Geriatrics Journal Club:

Longitudinal Neurocognitive Effects of Combined ECT & Pharmacotherapy in MDD in Older Adults: Phase 2 of the PRIDE Study

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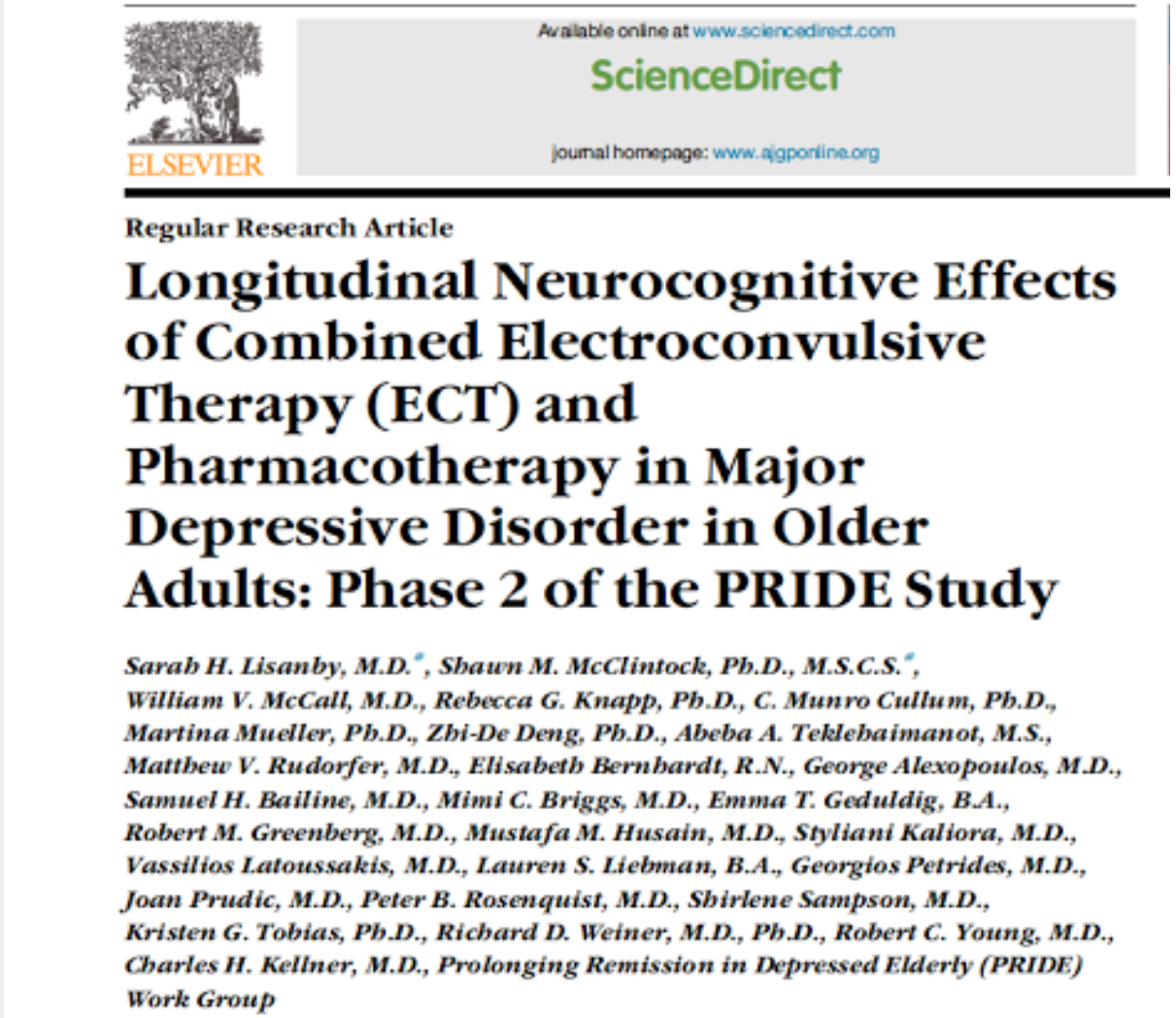
Overview

1. Background
2. Aims of the paper
3. Methods
4. Results
5. Authors' Conclusions
6. Limitations
7. Open Discussion

Why this paper?

