopher C. Abbott, M.D., M.S., Davin Quinn, M.D., Jeremy Miller, M.D., Enstin Ye, M.D., Sulaiman Iqbal, B.S., Megan Lloyd, M.A., Thomas R. Jones, M.S., Joel Upston, M.S., Zhi De Deng, Ph.D., Erik Erhardt, Ph.D., Shawn M. McClintock, Ph.D., M.S.C.S.

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ABSTRACT

Introduction: *Electroconvulsive therapy (ECT) pulse amplitude, which determines the induced electric field magnitude in the brain, is currently set at 800–900 milliamperes (mA) on modern ECT devices without any clinical or scientific rationale. The present study assessed differences in depression and cognitive outcomes for three different pulse amplitudes during an acute ECT series. We hypothesized that the lower amplitudes would maintain the antidepressant efficacy of the standard treatment and reduce the risk of neurocognitive impairment.* ***Methods:*** *This double-blind investigation randomized subjects to three treatment arms: 600, 700, and 800 mA (active comparator). Clinical, cognitive, and imaging assessments were conducted pre-, mid- and post-ECT. Subjects had a diagnosis of major depressive disorder, age range between 50 and 80 years, and met clinical indication for ECT.* ***Results:*** *The 700 and 800 mA arms had improvement in depression outcomes relative to the 600 mA arm. The amplitude groups showed no differences in the primary cognitive outcome variable, the Hopkins Verbal Learning Test-Revised (HVLT-R) retention raw score. However, secondary cognitive outcomes such as the Delis Kaplan Executive Function System Letter and Category Fluency measures demonstrated cognitive impairment in the 800 mA arm.* ***Discussion:*** *The results demonstrated a dissociation of depression (higher amplitudes better) and cognitive (lower amplitudes better) related outcomes. Future work is warranted to elucidate the relationship between amplitude, electric field, neuroplasticity, and clinical outcomes.* (Am J Geriatr Psychiatry 2021; 29:166–178)

From the Department of Psychiatry (CCA, DQ, JM, EY, SI, ML, TRJ, JU), University of New Mexico, Albuquerque, NM; Noninvasive Neuromodulation Unit (ZDD), Experimental Therapeutics and Pathophysiology Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD; Department of Mathematics and Statistics (EE), University of New Mexico, Albuquerque, NM; Division of Psychology, Department of Psychiatry (SMM), UT Southwestern Medical Center, Dallas, TX; and the Division of Brain Stimulation and Neurophysiology (SMM), Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, NC. Send correspondence and reprint requests to Christopher C. Abbott M.D., M.S., Department of Psychiatry, University of New Mexico, Albuquerque, NM 87131 e-mail: cabbott@salud.unm.edu

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INTRODUCTION

Despite the proven antidepressant efficacy of electroconvulsive therapy (ECT) for depressive episodes,[1] neurocognitive impairment remains a major concern of treatment, especially in areas of episodic memory and executive function.[2] Demographic (age, premorbid intelligence, and years of education), depression severity, and ECT treatment parameters (pulse-width, dose-titration, amplitude, and electrode placement) influence ECT-mediated neurocognitive outcomes.[3] The impact of variable pulse amplitudes on clinical and cognitive outcomes has yet to be investigated.

Pulse amplitude, which dictates the induced electric field magnitude in the brain, is presently fixed at 800 or 900 milliamperes (mA) with modern ECT devices. However, such fixed amplitude values lack any clinical or scientific rationale.[4] Computer modeling has shown that 800 mA pulse amplitude exceeds the neuronal activation threshold of the entire brain by more than sixfold, despite efforts to localize current density by changing electrode placements.[5] Further, research in the late 1940s reported effective seizure induction with amplitude values that ranged between 233 to 544 mA.[6] Lower pulse amplitudes reduce the magnitude of the induced electric field that could potentially decrease the risk of neurocognitive side effects. Case reports demonstrated that 500 −600 mA is sufficient to generate seizure induction, although seizure morphology may be poorer compared to standard 800 mA.[7,8] Randomized trials that compared amplitudes assessed seizure efficiency but included no clinical outcomes.[9,10] Recent, small (n = 7−22) investigations have demonstrated that low amplitude ECT results in improvement of depression severity and reduced suicidal thoughts with concordant fewer neurocognitive side effects.[11,12] To date, larger, randomized controlled trials have yet to assess antidepressant and cognitive outcomes over a range of pulse amplitudes.

The present investigation was designed to assess the dose-response relationship between ECT pulse amplitude and antidepressant and cognitive outcomes (ClinicalTrials.gov Identifier: NCT02999269). Subjects were randomized to three different pulse amplitudes: 600, 700, and 800 mA with the latter representing the active comparator. Subjects received clinical, cognitive, and imaging assessments before, during (fixed after the sixth ECT treatment), and after the acute ECT series (variable number of treatments). The overall focus of this investigation was to determine the relationship between hippocampal electric field magnitude, neuroplasticity, and clinical outcomes. Here, we report the clinical outcomes as a function of amplitude. Our primary clinical outcomes include depression severity (Hamilton Depression Rating Scale 24-item ($HDRS_{24}$) total score[13]) and cognition (Hopkins Verbal Learning Test-Revised (HVLT-R) Percent Retention Raw Score[14]). In addition to the primary cognitive outcome, we assessed amplitude differences on secondary cognitive measures. We hypothesized that the higher amplitude arms would have a superior antidepressant response with increased cognitive risk.

