

Continuation Electroconvulsive Therapy vs Pharmacotherapy for Relapse Prevention in Major Depression

A Multisite Study From the Consortium for Research in Electroconvulsive Therapy (CORE)

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Background: Although electroconvulsive therapy (ECT) has been shown to be extremely effective for the acute treatment of major depression, it has never been systematically assessed as a strategy for relapse prevention.

Objective: To evaluate the comparative efficacy of continuation ECT (C-ECT) and the combination of lithium carbonate plus nortriptyline hydrochloride (C-Pharm) in the prevention of depressive relapse.

Design: Multisite, randomized, parallel design, 6-month trial performed from 1997 to 2004.

Setting: Five academic medical centers and their outpatient psychiatry clinics.

Patients: Two hundred one patients with Structured Clinical Interview for *DSM-IV*-diagnosed unipolar depression who had remitted with a course of bilateral ECT.

Interventions: Random assignment to 2 treatment groups receiving either C-ECT (10 treatments) or C-Pharm for 6 months.

Main Outcome Measure: Relapse of depression, compared between the C-ECT and C-Pharm groups.

Results: In the C-ECT group, 37.1% experienced disease relapse, 46.1% continued to have disease remission at the study end, and 16.8% dropped out of the study. In the C-Pharm group, 31.6% experienced disease relapse, 46.3% continued to have disease remission, and 22.1% dropped out of the study. Both Kaplan-Meier and Cox proportional hazards regression analyses indicated no statistically significant differences in overall survival curves and time to relapse for the groups. Mean \pm SD time to relapse for the C-ECT group was 9.1 ± 7.0 weeks compared with 6.7 ± 4.6 weeks for the C-Pharm group ($P = .13$). Both groups had relapse proportions significantly lower than a historical placebo control from a similarly designed study.

Conclusions: Both C-ECT and C-Pharm were shown to be superior to a historical placebo control, but both had limited efficacy, with more than half of patients either experiencing disease relapse or dropping out of the study. Even more effective strategies for relapse prevention in mood disorders are urgently needed.

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WITH THE RECOGNITION that for most patients, mood disorders are chronic relapsing illnesses, physicians and researchers have turned their attention from acute treatment strategies to the evaluation of relapse prevention strategies. Electroconvulsive therapy (ECT) has repeatedly been demonstrated as an extremely effective acute treatment

for major depressive episodes.¹⁻³ It is also used clinically as a continuation and maintenance treatment, despite a lack of well-designed trials to support such use.⁴ We evaluated the role of continuation ECT (C-ECT) as a relapse prevention strategy compared with a combination pharmacotherapy (C-Pharm) strategy, lithium carbonate plus nortriptyline hydrochloride, in a multicenter randomized controlled trial. Because treatment options for relapse pre-

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vention are limited, evidence-based validation of C-ECT will provide important information for physicians and patients on which to base treatment decisions.

METHODS

STUDY DESIGN

The following participating centers compose the Consortium for Research in ECT (CORE): University of Medicine and Dentistry of New Jersey—New Jersey Medical School, Medical University of South Carolina, the Zucker-Hillside Northshore—Long Island Jewish Medical Center, University of Texas Southwestern Medical Center at Dallas, and Mayo Foundation. This study is a multicenter, National Institute of Mental Health–funded randomized controlled trial performed 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 randomized 1:1 to either C-ECT or C-Pharm (lithium-nortriptyline). The randomization scheme was a stratified permuted block (variable block size of 4 to 6), with psychosis status and clinical site as stratification variables. Patients in the randomized continuation phase (phase 2) were followed up for 6 months. Rating visits occurred at weeks 0 (baseline), 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24. The primary end point was time to relapse. This protocol was reviewed and approved by the institutional review boards of all 5 participating academic clinical centers. Patients provided informed consent before phase 1 and again before randomization in phase 2.

PATIENT SAMPLE

Patients enrolled in phase 1 were 18 to 85 years old, were referred for ECT, and met Structured Clinical Interview for DSM-IV 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.⁵⁻⁷ Additional inclusion criteria were pretreatment 24-item Hamilton Rating Scale for Depression (HRSD₂₄) total score of 21 or higher⁸ and ability to provide informed consent.