- Relevance to Geriatricians & Geriatric Psychiatrists:
  - ECT remains the “gold-standard” for treatment of depression
  - One of the major concern of patients and families with ECT is neurocognitive impact.
  - This is particularly relevant in the geriatric population, who are more impacted by neurocognitive disorders
  - RUL-UB ECT has become more prominent, given its lesser impact on cognitive load[1]
  - ECT remains used in the geriatric population for MDD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Regular Research Article

Longitudinal Neurocognitive Effects of Combined Electroconvulsive Therapy (ECT) and Pharmacotherapy in Major Depressive Disorder in Older Adults: Phase 2 of the PRIDE Study

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Aims of the paper

- Limited evidence regarding neurocognitive outcomes of RUL-UB in older adults[2]
- Examine the neurocognitive outcomes at 6 months in older adults of phase 2 of the PRIDE stud

PRIDE Study

- NIMH funded study began in 2009
- 1240 adults over age 60
- Randomized, multi-center study
- Contrasts pharmacotherapy vs RUL-UB ECT + pharmacotherapy
- Medications (Venlafaxine (titrated to 225 mg, as tolerated) + Lithium)
- Lithium levels titrated to 0.4 – 0.6 mEq/L
- ECT was initially fixed with taper
- Taper ~ 1x/week x 4 weeks
- Initial HAM-D (24) >= 21

STABLE Algorithm

- Variable Treatments per week as outlined in table
- Lithium held 24 hours prior to ECT
- Lithium levels almost weekly for 8 weeks, then every 4 weeks
- Telephone HAM-D (24) screenings performed by trained

TABLE 1. Algorithm for Continuation ECT in Phase 2 for the ECT Plus Medication Arm: Symptom-Titrated, Algorithm-Based Longitudinal ECT (STABLE)[a]

Weeks 1–4: Fixed ECT schedule
One treatment 2–5 days after randomization, one treatment 7–12 days after randomization, one treatment 14–19 days after randomization, and one treatment 23–28 days after randomization (a total of four ECT treatments in 1 month)

Weeks 5–24: Symptom-Titrated ECT Schedule			
Treatments per Week	Description	Corresponding HAM-D Condition	Relapse Potential
0	Current symptom level very low *or* Current symptom level low to moderate, with only small drift from baseline level *or* Last two HAM-D scores in remitted range with a flat trajectory (remission stable with less than 2-point change from previous)	Current HAM-D score ≤6 Current HAM-D score 7–12 *and* is ≤2 points higher than baseline score Current HAM-D score 7–10 *and* previous score was 5–10 *and* current score is ≤2 points higher than previous score	Low Low Low
2	Current symptom level very high *or* Current symptom level moderate to high, with trajectory increasing rapidly and large drift from baseline	Current HAM-D score ≥16 Current HAM-D score 11–15, *and* current score is ≥3 points higher than previous score, *and* current score is ≥8 points higher than baseline score	High High
1	Patients not requiring 0 or 2 treatments received 1 treatment	Current HAM-D score intermediate between criteria for low or high relapse potential	Moderate
Discontinue study	Current and previous HAM-D score ≥21, *or* the patient is suicidal, *or* the patient requires psychiatric hospitalization		

[a] HAM-D=24-item Hamilton Depression Rating Scale.