METHODS

Participants

The University of New Mexico (UNM) Human Research Protections Office (HRPO) approved this investigation. All subjects signed procedural consent or assented to the research protocol with the surrogate medical decision-maker providing consent. Subjects were recruited from December 2016 to September 2019. Subjects had a diagnosis of major depressive disorder (single episode or recurrent, non-psychotic or psychotic episodes, diagnosis confirmed with two independent psychiatric evaluations) and met the clinical indication for ECT. Additional inclusion criteria included right-handedness, which was confirmed with the Edinburgh Handedness Inventory,[15] and an age range between 50 and 80 years of age. This is the optimal age range to investigate targeted medial temporal lobe engagement and clinical outcomes. Older age is associated with an increased probability of antidepressant response[16,17] and ECT-mediated cognitive impairment.[18] Exclusion criteria included neurological or neurodegenerative disorder (e.g., history of head injury with loss of consciousness > 5 minutes, epilepsy, Alzheimer's disease), other psychiatric conditions (e.g., schizophrenia, schizoaffective disorder, bipolar disorder), or substance (except nicotine) or alcohol use disorder, and contraindications to magnetic resonance imaging (MRI). In order to reduce medication confounds, all subjects tapered and discontinued their scheduled psychotropic medications prior to the baseline assessment, but as-needed medications

were permissible for anxiety and insomnia: trazodone (maximal cumulative dose per day: 200mg), lorazepam (3mg) and quetiapine (200mg). All subjects who met eligibility criteria during active enrollment were offered participation in this study.

Clinical and Cognitive Assessments

Trained raters blinded to treatment-arm assignment performed the clinical and cognitive assessments at each visit. The assessments included the $HDRS_{24}$.[13] The initial study visit included the ECT Appropriateness Scale to assess the indication for ECT,[19] Maudsley Staging Method for Treatment Resistance,[20] Medical History form to gauge overall medical burden, and Framingham Stroke Risk Profile to measure vascular burden.[21]

The baseline visit included the Montreal Cognitive Assessment (MoCA), a measure of global cognitive function to screen for preexisting global cognitive impairment[22] and the Test of Premorbid Function (TOPF), an estimate of premorbid intellectual function.[23] The remaining cognitive measures were completed at each visit. The HVLT-R measured learning and immediate recall of 12 semantically related words across three learning trials, delayed recall, and recognition memory.[14] To minimize practice effects, we used alternate forms of the HVLT-R (Forms 1 and 4) and randomized the order across participants.[24] Following the published HVLT-R manual, we computed the HVLT-R retention raw score for our primary cognitive outcome measure.[25] The percent retention score measured hippocampal-dependent memory function and reduced the possibility of over-estimating memory function from immediate and delayed free recall scores.[25] The Dot Counting Test measured test-taking effort.[26] The Delis Kaplan Executive Function System (DKEFS) measured processing speed, verbal fluency, inhibition, and cognitive flexibility.[27] Specific measures from the DKEFS included Verbal Fluency, Category Fluency, and Color-Word Interference. The entire neuropsychological battery was well tolerated with a completion time of less than 60 minutes.

Electroconvulsive Therapy and Study Design

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 (Supplemental Material Section 1). 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 nonresponsive 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 toward 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 and the study Data Safety Monitoring Board, 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] (Supplemental Material Section 2). 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.

RESULTS

Subject Demographic, Clinical, and Treatment Characteristics

Demographic, clinical, and neuropsychological data are summarized in Table 1 by treatment arm. The average age for the subjects (n = 62; 18 males) was 65.6 years (standard deviation (SD) 8.4). Twenty subjects had a depressive episode with psychotic features, and six had a single episode. The average duration of a depressive episode was 18.0 (SD 21.9) months. The number of previous depressive episodes was 4.1 (SD 3.9), and the average age of depression onset was 36.3 (SD 19.5) years. The lifetime duration of depressive episodes was 7.3 (SD 9.9) years. The average number of antidepressant treatment trials prior to ECT was between 3 and 4 antidepressant trials reflecting a moderate level of treatment resistance. The ECT Appropriateness Scale of 8.1 (SD 1.5) (maximal score of 10) supported the clinical indication for ECT.

The subject flow is summarized in Figure 1. Subjects received an average of 10.5 (SD 3.3) treatments for the acute ECT series. Treatment arms reflected a difference in the initial titration step ("steps" defined as incremental increases in pulse train duration and frequency to induce seizure activity). The 600 mA arm required the fourth (final or highest) titration step in 4 of 20 subjects ($x^2(6) = 17.83$, $p = 0.007$). However, the initial ($F_{2,59} = 1.05$, $p = 0.35$) and final charge ($F_{2,59} = 0.25$, $p = 0.78$) were similar across treatment arms. With the bitemporal electrode placement contingency, the overall response rate was 62.9% (39/62) and the remission rate was 40.3% (25/62). The attrition rate was 21.0% after randomization (13/62), which did not differ across treatment arms ($x^2(2) = 0.03$, $p = 0.98$). The transition to bitemporal electrode placement was also similar across all treatment arms ($x^2(2) = 1.5$, $p = 0.46$). Subjects had comparable side effects (headache, muscle aches, and nausea) across amplitude arms but no serious adverse events.

Depression outcome: Hamilton Depression Rating Scale — 24 item

Full longitudinal model: Progress ($F_{2,\ 72} = 211.43$, $p < 0.0001$), amplitude ($F_{2,\ 35} = 3.69$, $p = 0.04$), and progress-by-amplitude interaction ($F_{4,\ 72} = 2.65$, $p = 0.04$) contributed to depression outcomes. Age ($F_{1,35} = 0.46$, $p = 0.50$), sex ($F_{1,35} = 0.89$, $p = 0.35$), pulse width ($F_{1,35} = 0.33$, $p = 0.57$), and the remaining interactions ($p > 0.05$) did not contribute to depression outcomes (Fig. 2).

