A Randomized Controlled Trial Comparing the Memory Effects of Continuation Electroconvulsive Therapy Versus Continuation Pharmacotherapy: Results From the Consortium for Research in ECT (CORE) Study

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Objective: To compare the memory effects of continuation electroconvulsive therapy (C-ECT) versus continuation pharmacologic intervention (C-PHARM) at 12 and 24 weeks after completion of acute electroconvulsive therapy (ECT).

Method: Eighty-five patients with Structured Clinical Interview for *DSM-IV*–diagnosed unipolar major depressive disorder, enrolled in a multisite, randomized, parallel-design trial conducted at 5 academic medical centers from 1997 to 2004, who had remitted with an acute course of bilateral ECT and remained unrelapsed through 24 weeks of continuation therapy, were included in this analysis. They were randomly assigned to C-ECT (10 treatments) or nortriptyline plus lithium (monitored by serum blood levels) for 24 weeks. Objective neuropsychological measures of retrograde and anterograde memory and subjective assessment of memory were obtained at baseline, 12 weeks, and 24 weeks. The Rey Auditory-Verbal Learning Test and the Autobiographical Memory Interview were the primary outcome measures.

Results: The C-PHARM group showed a greater group difference ($P < .01$) for baseline to 12-week change for the Autobiographical Memory Interview. No other memory measures showed group differences for change scores from baseline to 12 weeks. Groups showed no baseline to 24-week change-score differences on any of the memory measures. For both groups, 12-week objective anterograde memory scores (eg, Auditory-Verbal Learning Test percent retention $P = .0001$; Rey-Osterrieth Complex Figure or Taylor Figure percent retention $P < .002$) and 24-week subjective memory scores were significantly improved (Squire Subjective Memory Questionnaire $P < .02$) over baseline. This result reflects the apparent resolution of a presumed decrement in anterograde memory associated with acute ECT preceding this study.

Conclusions: The finding of no memory outcome differences between unrelapsed recipients of C-ECT and C-PHARM is consistent with clinical experience. Memory effects have only a small role in the choice between C-ECT and C-PHARM.

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We have previously reported efficacy outcomes for the Consortium for Research in Electroconvulsive Therapy (CORE)[1] multicenter clinical trial comparing continuation electroconvulsive therapy (C-ECT) and continuation pharmacotherapy (C-PHARM). This trial was motivated by the recognition of mood disorders as chronic relapsing illnesses, requiring relapse prevention strategies. Electroconvulsive therapy (ECT) is an effective acute treatment for major depressive episodes.[2–4] It is also used clinically as a continuation and maintenance treatment; there is, however, limited evidence from well-designed trials to support its efficacy in this context.[5] As reported elsewhere,[1] we have evaluated the role of ECT as a relapse prevention strategy compared with a commonly used pharmacotherapy strategy (lithium plus nortriptyline)[6] in a multicenter, randomized, controlled trial. We found essentially no differences in relapse prevention between the 2 treatment options.

Given the equal efficacy of C-ECT in comparison with pharmacotherapy in relapse prevention, the clinical value of C-ECT is sharply reduced if it results in substantially greater cognitive effects than pharmacotherapy following an acute ECT course. The long intervals between C-ECT

For Clinical Use

- Following acute course ECT, on average, nearly all recovery of retrograde memory function was complete before initiation of continuation/maintenance therapy. For anterograde memory, deterioration was present at the beginning of continuation/maintenance therapy, but nearly all recovery of function was complete within a 12-week window.
- In terms of long-term memory outcome for unrelapsed completers of continuation/maintenance therapy, there appear to be few differences between continuation ECT and continuation pharmacotherapy involving nortriptyline plus lithium.
- These findings, together with the findings of equal efficacy of the two modalities, suggest that factors such as patients' geographic access to ECT or their ability to comply with an aggressive medication regimen may have greatest import in selecting among continuation therapy options.

treatments are assumed to result in substantial recovery of memory function,[2] but there are limited empirical data to substantiate this claim. Consequently, our comparative clinical trial assessing the relative merits of C-ECT and C-PHARM included explicit attention to long-term cognitive consequences. Our expectation was that, over the continuation phase, recovery of cognitive function would be seen in both continuation therapy groups but that the slope of recovery would be less steep in the C-ECT group.

