Supplementary Materials

ECT Procedures

TABLE S1. Seizure Threshold Titration Schedule: Somatics Thymatron System IV

Step	Energy (%)	Program	Charge (mC)	Current (A)	Duration (s)	Frequency (Hz)	Pulse Width (ms)
Step 1	5	LOW 0.25	24.8	0.89	5.6	10	0.25
Step 2	10	LOW 0.25	49.7	0.89	5.6	20	0.25
Step 3	15	LOW 0.25	74.6	0.89	5.6	30	0.25
Step 4	20	LOW 0.25	99.4	0.89	7.4	30	0.25
Step 5	40	LOW 0.25	199.1	0.89	7.5	60	0.25

TABLE S2. Seizure Threshold Titration Schedule: MECTA spECTrum

Step	Parameter Set	Charge (mC)	Current (A)	Duration (s)	Frequency (Hz)	Pulse Width (ms)
Step 1	0.3 ms	24	0.8	2.5	20	0.3
Step 2	0.3 ms	48	0.8	5	20	0.3
Step 3	0.3 ms	72	0.8	7.5	20	0.3
Step 4	0.3 ms	100.8	0.8	7	30	0.3
Step 5	0.3 ms	192	0.8	8	50	0.3

ECT Timing and Session Procedures: Right unilateral (RUL) ECT was given with a Thymatron System IV device or MECTA SPECTRUM device. At baseline, 172 of 240 patients (71.7%) were treated with Thymatron; 68 (28.3%) with Mecta.

Seizure threshold (ST) was determined at the first treatment using the dose titration schedule described in Table S1 above. Dose at subsequent treatments was at 6 times ST. Three of 240 patients (1.3%) had a seizure threshold above possible "6x seizure threshold" but were kept in the study (listed as protocol violations) and were treated below their actual "6x seizure threshold" value.

A generalized seizure ≥ 15 s tonic-clonic motor activity was required for adequacy. Following an abortive or inadequate seizure, restimulation in the same session took place at a stimulus intensity 25% above the level that resulted in the abortive seizure, after a minimum 45 seconds to allow for dissipation of the refractory period following seizure elicitation. If seizure duration still remained below the motor (15 sec) duration cutoff, then the seizure was accepted for that particular treatment.

Blood pressure, pulse, ECG, and pulse oximetry were monitored prior to anesthetic induction and continuously during the procedure. Standardized anesthesia procedures included glycopyrrolate 0.2 mg IV only at the dose titration session, induction with methohexital (~1 mg/kg), muscle relaxation with succinylcholine (~0.75 mg/kg), and ventilation with 100% oxygen throughout. Glycopyrrolate was optional at other treatment sessions, as per clinical discretion. Seizure expression was monitored via left fronto-mastoid EEG, and EMG of the cuffed right foot to record motor manifestations.

Total stimulus charge and seizure duration: At baseline, the mean (±standard deviation) total stimulus charge charge was 30.5 mC ± 14.3; at last ECT, the mean charge was 276.6 mC ± 162.4. Mean motor seizure duration (determined by clinician) over all treatments was 29.2 sec ± 11.3; mean EEG seizure duration (determined by clinician) over all treatments was 48.7 sec ± 18.2.

Mid-Course Re-Titration during Phase 1: 32 of 126 patients (25.4%) who had 6 or more treatments had an increase in charge after treatment 6 and 25 out of 71 (35.2%) had an increase after treatment 9.

Missed Seizures: If no seizure was induced at a suprathreshold treatment session, the dosage was increased by 25% and the patient was restimulated. If the seizure was missed because of an increase in seizure threshold, the dosage used to obtain a seizure in this session was considered the new threshold, and the subsequent treatment was administered using a dosage at 6x the new threshold, or at maximal stimulator output in the case that 6x seizure threshold was higher than maximal stimulator output.

Abortive or Inadequate Seizures: If the motor seizure was less than 15 seconds (including the entire duration of the stimulus), the seizure was considered 'abortive' or 'inadequate.' Following an abortive or inadequate seizure, restimulation in the same session took place at stimulus intensity 25% above the level that resulted in the abortive seizure, after a minimum 45 seconds to allow for dissipation of the refractory period following seizure elicitation. If seizure duration still remained below the motor (15 sec) duration cutoffs, then the seizure was accepted for that particular treatment.