Longitudinal changes within each amplitude (Fig. 2A): The subjects in the 600 (pre-/post-ECT, $t_{72} = 5.09$, $p < 0.0001$), 700 (pre-/post-ECT, $t_{72} = 9.80$, $p < 0.0001$), and 800 mA (pre-/post-ECT, $t_{72} = 6.44$, $p < 0.0001$) conditions demonstrated improvement in depression severity. Subjects in the 600 mA arm had initial

TABLE 1. Demographic and Clinical Characteristics

Clinical and Demographic Features	600 mA (n = 20)	700 mA (n = 22)	800 mA (n = 20)	F or χ^2 (p value)
Age: mean (SD)	65.5 (8.3)	64.4 (6.7)	67.2 (10.2)	0.57 (0.57)
Sex: Male/Female	5/15	5/17	8/12	0.93 (0.63)
Single episode/recurrent	1/19	4/18	1/19	2.82 (0.24)
Psychotic/Non-psychotic	5/15	9/13	6/14	1.28 (0.53)
Episode duration (months): mean (SD)	16.5 (16.5)	14.2 (20.0)	23.7 (30.0)	1.06 (0.35)
Number of episodes: mean (SD)	4.9 (4.8)	3.14 (3.2)	4.32 (3.6)	1.06 (0.35)
Age of onset (years): mean (SD)	36.7 (17.9)	40.5 (22.4)	31.2 (17.4)	1.20 (0.31)
Lifetime duration (years): mean (SD)	5.7 (4.3)	7.3 (11.8)	8.8 (11.3)	0.50 (0.61)
Framingham Stroke Risk Profile (raw score): mean (SD)	8.7 (3.9)	7.6 (4.5)	8.8 (3.7)	0.49 (0.61)
ECT Appropriateness Scale: mean (SD)	7.9 (1.7)	8.4 (1.6)	8.25 (1.4)	0.49 (0.61)
Maudsley Treatment Failure: mean (SD)	2.0 (1.1)	1.9 (1.0)	2.2 (1.1)	0.42 (0.66)
Baseline MOCA: mean (SD)	23.4 (3.4)	24.1 (3.5)	24.8 (3.0)	1.00 (0.38)
ECT charge and seizure duration				
Titration step (% n)	1 (0%) 2 (15%) 3 (60%) 4 (25%)	1 (4.5%) 2 (54.5%) 3 (4.1%) 4 (0%)	1 (0%), 2 (50%) 3 (50%) 4 (0%)	17.8 (.007)
Titration charge (mC): mean (SD)	41.0 (21.0)	32.3 (19.8)	41.8 (29.4)	1.06 (0.35)
Final step (% n)	1 (0%) 2 (5%) 3 (40%) 4 (55%)	1 (0%) 2 (22.7%) 3 (50%) 4 (27.3%)	1 (0%) 2 (35%) 3 (45%) 4 (20%)	8.6 (.07)
Final charge (mC): mean (SD)	315.3 (102.2)	286.7 (146.7)	313.5 (182.7)	0.25 (0.78)
Average charge (mC): mean (SD)	241.0 (100.0)	218.3 (115.5)	230.3 (139.7)	0.19 (0.83)
RUL treatment number: mean (SD)	7.8 (2.4)	8.1 (2.6)	7.8 (2.8)	0.14 (0.87)
EEG seizure duration (s): mean (SD)	46.2 (14.8)	51.2 (16.6)	52.5 (18.2)	0.83 (0.44)
Baseline Measures				
Hamilton Depression Rating Scale - 24 items: mean (SD)	36.95 (7.8)	37.91 (7.5)	33.75 (6.7)	1.81 (0.17)
Hopkins Verbal Learning Test - Revised Retention Raw Score: mean (SD)	68.4 (40.4)	48.7 (36.9)	59.65 (38.7)	1.4 (0.26)

F-statistic degrees of freedom (2, 59)
x^2 degrees of freedom (2) for clinical and demographic features
x^2 degrees of freedom (6) for titration steps

improvement (Pre-/Mid-ECT: $t_{72} = 9.26$, $p < 0.0001$) followed by a response plateau (Mid-/Post-ECT: $t_{72} = -0.41$, $p = 0.91$).

Amplitude contrasts at mid- and post-ECT (Fig. 2B): The mid-ECT contrasts by amplitude were similar (600/700 mA: $t_{35} = 0.39$, $p = 0.92$; 600/800 mA: $t_{35} = 0.81$, $p = 0.70$; 700/800 mA: $t_{35} = 0.47$, $p = 0.88$). The post-ECT contrasts by amplitude demonstrated lower (improved) post-ECT depression ratings in the 700 and 800 mA arms relative to 600 mA arm (600/700 mA: $t_{35} = 3.72$, $p = 0.002$; 600/800 mA: $t_{35} = 2.66$, $p = 0.03$), but the 700 and 800 mA arms did not differ ($t_{35} = -0.70$, $p = 0.77$). By the end of the ECT series, subjects in the 600 mA condition had a final $HDRS_{24}$ total score 10 and 8 points higher than the 700 and 800 mA arms, respectively.

Sex and pulse width differences (Fig. 2C, D): Sex and pulse width had similar response trajectories and depression outcomes ($p > 0.05$).