For the randomized phase (phase 2), inclusion criteria were achievement of remission in phase 1 ($\geq 60\%$ decrease from baseline in HRSD₂₄ total score, HRSD₂₄ score of ≤ 10 on 2 consecutive ratings), maintenance of HRSD₂₄ score at 10 or less for 1 week while free of all psychotropic medication, modified Mini-Mental State Examination (mMMSE) score of 21 or higher, and ability to provide written informed consent. Additional psychotropic medications were prohibited throughout the study with the exception of lorazepam, up to 3 mg/d, for anxiety and diphenhydramine hydrochloride, up to 50 mg/d, for insomnia.

Exclusion criteria were a diagnosis of schizophrenia or 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 use, and ECT in the 3 months before phase 1.

TREATMENTS

ECT Procedures

The ECT procedures were standardized across all centers, using the Thymatron DGX ECT device (Somatics Inc, Lake Bluff,

Ill), 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.⁹ 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 3 times per week in phase 1 and weekly for 4 weeks, biweekly for 8 weeks, and monthly for 2 months in phase 2 (total of 10 ECT sessions throughout 6 months, with the final one given at week 20). Dose titration to determine seizure threshold was repeated at the first phase 2 treatment. No minimum or maximum number of ECT sessions was specified for a patient to be classified as having disease remission in phase 1.

Pharmacotherapy Procedures

Patients randomized to the C-Pharm arm were administered initial doses of 50 mg of nortriptyline hydrochloride and 600 mg of 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.¹⁰⁻¹² Oral dosages were adjusted based on repeated measurement of blood levels at specified intervals. These agents were chosen because their efficacy in relapse prevention is most evident in the literature.¹³ In addition, this study was designed to be comparable and complementary to the post-ECT relapse prevention study of Sackeim et al,¹³ which included nortriptyline-lithium, nortriptyline as monotherapy, and placebo but had no C-ECT arm.

ASSESSMENTS

Instruments

The primary instrument used to rate depressive symptoms was the HRSD₂₄, which was administered at baseline and after each ECT treatment in phases 1 and 2. The HRSD₂₄ 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 HRSD₂₄ total score was 16 or higher, with a minimum increase of 10 points from phase 2 baseline.

The impact of C-ECT and C-Pharm on neurocognitive performance was measured by an extensive battery of neuropsychological tests measured at phase 2 baseline, 3 months, and 6 months (study end). Patient performance on the mMMSE is reported as a measure of the neurocognitive effects of C-ECT and C-Pharm. The mMMSE is an expanded instrument that broadens the range of scores from a maximum of 30 on the standard MMSE to a maximum of 57. The mMMSE is a measure of global cognitive impairment that has shown sensitivity to ECT-induced deficits, including recovery of functioning after ECT.^{14,15} The full results of the neuropsychological, global functioning, and health status outcomes will be reported elsewhere.

The Treatment Emergent Symptom Scale, although administered to both treatment arms, was used mainly to assess medication adverse effects in the C-Pharm arm.¹⁶ The Antidepressant Treatment History Form¹⁷ was used to determine degree of prior medication treatment failure. Compliance in the C-Pharm arm was assessed by measuring blood levels of nortriptyline and lithium at each study visit.

Raters

The raters who acquired study data were the study psychiatrist, the continuous rater, and the neuropsychological tech-

PATIENT DISPOSITION AND STUDY SAMPLE CHARACTERISTICS

Patient Disposition

Figure 1 describes patient disposition. A total of 531 patients were entered into phase 1 from May 1997 to January 2004. Of these, 341 (64.2%) remitted and 137 (25.8%) dropped out. Early exits were due to protocol violations (42/137; 30.7%) (including primary diagnosis other than major depressive disorder [25/42], drug dependence [4/42], and medical problems [3/42]); withdrawal of consent (52/137; 38%) (including concern over possible memory effects [5/52] and refusal of further ECT with no reason given [27/52]); adverse events (37/137; 27%) (including memory and cognition complaints [21/37] and intercurrent medical conditions [8/37]); and other (4%).