HAM-D Training Procedures

The Hamilton Rating Scale for Depression (Ham-D) has been used to assess depression severity for over 50 years (Hamilton 1960, 1967). Multiple versions of the scale now exist and improved inter-rater reliability has been shown with the addition of structured and semi-structured interviews (Miller, Bishop, Norman, & Maddever, 1985; Moberg et al., 2001; Potts, Daniels, Burnam, & Wells, 1990; Williams et al., 2008). The HAM-D has been shown to be a valid and reliable measure in the assessment of geriatric depression (Yesavage et al., 1982). The PRIDE study used a 24-item version of the HAM-D that includes a semi-structured interview for each item, as well as descriptions for rating anchors. In addition, detailed guidelines were developed by the PRIDE team to standardize administration and scoring procedures across sites and raters. Following initial training and review of study guidelines, raters independently scored training tapes developed by the Clinical Coordinating Center (CCC). Raters were certified only after scoring within specified criteria (deviation not greater than one point per item and three points of the total score) on three tapes in comparison to the study "consensus criteria" established by consensus between the CCC Principal Investigator (PI) and the Project Coordinator (PC). Ongoing consistency was achieved through rater review of additional training tapes, posted on the PRIDE study data management system web site (WebDCU). If a rater's scores were not within the consensus criteria, the Project Coordinator scheduled a call with the rater to review guidelines and discuss the rationale for item ratings. The patterns of rater scores were evaluated for evidence of rater drift over time, and measures of inter-rater reliability (IRR)

were required by the Manual of Operating Procedures (MOP) to exceed 0.8. The minimum IRR for PRIDE was 0.88. If indicated, corrective feedback (additional training sessions) was implemented by the CCC via in-person visits or videoconferences. Rating procedures were also reviewed at annual investigator meetings in special half-day rater training sessions and on bimonthly teleconferences conducted by the Project Coordinator and Study Neuropsychologist and attended by Raters and site Study Coordinators.

References

Miller, I. W., Bishop, S., Norman, W. H., & Maddever, H. (1985). The Modified Hamilton Rating Scale for Depression: reliability and validity. Psychiatry Res, 14(2), 131-142.

Moberg, P. J., Lazarus, L. W., Mesholam, R. I., Bilker, W., Chuy, I. L., Neyman, I., & Markvart, V. (2001). Comparison of the standard and structured interview guide for the Hamilton Depression Rating Scale in depressed geriatric inpatients. Am J Geriatr Psychiatry, 9(1), 35-40.

Potts, M. K., Daniels, M., Burnam, M. A., & Wells, K. B. (1990). A structured interview version of the Hamilton Depression Rating Scale: evidence of reliability and versatility of administration. J Psychiatr Res, 24(4), 335-350.

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Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., & Leirer, V. O. (1982). Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res, 17(1), 37-49.