Primary cognitive outcome: HVLT-R Retention Raw score

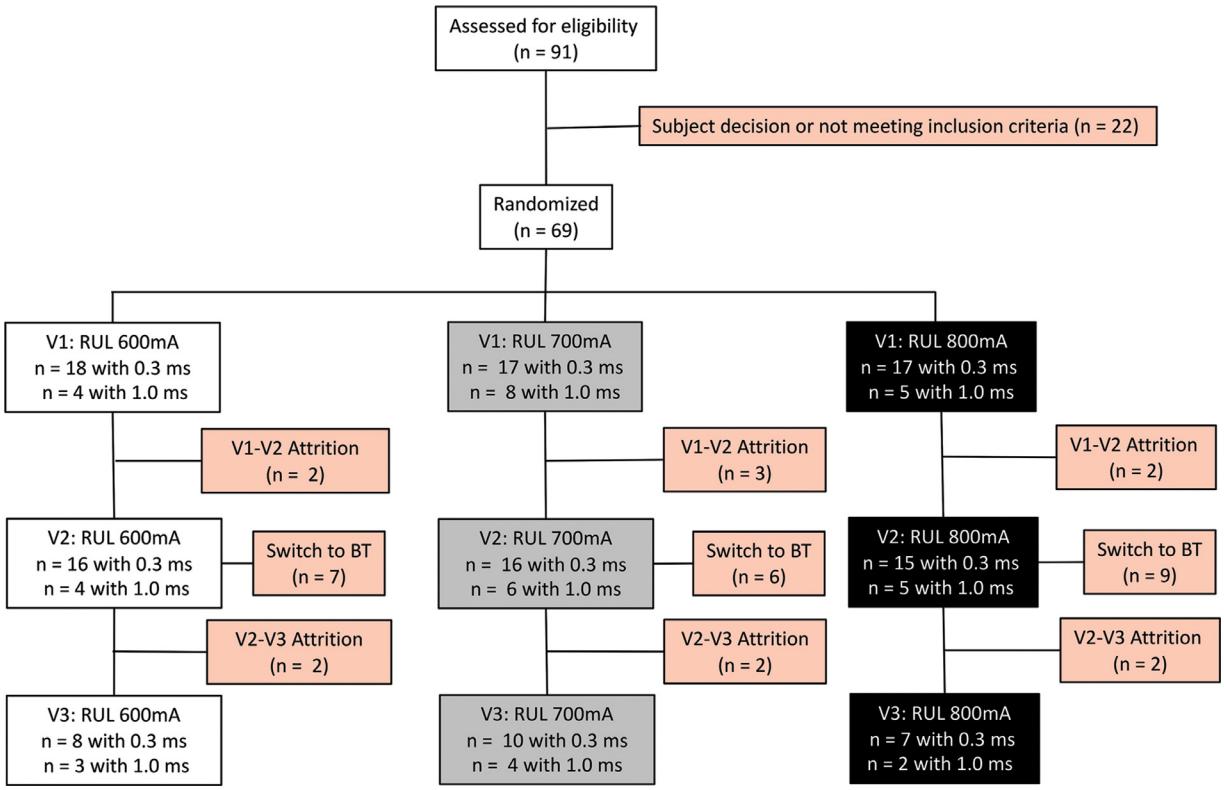
Full longitudinal model: Progress ($F_{2,71} = 0.70$, $p = 0.50$), amplitude ($F_{2,35} = 1.03$, $p = 0.37$), age ($F_{1,35} = 0.74$, $p = 0.40$), sex ($F_{1,35} = 2.51$, $p = 0.12$), pulse width ($F_{1,35} = 0.36$, $p = 0.55$), TOPF-Standard score total ($F_{1,71} = 0.68$, $p = 0.41$), and the interactions ($p > 0.05$) did not contribute to the HVLT-R Retention scores (Fig. 3).

Longitudinal changes within each amplitude (Fig. 3A): All amplitude arms had similar HVLT-R retention performance throughout the ECT series ($p > 0.05$).

Amplitude contrasts at mid- and post-ECT (Fig. 3B): Mid-, and post-ECT contrasts demonstrated similar HVLT-R retention performance across all amplitude arms ($p > 0.05$).

Sex and pulse width differences (Fig. 3C, D): Sex and pulse width had similar HVLT-R retention score trajectories and outcomes ($p > 0.05$).

FIGURE 1. Subject flow from recruitment and screening to the post-ECT assessment.



Secondary cognitive outcomes

We performed a likelihood-ratio test comparing the full model (with the "progress" variable) to the reduced models (without the progress variable and progress interactions). The likelihood ratio test indicates the degree that the progress variable explains the variability in the cognitive response variable. Large text statistics and small p values indicate a greater relationship with the progress variable and cognitive outcome. Table 2 summarizes these results from most to least sensitive for the detection of ECT-induced cognitive impairment. We focused on the two most sensitive measures for detection of ECT cognitive impairment in our sample, the DKEFS Letter and Category and Fluency tests.

Full longitudinal model: For Letter Fluency, progress ($F_{2,71} = 11.15$, $p = 0.0001$) and the Test of Premorbid Functioning ($F_{1,71} = 15.42$, $p = 0.0002$) contributed to the overall model. For Category Fluency, progress ($F_{2,71} = 16.56$, $p < 0.0001$), Test of Premorbid Functioning ($F_{1,71} = 4.88$, $p = 0.03$), and the progress-by-pulse width interaction ($F_{2,71} = 7.69$, $p = 0.0009$) contributed to the overall model (Fig. 4).

Longitudinal changes within each amplitude (Fig. 4A): For the Letter Fluency, the 600 mA arm had no performance change (pre-/post-ECT: $t_{71} = 1.13$, $p = 0.50$). In contrast, the 700 and 800 mA arms had impaired Letter Fluency performance (700 mA pre-/post-ECT: $t_{71} = 3.19$, $p = 0.006$; 800 mA pre-/post-ECT: $t_{71} = 3.46$, $p = 0.003$). For Category Fluency, the 700 mA arm had no performance change (pre-/post-ECT: $t_{71} = 1.53$, $p = 0.28$). The 600 and 800 mA arms had impaired Category Fluency performance (600 mA pre-/post-ECT: $t_{71} = 2.50$, $p = 0.04$; 800 mA pre-/post-ECT: $t_{71} = 3.06$, $p = 0.009$).