We reported in the previous article[1] that no persistent differences between C-ECT and C-PHARM were found on the modified Mini-Mental State Examination (mMMSE).[7] We report herein on the extensive neuropsychological memory assessment administered during the conduct of our continuation therapy clinical trial.[1] This assessment includes more focused and objective measures of memory. We hypothesized that (1) C-ECT would result in inferior performance on the learning and memory measures compared to C-PHARM but that (2) the deficits observed during and following C-ECT would be less severe than those observed immediately following acute-phase ECT.

METHOD

Study Design

This protocol was reviewed and approved by the institutional review boards of all 5 participating academic clinical centers. These participating centers (University of Medicine and Dentistry of New Jersey-New Jersey Medical School; Medical University of South Carolina; The Zucker Hillside Hospital, North Shore-Long Island Jewish Medical Center; University of Texas Southwestern Medical Center at Dallas; and Mayo Foundation) compose the Consortium for Research in Electroconvulsive Therapy (CORE). The current study is a multicenter, National Institute of Mental Health–funded randomized controlled trial carried out from 1997 to 2004. The trial consisted of 2 distinct phases: phase 1, in which acutely depressed patients received bilateral ECT 3 times per week until they met remission criteria, and phase 2, in which patients who maintained remission after 1 week were randomly assigned to either C-ECT or C-PHARM (lithium-nortriptyline). Patients in the randomized continuation phase (phase 2) were followed for 24 weeks. Patients provided informed consent prior to phase 1 and again prior to random assignment in phase 2.

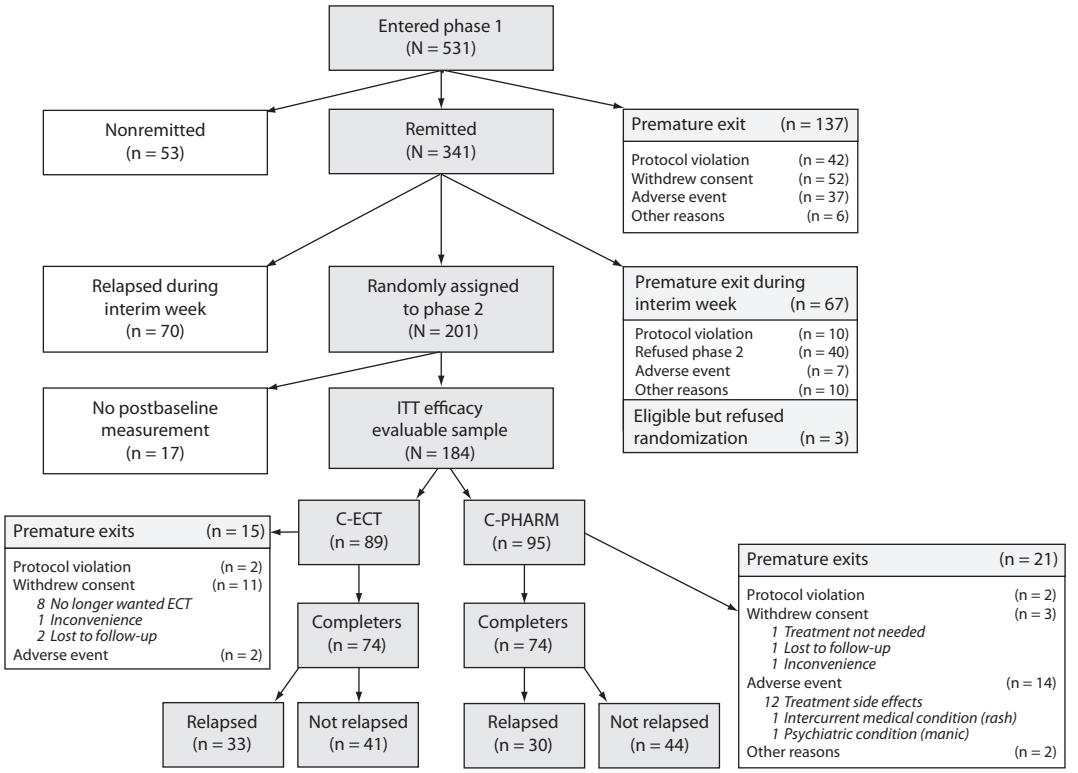
Patient Sample

Patients enrolled in phase 1 were 18 to 85 years old, were referred for ECT, and met the Structured Interview for *DSM-IV* Axis I diagnostic criteria for primary major depressive disorder, unipolar type, single or recurrent, with or without psychosis. Appropriateness for ECT was determined on a clinical basis after consultation with an attending-level ECT psychiatrist. Typical reasons for referral included failed medication trials and severity or urgency of illness.[1] Additional inclusion criteria were a pretreatment 24-item Hamilton Depression Rating Scale ($HDRS_{24}$)[8] total score ≥ 21 and the ability to provide informed consent.