Of the 341 patients who remitted, 70 (20.5%) relapsed and 67 (19.6%) dropped out during the interim week before randomization, leaving 204 (59.8%) eligible for randomization. Three patients refused randomization and 201 were randomized. Ten patients (3 in the C-ECT group and 7 in the C-Pharm group) did not receive a treatment and 7 patients (6 in the C-ECT group and 1 in the C-Pharm group) received 1 treatment but did not return for at least 1 postbaseline visit, yielding a modified intention-to-treat (ITT) efficacy evaluable sample of 184 patients (89 in the C-ECT group and 95 in the C-Pharm group). The primary reasons given for refusing treatment or failing to return for the week 1 visit included being afraid of memory problems or not wanting ECT (2) and no reason given (7) for the C-ECT group, and wanting ECT (3), meeting exclusion criteria (2), believing treatment no longer necessary (1), and no reason given (2) for the C-Pharm group. There were no statistically significant differences in demographic (age, race, and sex) and clinical characteristics (percentage with psychoses, HRSD₂₄ phase 1 baseline and end, age at illness onset, length of current episode, and number of prior episodes and hospitalizations) between phase 1 remitters who did (n=201) or did not (n=140) enter the randomized continuation phase (phase 2) or between randomized patients in the modified ITT efficacy evaluable sample (n=184) and those not in the modified ITT sample (n=17). In the modified ITT efficacy sample, 15 patients (16.9%) in the C-ECT group and 21 patients (22.1%) in the C-Pharm group exited early. The most common reason for early exit was that the patient no longer wanted or thought he or she needed further ECT in the C-ECT group (n=8) and adverse event occurrence for the C-Pharm group (n=13).

Study Sample Characteristics

For the modified ITT sample (n=184), 67.9% were female, 87.5% were white, and the mean±SD age was 57.2±16.1 years. Clinical characteristics included 35.9% with psychotic features, mean±SD age at illness onset of 42.4±19.6 years, a mean±SD of 2.2±2.9 prior episodes

nician. At specified time points (phase 1 baseline and end, phase 2 baseline, week 4, week 12, week 24, and study exit [relapse]), the continuous rater and study psychiatrist each performed independent HRSD₂₄ 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 clinical raters underwent an intensive prestudy training period conducted by a senior-level, highly experienced psychometrician (M.B.). An independent blind rater located at the University of Texas Southwestern Medical Center but not affiliated with the clinical center rated a random sample of time-blinded videotapes of HRSD₂₄ patient interviews (intra-class correlation¹⁸ between the independent blind rater and clinical ratings, 0.9). Additional longitudinal quality control measures to prevent rater drift over time required that clinical raters rate HRSD₂₄ videotapes mailed by the independent blind rater to the centers every 2 to 3 months. When significant deviations of clinical ratings from those of the independent blind rater were detected (ie, scores deviated outside a 2-point range for any 1 rater on more than 1 of the tapes), telephone-based corrective feedback was instituted by the independent blind rater. Three corrective training sessions were required during the study.

STATISTICAL ANALYSES

The primary efficacy analyses used a modified intention-to-treat sample that comprised all randomized patients who had at least 1 postbaseline assessment.¹⁹ Survival (ie, relapse-free) times were compared using Kaplan-Meier survival curves and the log-rank test. In the a priori specified primary analysis, Cox proportional hazards model regression analysis was used to compare time to relapse for C-ECT and C-Pharm in a model that contained only effects for treatment and clinical center. In additional secondary analyses, a full multivariable model with psychosis, age, and sex added was used to evaluate the effect of treatment adjusted for the added covariables. These covariables were included as a priori specified covariables. The 95% confidence interval (CI) estimates of the hazard ratio from the regression models were used to describe the unadjusted and covariate-adjusted treatment effects (effect size). Interaction terms (eg, treatment by psychosis status) were also added to the full model to determine if the treatment effect was different across strata of the a priori hypothesized moderating variables.

All statistical tests used a 2-tailed $\alpha = .05$ level of significance unless otherwise specified and were performed using SAS statistical software, version 9 (SAS Institute Inc, Cary, NC). For comparisons of survival distributions, we had approximately 80% power to detect a hazard ratio of 1.7 or larger.