Amplitude contrasts at mid- and post-ECT (Fig. 4B): Mid-, and post-ECT contrasts demonstrated similar Letter and Category Fluency performance across all amplitude arms ($p > 0.05$).

FIGURE 2. Primary antidepressant outcome (Hamilton Depression Rating Scale 24-items, $HDRS_{24}$) for right unilateral electrode placement. [A–D] The black dots are estimated marginal means, the blue bars are 95% confidence intervals, and the red arrows are for the comparisons between means; if the red "comparison arrow" from one mean does not overlap an arrow from another group, the difference is significant at a Tukey-HSD corrected significance level. [A] Longitudinal changes within each amplitude. The 600, 700, and 800 mA arms had early improvement, but the 600 mA arm had a response plateau after the mid-ECT assessment. [B] Amplitude contrasts at each assessment. Relative to the 600 mA arm, the 700, and 800 mA arms had lower (improved) post-ECT depression ratings. [C] Sex differences. Male and female subjects did not have differences in depression outcome. [D] Pulse width differences. Brief (1.0) and ultrabrief (0.3) pulse widths did not have differences in depression outcome.

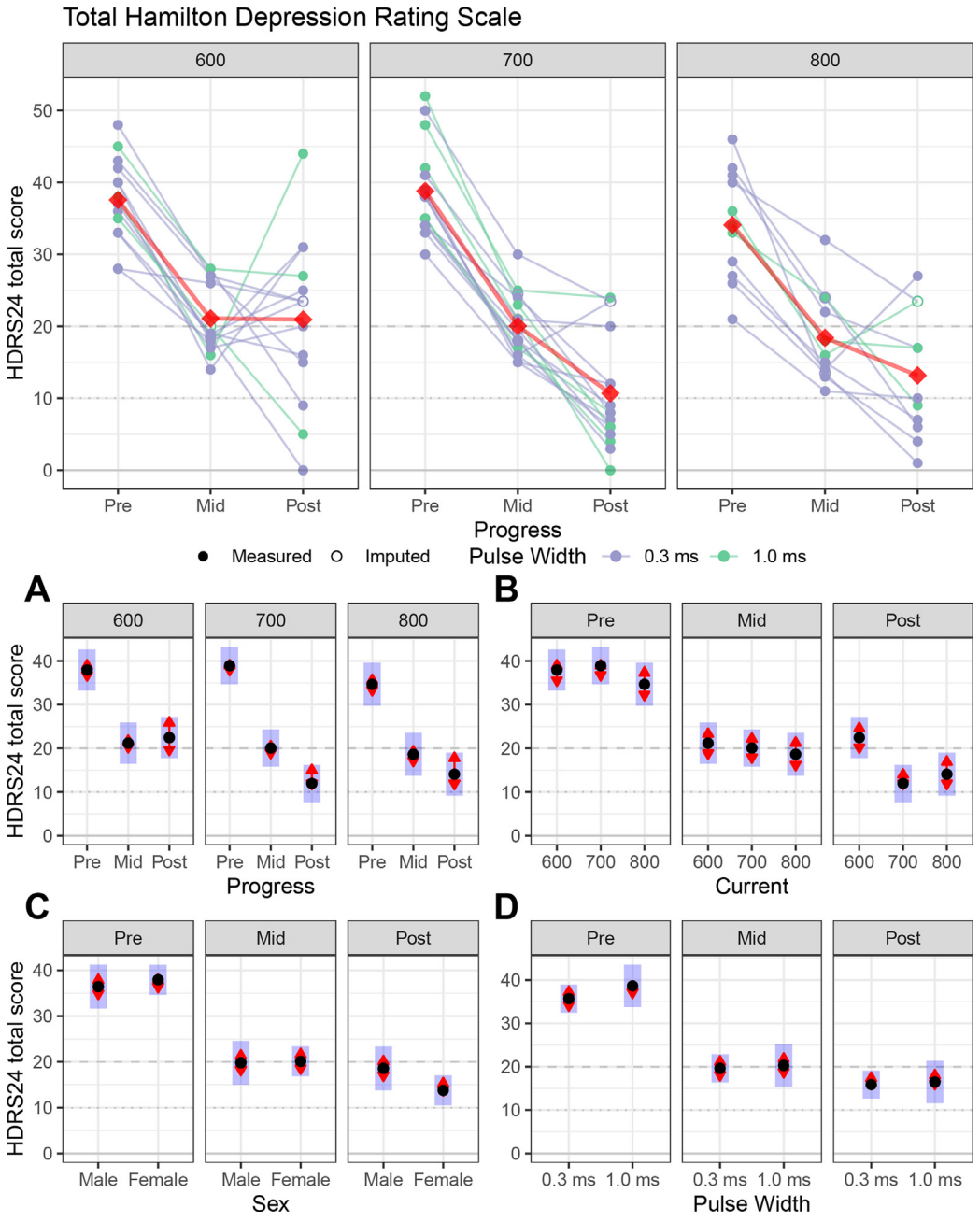


FIGURE 3. Primary cognitive outcomes (Hopkins Verbal Learning Test-Revised Retention Raw Scores, HVLT-R Retention Raw Score) for right unilateral electrode placement. For legend, see Figure 2. [A] Longitudinal changes within each amplitude. HVLT-R Retention Raw Score performance was similar throughout the ECT series for each amplitude arm (see Figure 2A for figure legend). [B] Amplitude contrasts at each assessment: Amplitude arms did not have HVLT-R Retention Raw Score differences at the mid- or post-ECT assessments. [C] Sex differences. Male and female subjects did not have HVLT-R Retention Raw Score performance differences. [D] Pulse width differences. Brief (1.0) and ultrabrief (0.3) pulse widths did not have HVLT-R Retention Raw Score differences.