Statistical Analysis

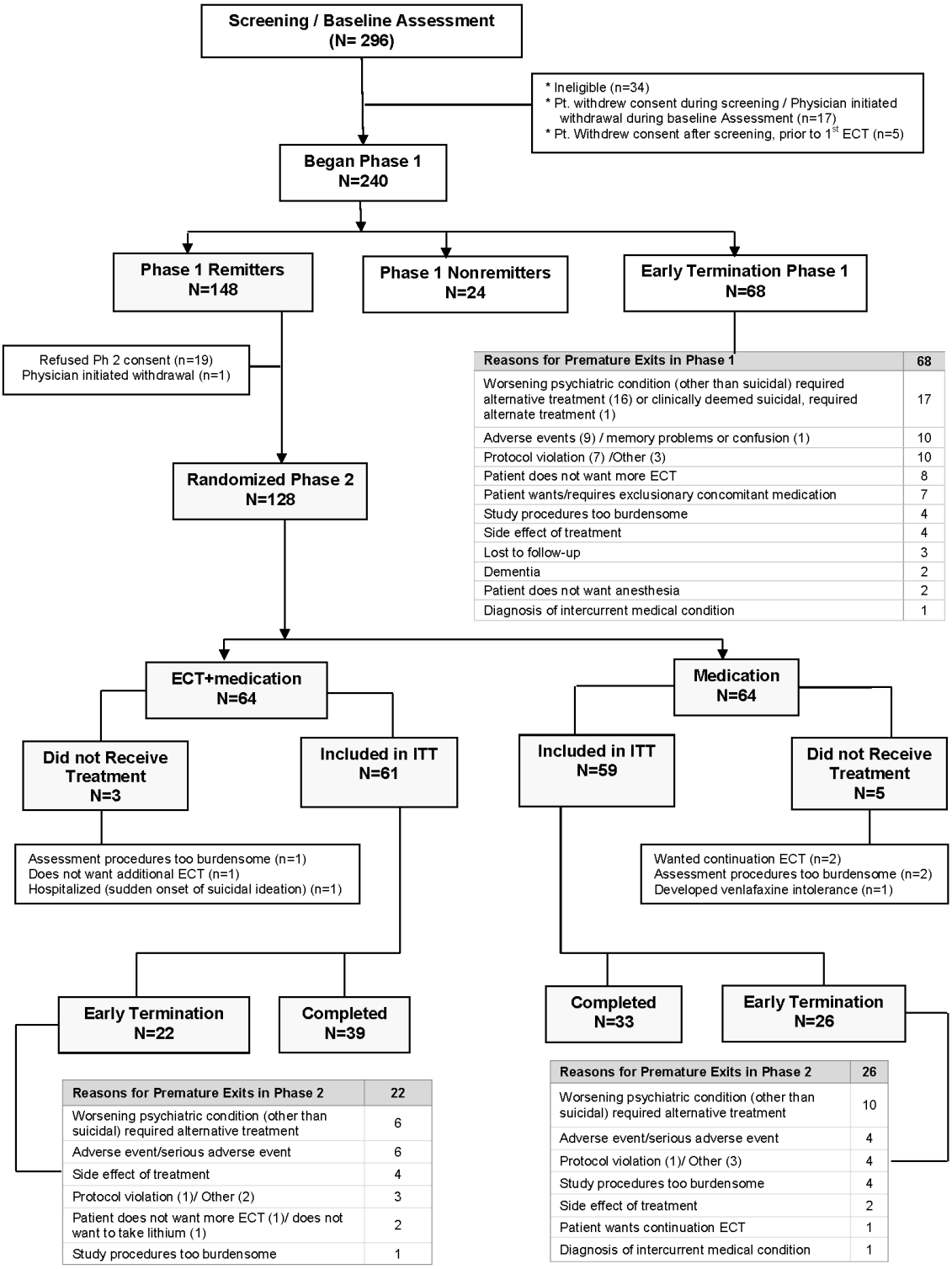
The primary efficacy outcome was Ham-D total score, measured at bi-weekly clinic visits over the 6-month study period, with the end-of-study (6-month) assessment as the primary time point for treatment comparisons. A mixed effects repeated measures longitudinal modeling approach (MMRM), with time (week) as categorical, was used to compare Ham-D total score for the ECT+medication and Medication groups at study end (week 24) (1,2). The basic model included fixed effects for treatment, time, time-by-treatment (interaction term) as independent variables and baseline Ham-D as an adjustment covariable. The correlation of repeated observations within subjects was taken into account by fitting an unstructured (UN) covariance to the correlated (R-side) errors. Potential clinical site effects and confounding by psychosis status were evaluated by adding these variables as covariables to the basic model. Differential effects of site or psychosis status on the treatment-outcome relationship were evaluated by including corresponding interaction terms in the model. The constancy of the effect of baseline Ham-D on the outcome over time was assessed by addition of baseline-by-visit interaction term. The interaction terms were not significant and inclusion of the additional variables in the more complex models did not substantively alter basic model results; therefore, results of the basic model were reported (Figure 2) to simplify interpretation. To compare the longitudinal trajectories (slopes) of treatment means, analyses were repeated using time as a continuous outcome (1). The presence of a curvilinear trend (rate of change in mean response depends on

time) was evaluated by inclusion of a quadratic term (time centered) and corresponding interaction in the model with the significance of the p-values and the likelihood ratio test used to determine retention of the higher order terms in the model. The quadratic term was not significant and results were reported assuming a linear trend in HAM-D means over time. A difference in trajectories (rate of change) of HAM-D means over the 24-week time period for ECT+medication vs Medication alone was indicated by a significant time-by-treatment interaction term in the baseline-adjusted and full (containing site and psychosis) models. Significance of the interaction term was tested using alpha=0.10. Following a significant interaction term, the significance of time trends (slopes based on main effect of time) within each treatment was evaluated using both the basic model (baseline-adjusted) and the full model (baseline, site, psychosis-adjusted).

References

1. Fitzmaurice GM, Laird NM, Ware JH. Applied Longitudinal Analysis, 2nd ed. John Wiley and Sons, Hoboken, NJ. 2011.
2. O'Kelly M, Ratitch B. Clinical trials with missing data. John Wiley and Sons, UK. 2014.