Inclusion criteria for the randomized phase (phase 2) were (1) achievement of remission in phase 1 (60% decrease from baseline in $HDRS_{24}$ total score, $HDRS_{24}$ score ≤ 10 on 2 consecutive ratings, and the $HDRS_{24}$ score did not change more than 3 points on the last 2 consecutive ratings); (2) maintenance of $HDRS_{24}$ score at ≤ 10 for 1 week while free of all psychotropic medication; (3) a mMMSE score ≥ 21; and (4) the ability to provide written informed consent. Concomitant psychotropic medications were prohibited throughout the study with the exception of lorazepam, up to 3 mg/d, for anxiety and diphenhydramine, up to 50 mg/d, for insomnia.

Exclusion criteria were a diagnosis of schizophrenia, bipolar disorder, dementia, delirium, or other central nervous system disease with the probability of affecting cognition or response to treatment; substance dependence within the past 12 months; medical conditions contraindicating ECT or nortriptyline-lithium; treatment failure in the index

Figure 1. Participant Flow for Acute Electroconvulsive Therapy (ECT) Phase (phase 1) and Randomized Continuation Phase (phase 2)[a]



[a]Reprinted with permission from Kellner et al.[1]
Abbreviations: C-ECT = continuation electroconvulsive therapy, C-PHARM = continuation pharmacotherapy, ITT = intent to treat

episode of the combination of a heterocyclic antidepressant and lithium; and treatment with ECT in the past 12 weeks.

Figure 1, which is reproduced from our primary outcome article,[1] lists the participant flow for this study. Five hundred thirty-one participants entered phase 1 of the study, 184 were ultimately randomly assigned to one of the 2 treatment arms, and 148 completed the study, either as relapsers or by remaining unrelapsed at the 24-week endpoint. As noted, only the 85 subjects who completed without relapse are used in these analyses. Demographic characteristics of the sample employed in the cognitive analyses are listed in Table 1.

Treatments

Electroconvulsive therapy procedures. Electroconvulsive therapy procedures were standardized across all centers, using the Thymatron DGX ECT device (Somatics Inc, Lake Bluff, Illinois), bilateral (bitemporal) electrode placement, dose titration to determine seizure threshold at initial treatment, and stimulus dosing at subsequent treatments of 1.5 times the seizure threshold. Procedures for anesthesia and determination of seizure adequacy (electromyography > 20 seconds; electroencephalography > 25 seconds) followed standardized clinical protocols compatible with current standards of care.[2] Treatments were administered 3 times per week in phase 1 and weekly for 4 weeks, biweekly for 8 weeks, and monthly for 2 months (total of 10 ECT treatments over 5 months) in phase 2. Dose titration to determine seizure threshold was repeated at the first phase 2 treatment. No minimum or maximum number of ECT treatments was specified for a patient to be classified as a remitter in phase 1.

For purposes of experimental design rigor, all participants needed to be treated with the same electrode placement. The choices were extensively discussed, both in the design phase of the study, as well as in the National Institutes of Health review process. Bilateral electrode placement was chosen, as it has been the standard for efficacy in the field for decades, there is agreement in the field about how to standardize electrical stimulus dosing, and it is believed to be less dose-sensitive.

Pharmacotherapy procedures. Patients randomly assigned to the C-PHARM arm were administered initial doses of 50 mg nortriptyline and 600 mg lithium carbonate. Blood levels obtained 24 hours later were used to make recommendations for doses needed to achieve steady-state levels of 125 ng/mL of nortriptyline and 0.7 mEq/L of lithium, based on a validated algorithm.[9] Oral dosages

Table 1. Patient Demographic, Clinical, and Treatment Characteristics for the ITT Sample and by Treatment Group