Phase 2 Criteria

- **Remit in Phase 1**
- No Schizoaffective, bipolar**, dementia,** substance abuse in last 6 months, active general medical/neurological conditions
- **No failure to respond to Venlafaxine or lithium**
- **No Contraindications to Lithium or Venlafaxine**

Methods

- Diagnosis of MDD made using SCID-I (study years 1-2), MINI (years 3-6)
- **HAM-D_{24} and Beck Scale for Suicidal Ideation**
- Raters masked, patients not to ECT vs pharmacotherapy
- Annual auditing of raters with MSSM
- **Neurocog Battery:** AMI-SF, CVLT-II, DKEFS, DRS-2 IP, Stroop Color & Word Test, TMT Parts A&B
- Alternative forms used to minimize practice effects
- Except AMI-SF all converted to demographic-adjusted scores
- Globally used MMSE; premorbid assessed with WTAR
- Monthly subset (AMI-SF, CVLT-II); all at 12 & 24 weeks

Statistical Analysis

- Patients removed if dropped out, HSRD24 >= 21, hospitalization, or suicidal
- MEM approach used: “MEM analyses allow for measurement of subjects at irregular time points, missing data, and time varying or invariant covariates, and can also account for the effect of clustering (e.g., within subjects and clinical sites)”
- NP variables were used separately as the dependent variable with treatment status (pharmacotherapy, STABLE plus pharmacotherapy), time, and time × treatment interaction as primary fixed independent variables. Additional covariates were added to the model to adjust for age, clinical center (site), psychosis, premorbid intellectual functioning (measured by the Wechsler Test of Adult Reading [WTAR]), and time-varying changes (over the 6-month period) in depression severity ($HAM\text{-}D_{24}$ total score)
- Random subject effects were incorporated using random intercepts and slopes
- Because the STABLE algorithm directed rescue ECT at any time point in the flexible phase as indicated by increased depression symptom severity prior to that point, the final time point (6 months) represented the cumulative effect of treatment on cognitive function across all neurocognitive measures and was considered the primary analysis time point
- Effect sizes for neurocognitive scores for STABLE plus pharmacotherapy vs pharmacotherapy, therefore, were determined from the MEM as differences in least squares means, with corresponding 95% confidence intervals, at study end (6 months) using either the linear or quadratic MEM model depending on optimal model fit
- Bonferroni-adjusted and unadjusted p-values were reported

Results

- Demographics at right
- 148 remitted in phase 1; 120 went on to phase 2
- 62% female, 95% White, 14 yrs education
- Mena age = 70.5
- Pharmacotherapy only had a non-statistically significant higher number of those with psychosis
- 34% (21/61) in STABLE group received additional ECT beyond the first 4
- 7 of these received only 1

TABLE 1. Demographic and Baseline Patient Characteristics for the Intent-to-Treat Sample in a Study of Symptom-Titrated Algorithm-Based Longitudinal ECT (STABLE) Plus Medication Versus Medication Alone in Geriatric Depression

Characteristic	Total Sample (n = 120)		STABLE+PHARM (n = 61)		PHARM (n =59)		Test statistics	df	p value[a]
	Mean	SD	Mean	SD	Mean	SD			
Age (y)	70.5	7.2	70.8	7.2	70.3	7.3	-0.35	118	0.73
Education (y)	14.5	3.3	14.4	3.3	14.5	3.4	0.09	118	0.93
HRSD24 baseline Phase 1	30.3	7.4	29.6	6.8	31.1	7.9	1.13	118	0.26
HRSD24 baseline Phase 2	6.1	2.5	6.0	2.5	6.1	2.5	0.04	118	0.97
MMSE baseline Phase 1	27.5	2.2	27.6	2.2	27.4	2.3	-0.28	118	0.78
MMSE baseline Phase 2	27.9	2.4	27.9	2.5	27.8	2.4	-0.27	118	0.79
CGI-S baseline Phase 1	5.2[b]	0.9	5.1[b]	0.8	5.3	0.9	1.1	117	0.28
CGI-S baseline Phase 2 Seizure threshold (mC) (baseline Phase1)	1.9	0.9	1.9	0.9	1.8	0.8	-0.98	118	0.33
Prior antidepressants (baseline Phase1)	29.8[b]	12.8	29.4[b]	12.7	30.1	13.0	0.28	117	0.78
Wechsler Test of Adult Reading	2.3[c]	1.5	2.3[d]	1.6	2.4[e]	1.5	0.13	1	0.72
STABLE+PHARM (n=61)	106.2[f]	10.2	106.3[c]	9.8	106.0[g]	10.8	-0.17	107	0.86
	N	%	N	%	N	%			
Age group (%)									
60-69	57	47.5	29	47.5	28	47.5			
70-79	49	40.8	24	39.3	25	42.4			
80–89	14	11.7	8	13.1	6	10.2			
Female	74	61.7	37	60.7	37	62.7	0.05	1	0.82
White	114	95	58	95.1	56	94.9	3	1	1.0
Patients with psychosis (baseline)	17	14.2	5	8.2	12	20.3	3.64	1	0.06