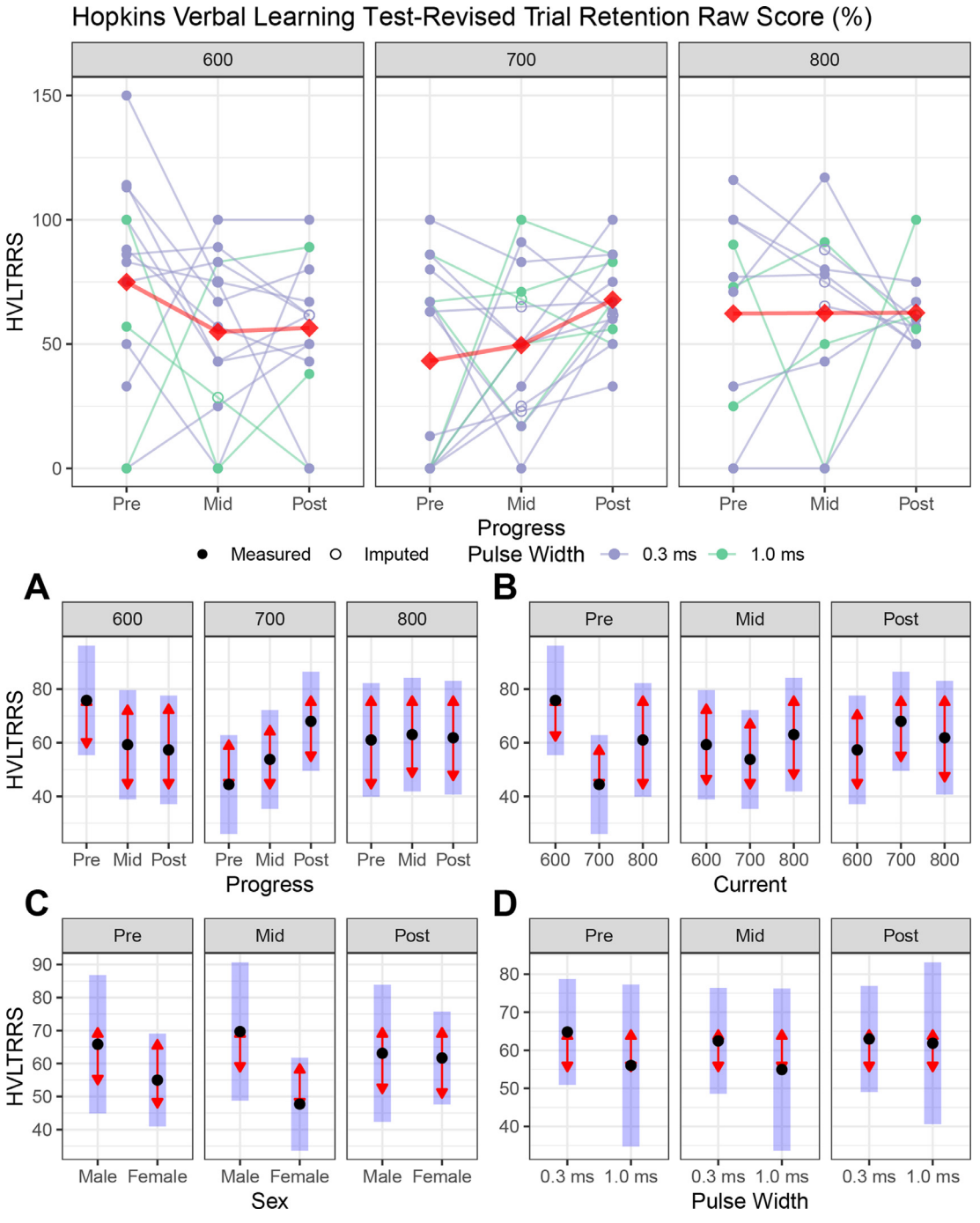


TABLE 2. Primary and Secondary Cognitive Measures. The Likelihood-Ratio Test to Assess Ordered the Neuropsychological Tests From Most to Least Sensitive to Detect ECT-Mediated Cognitive Impairment

Neuropsychological Test	Likelihood Ratio Test Statistic	Likelihood Ratio p value
DKEFS Category Fluency Scaled Score	44.85	0.0000
DKEFS Letter Fluency Scaled Score	28.02	0.0018
Dot Counting Mean Ungrouped Time	20.25	0.0270
Dot Counting Mean Grouped Time	19.32	0.0363
DKEFS Category Switching Accuracy Scaled Score	17.42	0.0656
HVLT Total Recall T-score	17.18	0.0705
DKEFS Color Word Interference Condition 3 Scaled Score	16.39	0.0891
DKEFS Color Word Interference Condition 4 Scaled Score	13.05	0.2210
HVLT-R Total Recall Raw Score	12.52	0.2520
HVLT-R Trial 1 Free Recall Raw Score	12.15	0.2750
HVLT-R Delayed Recall Raw Score	11.56	0.3152
HVLT-R Retention Raw Score	10.29	0.4156
HVLT-R Delayed Recall T-Score	9.22	0.5112

DKEFS: Delis Kaplan Executive Function System; HVLT-R: Hopkins Verbal Learning Test-Revised.