Characteristic	Total Sample (N = 85)	C-ECT (n = 41)	C-PHARM (n = 44)	*P* Value	Statistic	*df*
Demographic						
Age, mean ± SD, y	59.2 ± 15.7	60.5 ± 15.8	57.9 ± 15.6	.43[a]	$t = 0.78$	83
Age group, % (n/N)						
18–44 y	20.0 (17/85)	19.5 (8/41)	20.5 (9/44)			
45–64 y	38.8 (33/85)	34.2 (14/41)	43.2 (19/44)			
65–85 y	41.2 (35/85)	46.3 (19/41)	36.4 (16/44)			
Level of education, % (n/N)				.058[b]	$\chi^2 = 5.69$	2
Less than high school	29.9 (23/77)	40.5 (15/37)	20.0 (8/40)			
High school to college	62.3 (48/77)	48.7 (18/37)	75.0 (30/40)			
At least some graduate training	7.8 (6/77)	10.8 (4/37)	5.0 (2/40)			
Sex, female, % (n/N)	71.6 (61/85)	70.7 (29/41)	72.7 (32/44)	.838[b]	$\chi^2 = 0.04$	1
Race, white, % (n/N)	84.7 (72/85)	87.8 (36/41)	81.8 (36/44)	.742[b]	$\chi^2 = 0.59$	1
Clinical						
Psychosis status, psychotic, % (n/N)	44.7 (38/85)	36.6 (14/41)	52.3 (23/44)	.146[b]	$\chi^2 = 2.11$	1
$HDRS_{24}$ score at baseline phase 1, mean ± SD	34.8 ± 6.7	36.3 ± 7.2	33.3 ± 5.9	.037[a]	$U = 2.12$	83
$HDRS_{24}$ score at phase 1 end, mean ± SD	5.5 ± 2.8	5.3 ± 2.9	5.6 ± 2.6	.570[a]	$U = -0.57$	83
$HDRS_{24}$ score at baseline phase 2, mean ± SD	6.1 ± 2.6	6.2 ± 2.6	6.0 ± 2.6	.731[a]	$U = 0.34$	83
mMMSE score at baseline phase 1, mean ± SD	45.9 ± 9.4	42.5 ± 12.3	46.5 ± 5.5	.012[a]	$U = 2.56$	64
mMMSE score at baseline phase 2, mean ± SD	46.1 ± 7.4	42.0 ± 8.6	45.3 ± 6.0	.149[a]	$U = 1.46$	80
Age at illness onset, mean ± SD, y	46.4 ± 19.2	46.9 ± 20.6	46.0 ± 18.1	.842[a]	$t = 0.20$	78
No. of prior episodes, mean ± SD	1.7 ± 2.5	1.7 ± 1.7	1.8 ± 3.1	.804[a]	$U = -0.25$	78
Length of current episode, mean ± SD, wk	40.0 ± 48.3	43.6 ± 61.8	36.9 ± 33.3	.553[a]	$t = 0.60$	74
WAIS-R information score, mean ± SD	8.2 ± 3.4	7.8 ± 3.5	8.6 ± 3.3	.304[a]	$t = -1.04$	76
WAIS-R vocabulary score, mean ± SD	8.3 ± 3.2	7.3 ± 3.4	9.2 ± 2.8	.008[a]	$t = -2.72$	76
Treatment						
Seizure threshold at baseline phase 1, mean ± SD	25.2 ± 14.6	29.3 ± 15.4	21.5 ± 12.8	.013[a]	$t = 2.54$	83
No. of ECT treatments in phase 1, mean ± SD	7.4 ± 3.2	7.0 ± 2.7	7.8 ± 3.6	.297[a]	$t = -1.11$	83

[a] *P* value is from pooled *t* test or Wilcoxon rank sum test comparing means for C-ECT group and C-PHARM group. Wilcoxon test was used for those variables with truncated and therefore nonparametric distributions (eg, number of depressive episodes or $HDRS_{24}$ score at end of phase 1).
[b] *P* value is from χ^2 test comparing probability for C-ECT group and C-PHARM group.
Abbreviations: C-ECT = continuation electroconvulsive therapy, C-PHARM = continuation pharmacotherapy, ECT = electroconvulsive therapy, $HDRS_{24}$ = 24-item Hamilton Depression Rating Scale, ITT = intent to treat, mMMSE = modified Mini-Mental State Examination, WAIS-R = Wechsler Adult Intelligence Scale-Revised.

were adjusted on the basis of weekly blood levels. These procedures were followed in an effort to maximize the effectiveness and tolerability of the C-PHARM treatment. These agents were chosen on the basis of a review of the literature on pharmacotherapy relapse prevention strategies in major depression.[5] In addition, this study was designed to complement the post-ECT relapse prevention study of Sackeim et al,[6] which included nortriptyline-lithium, nortriptyline as monotherapy, and placebo, but no continuation ECT arm.