[a] p-values for comparing STABLE+medication vs Medication are from pooled t-test for continuous variables and chi-square (or Fisher's exact test or Kruskal-Wallis) for categorical variables.
[b] missing data for 1 subject.
[c] missing data for 15 subjects.
[d] missing data for 10 subjects.
[e] missing data for 5 subjects.
[f] missing data for 11 subjects.
[g] missing data for 6 subjects.

Results

- For both groups at Phase 2 baseline, following an acute course of ECT and venlafaxine, the mean demographic adjusted scores for the neurocognitive variables (Table 2) ranged from low average to mildly and moderately impaired (impairment was defined based on the recommendations of Brooks and Iverson with 1.5 standard deviations representing mild to moderate impairment[36]).
- Within each treatment condition, there was statistically significant improvement across most neurocognitive scores from Phase 2 baseline to the 24-week end time point

Longitudinal Neurocognitive Effects of Combined Electroconvulsive Therapy (ECT)

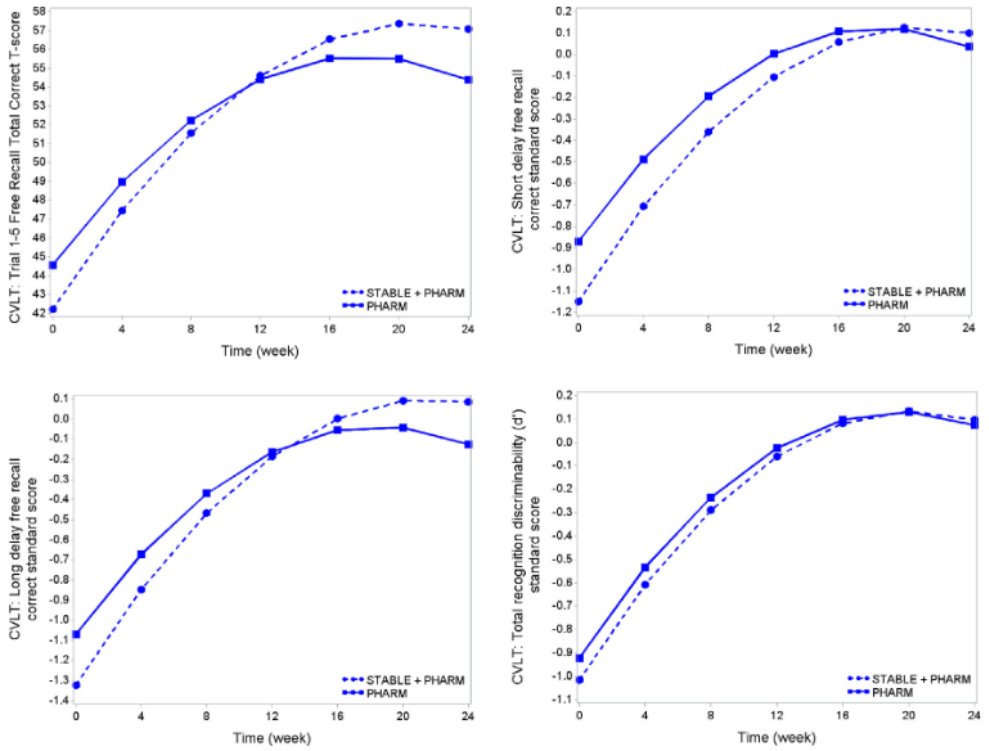
TABLE 2. Model Adjusted* Difference in Post-treatment Neuropsychological Assessment Scores Between STABLE+Medication and Medication (ΔTx) With 95% Confidence Interval (CI) and p Values