FIGURE S1. Patient Flow in Phase 1 and Phase 2 of PRIDE Study (CONSORT Tree)



Reasons for Premature Exits in Phase 1	68
Worsening psychiatric condition (other than suicidal) required alternative treatment (16) or clinically deemed suicidal, required alternate treatment (1)	17
Adverse events (9) / memory problems or confusion (1)	10
Protocol violation (7) /Other (3)	10
Patient does not want more ECT	8
Patient wants/requires exclusionary concomitant medication	7
Study procedures too burdensome	4
Side effect of treatment	4
Lost to follow-up	3
Dementia	2
Patient does not want anesthesia	2
Diagnosis of intercurrent medical condition	1

Reasons for Premature Exits in Phase 2	22
Worsening psychiatric condition (other than suicidal) required alternative treatment	6
Adverse event/serious adverse event	6
Side effect of treatment	4
Protocol violation (1)/ Other (2)	3
Patient does not want more ECT (1)/ does not want to take lithium (1)	2
Study procedures too burdensome	1

Reasons for Premature Exits in Phase 2	26
Worsening psychiatric condition (other than suicidal) required alternative treatment	10
Adverse event/serious adverse event	4
Protocol violation (1)/ Other (3)	4
Study procedures too burdensome	4
Side effect of treatment	2
Patient wants continuation ECT	1
Diagnosis of intercurrent medical condition	1

Safety Results: Adverse Events and Serious Adverse Events in Phase 2 of PRIDE Study

TABLE S3. Adverse Events (AE) for Patients Randomized to ECT+medication (n=61) and Medication alone (n=59)[a,b]

	ECT+		Relation to Treatment (n)		
Symptom (AE)	**Medication**	**Medication**	**Venlafaxine**	**ECT**	**Lithium**
Cardiovascular					
Abnormal EKG	1		NR	NR	Po
Chest pain - indigestion	1		Pr	NR	Po
Decreased heart rate	1		NR	Pr	NR
Orthostatic hypotension	1		Pr	NR	NR
Premature Atrial Complexes		1	Po	NR	U
Sinus pause	1		NR	Pr	NR
Supraventricular tachycardia	1		U	Po	U
Neurological					
Disequilibrium	1		NR	NR	Po
Gait instability		1	U	U	Po
Tremor, Tremor/Jerking	1	1	Po (2)	NR (2)	Po (2)
Other					
Abnormal BUN	1		NR	NR	Po
Cut/Abrasion of Knee	1				
Ecchymosis of Ring Finger		1	NR	NR	Po
Elevated PSA	1		NR	NR	NR
Frequent Urination -- Polyuria/Polydipsia	3		U (3)	NR (3)	Pr (3)
Severe nausea and dizziness	1		Po	NR	Po
Scalp Rash	1		NR	NR	Po
Vomiting		1	Po	NR	Po

[a] NR=Not related, U=Unlikely, Po=Possibly, Pr=Probably, D=Definitely.

[b] The data presented in the table are counts. A patient can have one or more symptoms and may be counted more than once. When the number of patients reporting a given symptom is more than one, the numbers in parentheses in the columns that list "Relation to treatment" (last 3 columns) indicate the number of patients (n) for each relationship. For example, 3 patients experienced frequent urination; all 3 were indicated as unlikely to be related (U) to venlafaxine, not related (NR) to ECT, and probably (Pr) related to lithium.

TABLE S4. Serious Adverse Events for Patients in the ECT+medication (n=61) and Medication Alone Treatment Arms (n=59)[a,b]

	ECT+		Relation to Treatment (n)		
Symptom (SAE)	**Medication**	**Medication**	**Venlafaxine**	**ECT**	**Lithium**
Behavioral/Psychiatric					
Worsening of depression		2	NR (2)	NR (2)	NR (2)
Suicidal ideation/thought	3[b]		NR(2), Po(1)	NR (3)	NR (3)
Emergence of Active Suicidality		1	NR	NR	NR
Psychiatric Hospitalization	1		NR	NR	NR
Psychosis		1	U	NR	U
Cardiovascular					
Acute cardiac ischemia		1	NR	NR	NR
Neurological					
Transient ischemic attack	1		NR	NR	NR
Other					
Abdominal pain followed by acute bleeding	1		U	NR	NR
Acute renal failure		1	NR	NR	NR
Broken nose		1	NR	NR	NR
Diarrhea, Small bowel obstruction	1		U	NR	U
Hip Fracture		1	NR	U	NR
Lithium Toxicity	1		NR	NR	D
Pneumonia	1		NR	NR	NR
Possible Serotonin syndrome	1		Po	NR	U
Urinary retention		1	NR	NR	NR

[a] NR=Not related, U=Unlikely, Po=Possibly, Pr=Probably, D=Definitely. The data presented in the table are counts. A patient can have one or more symptoms and may be counted more than once, e.g. 1 patient had small bowel obstruction at week 10 and diarrhea at week 20. When the number of patients reporting a given symptom is more than one, the numbers in parentheses in the columns that list "Relation to treatment" (last 3 columns) indicate the number of patients (n) for each relationship. For example, 3 patients experienced suicidal ideation; of these, 2 were indicated as not related (NR) to venlafaxine and 1 was indicated as possibly related (PO) to venlafaxine. All were indicated as not related (NR) to either ECT or lithium.

[b] One additional patient exited immediately after randomization and received no randomized treatment.