Assessments

Efficacy assessment. The primary instrument used to rate depressive symptoms was the $HDRS_{24}$ administered at baseline and after each ECT treatment in phases 1 and 2. The $HDRS_{24}$ associated with each treatment was assessed on the day of the next treatment visit. The primary efficacy outcome measure was time to relapse. Relapse was declared if, at 2 consecutive ratings, a patient's $HDRS_{24}$ total score was 16 or greater, with a minimum increase of 10 points from phase 2 baseline. A potential relapse was signaled if an $HDRS_{24}$ score increased by 4 points over phase 2 baseline, and the evaluation was repeated in 1 week. As long as the $HDRS_{24}$ scores indicated potential relapse, evaluations continued weekly.

Neuropsychological assessment and timing of assessments. The primary cognitive aim of this study was to assess the impact of C-ECT and C-PHARM on neurocognitive performance. An abbreviated neuropsychological battery was administered to all patients on the day prior to the start of phase 1 ECT, and a full neuropsychological battery was administered at baseline of phase 2 (6 days following the last acute-phase ECT [prerandomization]), after 12 weeks in phase 2 (12–14 days after the most recent medication visit or C-ECT), and at study completion (24-week follow-up: 26–28 days after the last medication visit or C-ECT treatment, or at point of relapse). As with clinical outcome, every attempt was made to complete follow-up

neuropsychological evaluations on all patients in phase 2, including those who did not adhere to treatment regimens or who reached the end point of relapse before 6 months. Patients who relapsed were invited to return for postrelapse cognitive assessments at the normally scheduled 12- or 24-week time points. However, to isolate the cognitive effects of the treatment arm, unconfounded by recurrent mood disturbance or off-protocol treatments, only nonrelapsed completers are included in the present analyses. Whenever alternate forms were used, counterbalancing methods were used to avoid confounding effects of repeatedly administering different versions of the same test in identical order.

Global Measures

Wechsler Adult Intelligence Scale-Revised. For purposes of sample characterization, at baseline of phase 2, patients were administered the vocabulary and information subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R).[10] These measures were not repeated at 12 and 24 weeks.

Memory Measures

Anterograde verbal memory. The Rey Auditory-Verbal Learning Test (AVLT)[11–13] is a structured, well-validated instrument to assess anterograde verbal learning and memory. The AVLT is normed[14] and shows moderate retest stability in controls over long intervals, and it has equivalent alternative versions.[15] Similar procedures, such as delayed scores on the Buschke Selective Reminding Test,[16] have shown marked sensitivity to ECT-induced deficits and to ECT technique.[17] Participants for the AVLT have 5 trials in which to learn 15 words. Following an interference trial, there is a short delay and then a 30-minute delayed recall. Two forms were alternated with counterbalancing over the 3 assessments (phase 2 baseline, 12 weeks, and 24 weeks). The primary score on this measure was percent retention at 30-minute delay (ie, 100 × [30-minute delay/trial 5]).[18]

Paired-words and story recall measures commonly used in ECT research[19] are subtests from the Randt Memory Test[20] and were used in our study to supplement the AVLT. These subtests were designed to be sensitive over a broad spectrum of mild-to-moderate memory deficits. The paired-words (6 pairs) and story recall tests assess acquisition and delayed recall at 30 minutes. Three of the 5 alternative versions of these subtests were used.[20] Both the original Rey-Osterrieth Complex Figure[21] and the Taylor Figure[13] were alternately used. Standard procedures were followed involving figure copying (including timing), immediate recall, and 30-minute delayed recall. The Rey-Osterrieth Complex Figure Test delayed recall measures are particularly sensitive to ECT-induced impairments and to variation in ECT technique.[19] The delayed recall score, relative to the copying score, was our primary measure of nonverbal memory.[22] Like the AVLT and the Randt Memory Test, baseline on this measure was established at the beginning of phase 2.