Instrument	STABLE		PHARM		ΔTx Wk24 (P-S)	95% CI ΔTx	$P_{\Delta Tx}$ (DF, t-Statistic)
	Baseline	End	Baseline	End			
Memory							
AMI-SF - assesses retrograde amnesia for autobiographical information							
AMI Total Score	37.2	37.5	37.0	37.1	−0.4	(−4.0, 3.2)	0.82 (140, −0.22)
CVLT-II - assesses anterograde verbal learning and memory							
Trial 1-5 Free Recall Total Correct t-score	42.2	57.1[I]	44.6	54.4[I]	−2.7	(−7.4, 2.0)	0.25 (207, −1.14)
Short delay free recall correct standard score	−1.2	0.1[I]	−0.9	0.0[I]	−0.1	(−0.5, 0.4)	0.78 (198, −0.28)
Long delay free recall correct standard score	−1.3	0.1[I]	-1.1	−0.1[I]	−0.2	(−0.7, 0.3)	0.37 (205, −0.90)
Delayed recognition: Total recognition discriminability (d') standard score	−1.0	0.1[I]	−0.9	0.1[I]	0.0	(−0.5, 0.4)	0.92 (211, −0.10)
Executive Function							
D-KEFS −tests frontal lobe dysfunction							
Letter fluency total correct scaled score	8.3	10.8[I]	8.3	10.3[I]	−0.6	(−2.4, 1.2)	0.54 (196, −0.61)
DRS-IP - tests verbal initiation & verbal, motor & graphomotor perseveration							
Initiation/Perseveration AMSS score	7.4	9.2[I]	8.0	9.6[I]	0.4	(−0.9, 1.7)	0.53 (231, 0.63)
Initiation/Perseveration Raw score	32.2	34.8[I]	32.7	35.4[I]	0.6	(−1.3, 2.6)	0.52 (230, 0.65)
Item E-Complex Verbal Initiation/Perseveration	15.9	18.3[I]	16.5	18.8[I]	0.5	(−1.2, 2.2)	0.57 (217, 0.56)
STROOP - is a measure of selective and divided attention and cognitive flexibility							
Word T-Score	31.8	35.3[I]	32.3	38.3[I]	2.9	(−2.2, 8.1)	0.26 (185, 1.13)
Color T-Score	32.9	37.2[I]	34.3	38.5[I]	1.3	(−3.4, 6.1)	0.58 (191, 0.55)
Color-Word T-Score	38.2	43.1[I]	40.5	42.5	−0.6	(−5.2, 4.0)	0.80 (163, −0.26)
Trail Making Test Part A - measures visual scanning/motor speed							
Score	7.2	8.1[I]	7.6	8.2	0.1	(−1.0, 1.2)	0.87 (163, 0.17)
Trail Making Test Part B - measures cognitive flexibility							
Score	7.0	8.2[I]	6.9	9.2[I]	0.9	(−0.5, 2.3)	0.19 (184, 1.31)

Results – Performance

- Patients in both conditions showed statistically significant improved performance across time on measures of complex visual scanning, psychomotor processing speed, and cognitive flexibility, verbal learning, short-term and long-term free recall, and recognition of learned words, initiation and perseveration, and phonemic fluency
- After Bonferroni adjustment for multiple comparison, change in performance was no longer statistically significant for measures of complex visual scanning, psychomotor processing speed, and cognitive flexibility and initiation and perseveration