Sex and pulse width differences (Fig. 4C, D): For Letter Fluency, sex had similar trajectories and outcomes ($p > 0.05$). The progress-by-pulse width interaction for Letter Fluency was related to impaired mid-ECT performance for brief pulse width ($t_{35} = 2.67$, $p = 0.01$); the pulse width differences in Letter Fluency were no longer evident post-ECT ($t_{35} = 1.36$, $p = 0.18$). For Category Fluency, sex and pulse width had similar trajectories and outcomes ($p > 0.05$).

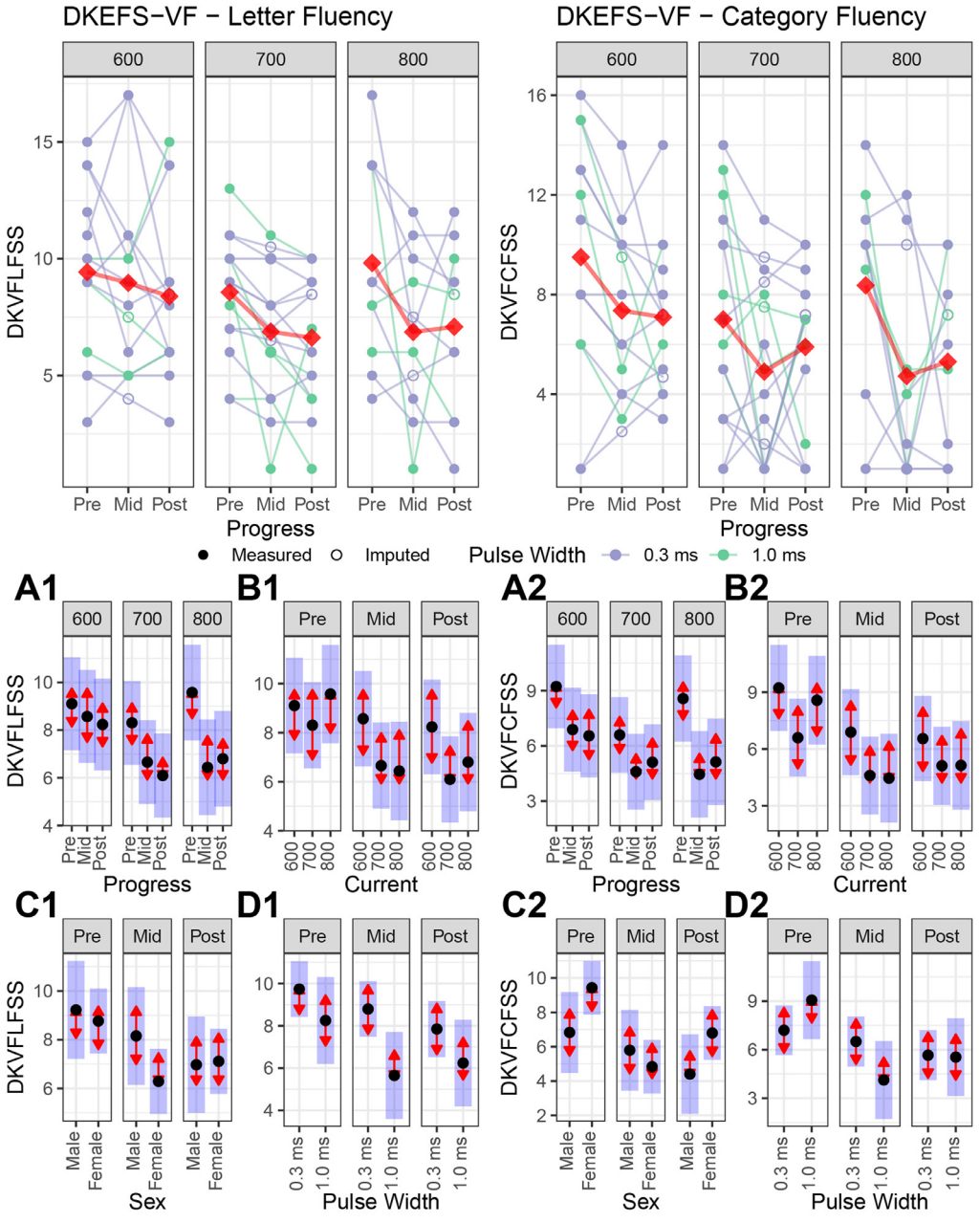
Subjects who were non-responsive to the assigned pulse amplitude received bitemporal electrode placement (800 mA, 1.0 ms pulse width) for the remainder of the ECT series. The bitemporal clinical and cognitive results are presented in Supplemental Material Section 3.

DISCUSSION

This double-blind, randomized clinical trial compared clinical and cognitive outcomes with ECT administered with 600 (experimental), 700 (experimental), and 800 mA (active comparator). The study sample included older subjects (age: 50–80 years) with a major depressive disorder who met clinical indications for ECT. Other ECT parameters (frequency and pulse train duration) were fixed within each amplitude arm and based on the initial seizure titration and subsequent adjustments to charge based on clinical judgment. The subjects randomized to the 600 mA arm had worse post-ECT depression outcomes relative to the 700 and 800 mA arms. The primary cognitive outcome, the HVLT-R Retention Raw Score, was insensitive to amplitude-mediated cognitive impairment. However, secondary cognitive outcomes, such as the DKEFS Verbal Fluency variables, were more sensitive to the detection of amplitude mediated neurocognitive impairment in the 800 mA arm. Overall, the results provide new evidence that amplitude is an important ECT parameter that differentially impacts antidepressant (higher amplitudes better) and cognitive (lower amplitudes better) outcomes.