Adjusted means for mMMSE (adjusted for baseline and clinical center) for the 3- and 6-month (end of study) time points were compared using a general linear model approach. To take into account the comparisons at multiple time points, we used Bonferroni corrected *P* values. The primary comparisons were performed for the group who had not relapsed at the given time point (observed data) for whom a baseline assessment was also made. Adverse events are reported as proportions for each group. Mean blood levels for lithium and nortriptyline at the end of study are reported.

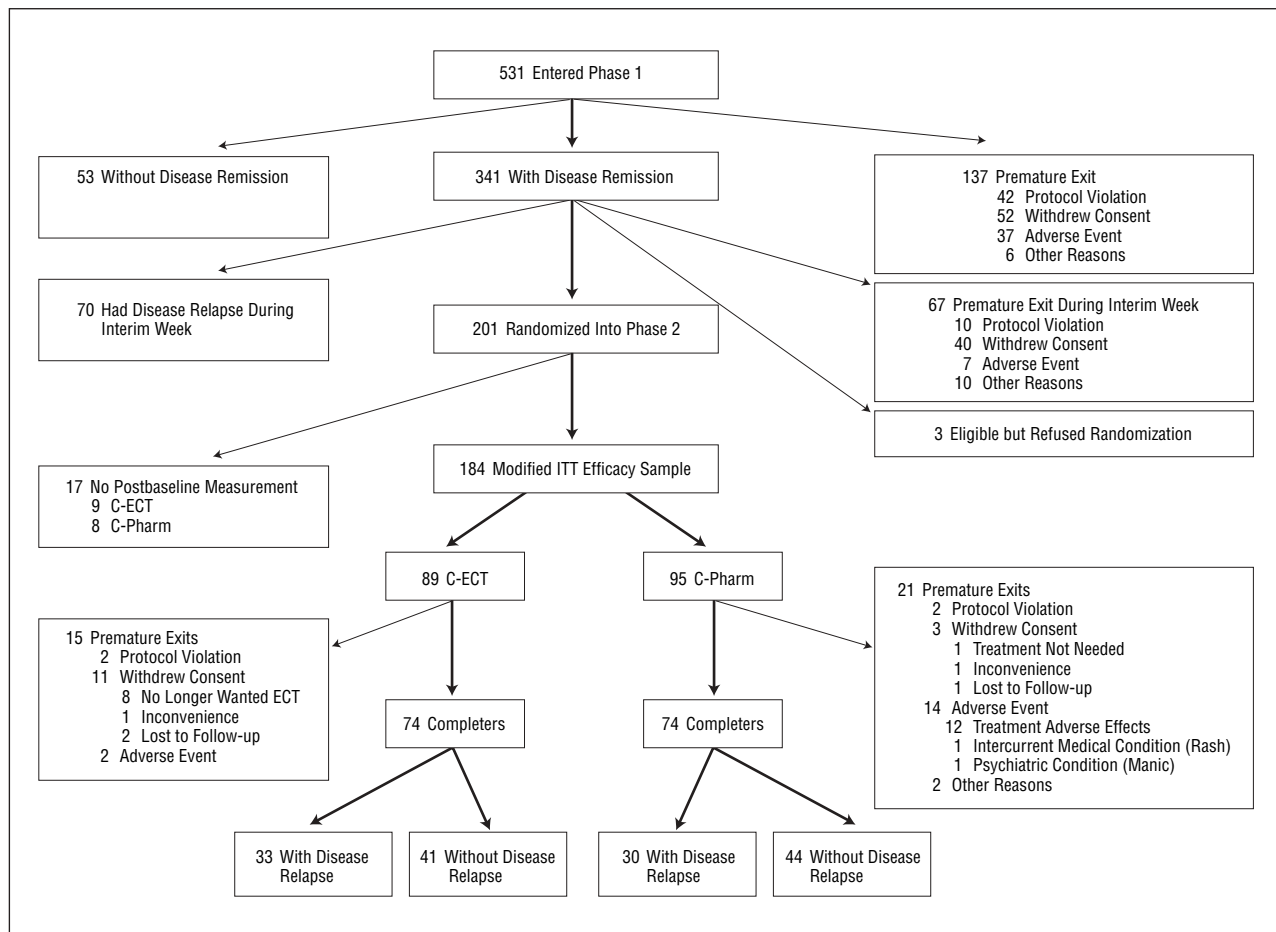


Figure 1. Participant flow for acute electroconvulsive therapy (ECT) phase (phase 1) and randomized continuation phase (phase 2). C-ECT indicates continuation ECT; C-Pharm, combination of lithium carbonate plus nortriptyline hydrochloride.