Retrograde memory. Retrograde amnesia for autobiographical information may be a particularly robust and persistent effect of ECT.[19,23,24] The best studied instrument in this area is a structured interview developed by Sackeim and colleagues, the Autobiographical Memory Interview-Short Form (AMI).[25] This version of the AMI has 30 items (5 common questions about 6 recent personal events). The AMI has shown considerable sensitivity to both short-term and persistent ECT-associated decrement. This instrument was administered at phase 1 baseline, and all subsequent scoring is referenced to responses at phase 1 baseline.

Subjective memory. We have described the Squire Subjective Memory Questionnaire (SSMQ)[26] and the outcomes for it elsewhere.[1] We repeat these results here for comparison purposes.

Self-ratings of memory are obtained with the SSMQ.[26] This instrument is the one most commonly used to assess subjective evaluation of ECT effects on memory.[24] Almost all recent studies have found that SSMQ scores improve shortly after ECT relative to the pre-ECT baseline and that this improvement is further enhanced at later follow-up.[19,27,28] Our data examine whether the extent of improvement in SSMQ scores during phase 2 is comparable in the 2 treatment arms. There are no alternative versions of the SSMQ (or other subjective memory measures).

Raters

The raters who acquired study data were the study psychiatrist, the continuous rater, and the neuropsychological technician. The continuous rater conducted study assessments at all time points and was the same person for both the C-ECT and C-PHARM groups. Because participants would discuss their treatment with the continuous rater, it was not possible to blind the continuous rater to treatment assignment. The study psychiatrists administered acute-phase ECT, C-ECT, and C-PHARM. Different study psychiatrists delivered C-ECT and C-PHARM because blind delivery was not feasible and maximal effort and specific expertise were needed to deliver each. The continuous rater and the study psychiatrist had no role in memory data collection. At prespecified time points (phase 1 baseline and end, phase 2 baseline, 1 month, 3 months, and 6 months or study exit [relapse]), the continuous rater and the study psychiatrist performed $HDRS_{24}$ "consensus ratings," with the mean of the ratings used for analyses. The neuropsychological technician administered the neuropsychological battery and was blinded to treatment condition.

Standardization and Quality Assurance Assessment

All raters underwent an intensive prestudy training period conducted by a senior-level, highly experienced psychometrician. Additional in-person training sessions were scheduled if indicated. Standardized administration and scoring by the published manual were required for tests for which such a manual exists. For those tests for which

Table 2. Baseline, 12-Week, and 24-Week Memory Outcomes by Continuation Therapy Group (total N = 85)

	Phase 2 Baseline, Mean (SD)			12-Week Follow-Up, Change From Baseline,[a] Mean (SE)			24-Week Follow-Up, Change From Baseline,[a] Mean (SE)		
Domain/Measure	C-ECT (n = 41)	C-PHARM (n = 44)	*P* Value[b]	C-ECT (n = 41)	C-PHARM (n = 44)	*P* Value[b,c]	C-ECT (n = 41)	C-PHARM (n = 44)	*P* Value[b,c]
Depression									
$HDRS_{24}$ score	6.2 (2.6)	6.0 (2.6)	.73	−0.5 (3.4)	0.3 (4.4)	.39	−0.5 (4.0)	0.4 (6.4)	.40
Anterograde verbal memory									
AVLT, % retention	37.7 (3.0)	40.1 (2.9)	.57	24.0 (4.7)	21.0 (4.6)	.71	18.0 (4.1)	22.0 (3.7)	.47
Randt Memory Test, paired-words score	4.1 (0.2)	4.0 (0.2)	.76	0.3 (0.3)	0.3 (0.3)	.95	0.0 (0.3)	−0.5 (0.2)	.14
Randt Memory Test, short-story score	52.0 (6.4)	70.0 (6.1)	.04	12.6 (6.3)	11.0 (6.1)	.87	12.2 (9.3)	17.5 (8.0)	.67
Anterograde nonverbal memory									
Rey-Osterrieth Complex Figure, % retention	36.9 (2.3)	40.9 (2.2)	.21	7.6 (2.3)	8.4 (2.3)	.81	13.0 (3.3)	6.8 (3.1)	.17
Retrograde memory									
Autobiographical Memory Interview score	29.7 (1.1)	33.6 (1.0)	.01	−0.5 (1.0)	2.4 (0.9)	.04	−1.0 (1.5)	1.5 (1.2)	.19
Subjective memory									
Squire Subjective Memory Questionnaire score	1.0 (3.5)	1.9 (3.2)	.84	4.2 (3.8)	8.6 (3.5)	.38	12.5 (4.9)	14.4 (4.1)	.77