The subjects in the 600 mA arm had inferior post-ECT depression outcomes. Our post-ECT depression outcomes diverge from previous investigations with 500 mA ECT that demonstrated improved depression outcomes.[11,12] The subjects randomized to the 600 mA arm in this study demonstrated an early mid-ECT response (25% reduction in $HDRS_{24}$) that was equivalent to the 700 and 800 mA arms. The 600 mA subjects' rate of improvement failed to continue in the second half of the ECT series with equivalent pre- and post-ECT depression outcomes. The reasons for the atypical low amplitude response trajectory are unclear but may be related to placebo response or the modest impact of seizure activity with sub-therapeutic stimulation. All treatment arms had similar seizure duration throughout the ECT series (forthcoming analysis will focus on seizure morphology related to pulse amplitude). Similar to RUL at seizure threshold and bitemporal with ultrabrief pulse width, the ineffectiveness of the 600 mA arm adds to the evidence that seizure activity is "necessary but not sufficient" for clinical response.[34] Our results differ from recent

FIGURE 4. Secondary cognitive outcomes included the Delis Kaplan Executive Function System (DKEFS) Letter and Category Fluency. For legend, see Figure 2. [A] Longitudinal changes within each amplitude. For the Letter Fluency (A1), the 600 mA arm had no change in performance, but the 700 and 800 mA arms had impaired performance. For Category Fluency (A2), the 700 mA arm had no change in performance, but the 600 and 800 mA arms had impaired performance. [B] Amplitude contrasts at each assessment: Amplitude arms did not have Letter (B1) or Category (B2) Fluency differences at the mid- or post-ECT assessments. [C] Sex differences: Male and female subjects did not have Letter (C1) and Category (C2) Fluency performance differences. [D] Pulse width differences. Brief pulse width (1.0 ms) was associated with worse Letter Fluency (D1) at the mid-ECT assessment, but the post-ECT assessment did not demonstrate Letter Fluency differences. Brief (1.0) and ultrabrief (0.3) pulse widths did not have Category Fluency (D2) differences.



low amplitude (500 mA) investigations that demonstrated improvement in depression severity.[11,12] This difference in findings could be related to study methodology as those investigations included relatively younger adult subjects (~40 years average), heterogeneous patient samples (mood and psychotic disorders), and different primary endpoints (seizure initiation or suicidality).

Contrary to the a priori hypothesis that the ECT amplitude conditions would have differential effects on memory function, this study found equivalent memory function across all three amplitude conditions. The findings of little change on the HVLT-R are similar with one prior study,[35] but are in stark contrast to consistent evidence over the past three decades that have demonstrated that ECT negatively impacts verbal learning and memory.[36,37] The HVLT-R may have less cognitive demand than other complex verbal learning and memory measures (e.g., Rey Auditory Verbal Learning Test, California Verbal Learning Test),[38,39] and highlights that ECT may impact memory function through effects on executive function. Indeed, research has found that elderly adults with major depressive disorder have executive dysfunction that moderates memory function,[40] thus implicating frontotemporal neurocircuitry that underlies memory performance. While prior ECT research and new neuromodulation therapies (e.g., magnetic seizure therapy) [41] have aimed to minimize stimulation of the hippocampus in order to minimize or avoid memory adverse effects, it is possible that neuromodulation targeting needs to focus on both frontal and temporal lobe structures. As there is limited research regarding the complex association between memory, executive function, and ECT mediated cognitive adverse effect, future research is warranted to discern the underlying mechanisms by which ECT impacts cognition.[42] This direction of research is supported by the findings in this study, which are consistent with prior research[36,37] that ECT adversely impacts executive function, specifically letter (phonemic) fluency, inhibition, and cognitive flexibility.

Several limitations warrant discussion for interpretation of study findings. First, subjects discontinued scheduled antidepressant and antipsychotic medications prior to the first imaging assessment, but as-needed medications (lorazepam, quetiapine, trazodone) were permissible with dose restrictions during the ECT series. Second, our study focused on an older adult sample of ECT subjects (50–80 years) who received RUL ECT. The results may not be generalizable to younger adult ECT patients and other traditional (bitemporal or bifrontal) electrode placements. Third, our response and remission rates were modest and reflected the inclusive nature of subject recruitment (all subjects who met inclusion criteria were offered study participation) and mid-point demonstration of response in order to continue in the assigned treatment arm. Fourth, our study design included a change in pulse width (from 0.3 to 1.0 ms). The hypothesized rationale of increased efficacy in the lower amplitude arm with an increased pulse width (see Methods) was not supported. However, each amplitude arm had a very limited number of subjects with brief pulse width. The relationship between amplitude and pulse width will require more research.

The trade-off between clinical (improved with higher amplitudes) and cognitive (improved with lower amplitudes) outcomes demonstrates the trade-off between antidepressant and cognitive outcomes related to pulse amplitude. The majority of the subjects (n = 60) participated with neuroimaging acquisitions aligned with each clinical and cognitive assessment. Structural imaging (to be reported later) will determine electric field modeling for each subject and demonstrate significant variability within and overlap between each amplitude arm. Future work will address the translational implications of electric field variability within each amplitude arm. The "sweet spot" of antidepressant response and no cognitive impairment may be possible with individualized and precision amplitude dosing.

AUTHOR CONTRIBUTIONS

CA, DQ, ZD, EE, and SM designed the study. CA, DQ, EY, SI, ML, and SM completed assessments and quality assurance. CA, EE, SM, TJ and JU performed the analysis. All authors wrote, revised, approved, and agreed to be accountable to all apsects of the final manuscript.

DISCLOSURE

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SUPPLEMENTARY MATERIALS

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