of major depressive disorder, and mean \pm SD HRSD₂₄ scores of 34.8 ± 7.2 at study entry (acute phase) and 6.4 ± 2.7 at the time of randomization. Patients in the C-ECT group were older than those in the C-Pharm group (59.6 ± 15.3 vs 55.0 ± 16.5 ; $t_{182} = -1.97$; $P = .05$); no other statistically significant differences in demographic or clinical variables for the treatment groups were observed (**Table 1**). Mean \pm SD blood levels at the final visit for the C-Pharm group were 81.4 ± 58.5 ng/mL for nortriptyline and 0.53 ± 0.38 mEq/L for lithium. Mean blood levels of nortriptyline and lithium were not significantly different between those with and without disease relapse. Of the 117 patients who had usable Antidepressant Treatment History Form information, 50 (42.7%) were rated as having had at least one adequate pharmacotherapy trial. No significant difference was found in this proportion for the C-ECT arm compared with the C-Pharm arm (48.2% vs 37.7%, respectively; Fisher exact test: $df = 1$, $P = .27$).

Dropouts

Among the modified ITT sample, 36 (19.6%) of 184 exited the study prematurely with no statistically significant differences in baseline demographic or clinical characteristics between completers and early exits. Fifteen (16.9%) of 89 patients in the C-ECT group and 21 (22.1%) of 95 patients in the C-Pharm group exited early ($\chi^2_1 = 0.81$;

$P = .37$), with no statistically significant differences in demographic and baseline clinical characteristics for these 2 groups. Among the early exits, the mean \pm SD time in the study was 7.9 ± 5.9 weeks for the C-ECT group compared with 7.7 ± 5.2 weeks for the C-Pharm group ($t_{34} = -.08$; $P = .94$), with a median time in the study of 6 weeks for both groups. In addition, no statistically significant difference was found in mean HRSD₂₄ total score for the last study visit before early exit for the 2 treatment groups (C-ECT: 12.3 ± 8.6 ; C-Pharm: 10.4 ± 7.6 ; $t_{34} = -.72$; $P = .48$). Ten (67%) of 15 dropouts in the C-ECT group and 11 (52.4%) of 21 in the C-Pharm group had HRSD₂₄ scores of 10 or less (ie, remained fully remitted) at the time of dropout.

EFFICACY RESULTS

In the C-ECT group, 37.1% relapsed, 46.1% remained remitted at study end, and 16.8% dropped out. In the C-Pharm group, 31.6% relapsed, 46.3% remained remitted, and 22.1% dropped out, with no statistically significant difference among groups in the 3 outcome categories (relapse, no relapse, and dropout) ($\chi^2_2 = 1.05$; $P = .59$). Among study completers (74 in the C-ECT group and 74 in the C-Pharm group), the relapse proportions were 44.6% (95% CI, 33.3%-55.9%) for C-ECT and 40.5% (95% CI, 29.4%-51.7%) for C-Pharm.

Table 1. Patient Characteristics for the Intention-to-Treat Sample and by Treatment