[a]Data reported are baseline and clinical-site adjusted least-squares means (standard error of estimate) from general linear model: memory variable = baseline, site, age, psychosis, and $HDRS_{24}$ change score.
[b]Between-group comparison.
[c]Higher change scores represent greater improvement.
Abbreviations: AVLT = Rey Auditory-Verbal Learning Test, C-ECT = continuation electroconvulsive therapy, C-PHARM = continuation pharmacotherapy, $HDRS_{24}$ = 24-item Hamilton Depression Rating Scale.

a published manual did not exist, administration followed the guidelines from Lezak.[11] Each neuropsychological technician was observed until 2 administrations met standardization guidelines. In addition, each neuropsychological technician attained scoring accuracy of greater than 95% prior to certification as a study neuropsychological technician. Copies of all cognitive data were sent to the primary author's location, where all scoring was being rechecked by the senior study psychometrist (M.D.F.-D.). Notification of any required revisions in scoring was forwarded to the data management center as well as the origination site. Error tracking was used to explore for patterns of scoring errors and to correct them.

Data Analysis

Least-squares adjusted mean change scores for the memory variables (for the 12- and 24-week [end of study]) time points were calculated. We compared groups' adjusted mean change scores using the general linear model (GLM) approach, which provides the basis for most common inferential statistics, including analysis of variance and regression (SAS software; SAS Institute Inc, Cary, North Carolina). We examined for longitudinal change within groups and differences between groups. Each analysis included adjustments for baseline memory score, $HDRS_{24}$ change score, age, psychosis status, and clinical center. By statistical convention, we adjusted for stratification variables in the randomization scheme, which in this case were psychosis and site. Since we were analyzing memory change scores—and baseline memory score impacts the range of subsequent change scores, we adjusted baseline memory score. We adjusted for age and $HDRS_{24}$ to remove "noise" in the memory scores due to age and depression effects. Given our sample size and the observed variance of the memory measures, we estimated having an 80% chance of detecting a moderate (≈ 0.66 or greater) effect size.

RESULTS

Group Comparisons

Table 2 provides baseline, 12-week, and 24-week memory outcomes by continuation therapy group. Table 2 lists these memory results including (1)) anterograde verbal memory, (2) anterograde nonverbal memory, (3) retrograde memory, and (4) subjective memory.

As can be seen from Table 2, there were no statistically significant baseline to 24-week change-score differences on any of the memory measures. The baseline to 12-week change did show a modest group difference for the AMI (favoring the C-PHARM group) but not for any other measure. The AMI difference did not maintain statistical significance at 24 weeks.

Time Trends

We examined for longitudinal change by comparing baseline to 12-week changes and 12-week to 24-week changes within groups. For both groups, 12-week scores were significantly improved over baseline for AVLT percent retention ($P = .0001$ for both groups), Rey-Osterrieth Complex Figure or Taylor Figure percent retention ($P < .002$ for C-ECT;

$P = .0005$ for C-PHARM). By week 24, both groups showed improvement on the SSMQ ($P < .02$ for C-ECT; $P < .001$ for C-PHARM). These findings reflect the apparent resolution of a presumed decrement in anterograde memory (verbal and nonverbal) associated with the acute course of ECT that preceded the phase 2 baseline. The AMI scores showed a significant change ($P < .01$) from baseline to 12 weeks in the C-PHARM group but not in the C-ECT group, resulting in the group difference on AMI noted above. In addition, the C-ECT group showed a significant change from phase 2 baseline to 12 weeks on the Randt Memory Test short-story memory ($P < .01$). This change did not reach significance in the C-PHARM group.

DISCUSSION

Acute ECT is a highly efficacious intervention for depression. However, relapse rates remain high, even in those treatment-refractory patients whose acute episode of depression is successfully treated with ECT. We have previously found no differences between continuation ECT and aggressive pharmacologic management in preventing relapse following acute ECT treatment.[1] We sought to compare the relative memory effects of C-ECT and continuation pharmacotherapy in order to assist practitioners and patients in choosing between these 2 treatment modalities with similar efficacy.