FIGURE 1. Trajectories of memory domain neurocognitive outcomes over the 6-month study period by treatment arm using model-derived adjusted treatment means. California Verbal Learning Test (CVLT) - anterograde verbal learning and memory: **These graphs show adjusted least squares means from quadratic mixed effects models with random intercept using unstructured covariance adjusted for site, psychosis, age, Wechsler Test of Adult Reading and Ham-D (time varying).The *within group* improvement from baseline was statistically significant at p ≤0.05 for all CVLT items in both treatment groups (Item, p-value [DF, t-statistic]: Item12 Stable: <0.0001 [474, 9.67], Pharm: <0.0001 [479, 6.10]; Item16 Stable: <0.0001 [469, 8.55], Pharm: <0.0001 [475, 5.93]; Item20 Stable: <0.0001 [472, 9.31], Pharm: <0.0001 [478, 5.97]; Item44 Stable: <0.0001 [473, 7.01], Pharm: <0.0001 [480, 6.00]). There were no significant differences between the ECT plus Medication and Medication only treatment arms at the post-treatment (24 weeks) time point. For the comparison of trajectories of CVLT mean scores over time (time as continuous), there was a significant interaction for CVLT Trial 1-5 Free Recall Total Correct t-score (p [DF, t-statistic]: 0.02 [480, −2.27]) and CVLT Long delay free recall correct standard score (p [DF, t-statistic]: 0.04 [479, −2.11]).** AMI-SF - retrograde amnesia for autobiographical information: **This graph shows adjusted least squares means from linear mixed effects model with random intercept using unstructured covariance adjusted for site, psychosis, age, Wechsler Test of Adult Reading and Ham-D (time varying). There was no significant differences between the ECT plus Medication and Medication only treatment arms at the post-treatment (24 weeks) time point. The *within group* improvement from baseline was not statistically significant in both treatment groups.**



End Results

- Only patients in the STABLE condition showed significantly improved performance on measures of simple visual scanning and psychomotor processing speed and inhibition
- Patients in the pharmacotherapy-only condition showed significantly improved performance on a neurocognitive measure of cognitive processing speed
- After Bonferroni adjustment only inhibition remained statistically significantly different
- No significant change in autobiographical memory consistency
- Qualitatively: performance across most neurocognitive variables improved from low average and mildly/moderately impaired to average

Authors' Conclusions

First report of the long-term outcomes in older adults with depression of an acute course of RUL-UB ECT + VLF, followed by one of two prolonging remission strategies (STABLE+VLF+Li versus VLF+Li)

Key finding is that neurocognitive function improved over the 6-month follow-up period

Patients demonstrated recovery of the mild-to-moderate neurocognitive impairments they experienced after the acute course of RUL-UB ECT + VLF. For the group as a whole, performance on most neurocognitive measures returned to the average range

Long-term safety of RUL-UB ECT + VLF in the acute treatment of depression in the older adult population, followed by VLF+Li, with or without STABLE in the prolonging of remission

STABLE remission strategy conferred antidepressant benefit without added cognitive adverse effects

Authors' Conclusions: Part 2

STABLE+VLF+Li was found to be more effective in prolonging remission following an acute course of ECT than VLF+Li alone

Remission strategies were similar in safety suggesting that the additional ECT treatments provided in the STABLE algorithm did not interfere with the expected recovery of neurocognitive function following an acute course of RUL-UB ECT

Confirmed: Prior research that compared a fixed maintenance ECT schedule with pharmacotherapy (nortriptyline plus lithium) in an adult cohort and found that both prolonging remission strategies at the 6-month time point demonstrated similar neurocognitive outcomes

Limitations

👍 Agree with authors' conclusions overall

📽 Limitations:

Group Demographics (White, educated, possible protection from cognitive effects of ECT, no substance use, few over 80)

Stabilization of cognitive function after the Phase 1 acute RUL-UB ECT plus venlafaxine treatment course took longer than one-month, which is in contrast to prior research

Patients not blind to receiving ECT; raters were

Did not compare fixed to STABLE

Remission in phase 1 only; only up to 6 months

Open Discussion