It is well known that acute ECT results in stereotyped cognitive effects, the nature and magnitude of which are highly sensitive to treatment parameters.[17,23] Global effects on mental status are present for minutes to hours after ECT but typically subside quickly. The degree of such immediate impairment has been shown to correlate with more persistent amnestic effects.[29] The amnestic side effects include deficits in the retention of newly learned information (delayed recall or recognition). This rapid forgetting forms the basis for the anterograde amnesia associated with ECT.[17,19] This deficit may be cumulative over the course of acute-phase ECT and, like disorientation, is most profound immediately following seizure termination. Typically, the anterograde amnesia resolves following the termination of acute-phase ECT. Controlled studies do not document anterograde amnesia lasting more than a few weeks following the acute treatment phase.[24] Acute ECT also results in retrograde amnesia, which is most dense immediately following seizure termination and includes amnesia for both autobiographical information and for public events.[23] Retrograde amnesia displays a temporal gradient, with the most distal memories returning first, as time from ECT increases.[23] Despite the evidence of immediate cognitive effects following each seizure, long-term studies fail to find evidence of persistent effects in cognition in recovered patients.[3] In the few patients who report persistent complaints, the focus is on autobiographical memory, without signs of impairment on other cognitive tests. The emphasis in this study was on the memory domain, wherein we examined verbal and nonverbal anterograde memory, retrograde memory, and subjective memory reports.

Longitudinal Findings

For retrograde amnesia, nearly all recovery of function was complete by the phase 2 baseline, 1 week after acute treatment cessation. All effects on the AMI were present at phase 2 baseline, with no further improvement or worsening of effects over continuation therapy. For anterograde memory function, the present data suggest that from the nadir of phase 2 baseline, nearly all recovery of function is complete within the 12-week window. No further mean improvement was seen in the 12- to 24-week window.

Group Comparisons

The present results show few differences between C-ECT and C-PHARM in terms of long-term memory outcome for unrelapsed completers. These findings are consistent with the supposition that the long intervals between C-ECT treatments do result in substantial recovery of cognitive function.[2]

Limitations

In spite of random assignments, there were differences between the 2 treatment arms in the level of educational attainment and vocabulary skills. Vocabulary skills are highly correlated with overall IQ. These differences may have arisen from the stochastic failure of randomization to equate groups on all covariates. To assess this possibility, we compared the full sample (N = 184) who progressed to randomization and found that the education difference but not the vocabulary difference was present at that level. This raises the possibility that the randomization failure was compounded by a retention bias in continuation arm. More participants randomly assigned to C-ECT withdrew consent compared to those assigned to C-PHARM (11 versus 3, respectively), and, alternatively, there were more adverse events on the C-PHARM side. It is possible that either withdrawal of consent or adverse event reports, or both, interacted with vocabulary to produce the baseline differences in education and vocabulary reported in Table 1. The modest association between education/IQ and memory helps explain the baseline differences between C-ECT and C-PHARM on the AMI and Randt Memory Test short stories.

This study focuses only on those continuation patients that remained unrelapsed throughout the course of 24-week follow-up. Clearly, this is a select group. The memory outcomes in those who relapsed may be different than those reported here. But those outcomes are confounded by the impact of recurrent depression on cognitive function. In this study, we sought to examine cognitive differences in treatment outcome unconfounded by recurrent depression.

In an effort to be rigorous, we used a fixed continuation schedule in this study. However, in clinical practice, the frequency of treatments is usually adjusted according to clinical status. These results may then overestimate or underestimate the cognitive effects of C-ECT as it is provided in routine clinical practice.

Finally, this report, as with much of the literature, focuses only on memory function. Other cognitive domains such as attention may be affected by depression and its treatment. Investigation of these additional cognitive domains is encouraged.

CONCLUSION

According to the World Health Organization,[30] by the year 2020, depressive illness will be the second leading cause of disability worldwide. Yet, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial showed that even with multiple antidepressant medication trials, most patients either fail to remit or they relapse soon after remission.[31] This means that there is a large population of depressed patients needing further treatment strategies including a range of continuation therapies. Our results suggest that memory side effects should play only a small role in choosing between C-ECT and C-PHARM as the appropriate continuation or maintenance strategy for a given ECT recipient. These findings, together with the findings of equal efficacy of the 2 modalities, suggest that other factors such as patients' geographic access to ECT or their ability to comply with an aggressive medication regimen may have greatest import in selecting among continuation therapy options.

Drug names: diphenhydramine (Benadryl and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), nortriptyline (Pamelor and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this article.

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