Characteristic*	Total Sample (N = 184)	C-ECT (n = 89)	C-Pharm (n = 95)	P Value (Test Statistic, df)
Age, y	57.2 ± 16.1	59.6 ± 15.3	55.0 ± 16.5	.05† (-1.97, 182)
Age group, y				
18-44	24.4 (45/184)	16.9 (15/89)	31.6 (30/95)	
45-64	39.7 (73/184)	42.7 (38/89)	36.8 (35/95)	
65-85	35.9 (66/184)	40.5 (36/89)	31.6 (30/95)	
Female	67.9 (125/184)	70.8 (63/89)	65.3 (62/95)	.42‡ (0.64, 1)
White	87.5 (161/184)	89.9 (80/89)	85.3 (81/95)	.34‡ (0.90, 1)
Patients with psychosis	35.9 (66/184)	34.8 (31/89)	36.8 (35/95)	.78‡ (0.08, 1)
HRSD ₂₄ at baseline phase 1	34.8 ± 7.2	35.6 ± 8.0	33.9 ± 6.3	.13† (-1.58, 182)
HRSD ₂₄ at phase 1 end	5.9 ± 2.9	5.7 ± 3.0	6.1 ± 2.8	.39† (0.87, 182)
HRSD ₂₄ at baseline phase 2	6.4 ± 2.7	6.5 ± 2.7	6.3 ± 2.7	.67† (-0.43, 182)
mMMSE at baseline phase 2	47.0 ± 6.6	46.2 ± 7.1	47.7 ± 6.1	.13† (-1.57, 172)
Age at illness onset, y	42.4 ± 19.6	44.3 ± 20.7	40.7 ± 18.4	.23† (-1.20, 169)
Prior episodes	2.2 ± 2.9	2.1 ± 2.8	2.2 ± 3.1	.71† (0.37, 161)
Prior hospitalization	2.5 ± 2.0	2.8 ± 2.3	2.3 ± 1.7	.14† (-1.47, 169)
Length of current episode, wk	46.9 ± 64.4	49.3 ± 67.3	44.8 ± 62.1	.66† (0.45, 165)
Seizure threshold (baseline phase 1)§	26.0 ± 15.0	28.1 ± 15.5	23.9 ± 14.4	.06† (-1.91, 182)
ECT in phase 1	7.3 ± 3.1	7.2 ± 2.9	7.5 ± 3.3	.54† (0.62, 182)

Abbreviations: C-ECT, continuation electroconvulsive therapy; C-Pharm, combination of lithium carbonate plus nortriptyline hydrochloride; HRSD₂₄, 24-item Hamilton Rating Scale for Depression; mMMSE, modified Mini-Mental State Examination.

*Data are presented as mean ± SD for continuous variables and percentages (No./total No.) for categorical variables.

†P value from pooled *t* test or Wilcoxon rank sum test comparing means for C-ECT vs C-Pharm groups.

‡P value from χ^2 test comparing probability for C-ECT vs C-Pharm groups.

§Seizure threshold units are percentage of total device charge output.

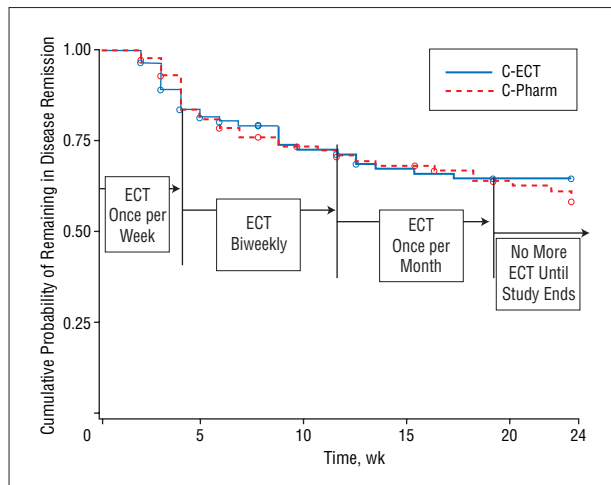


Figure 2. Kaplan-Meier curves showing proportion of patients who remained in disease remission (not disease relapse) during the continuation phase (phase 2). Log-rank test comparing distributions of time to relapse for C-ECT vs C-Pharm: $\chi^2=0.30$; $P=.59$. C-ECT indicates continuation electroconvulsive therapy; C-Pharm, combination of lithium carbonate plus nortriptyline hydrochloride.

As indicated by the Kaplan-Meier survival curves shown in **Figure 2**, the patterns of relapse-free times were similar for the C-ECT and C-Pharm groups (log-rank test comparing distributions of time to relapse; $\chi^2=0.297$; $P=.59$). Note that week 4 is the final weekly ECT session and week 16 is the first of the monthly C-ECT treatments, with the final ECT session given at week 20. Among patients who relapsed ($n=63$), the mean ± SD time to relapse for the C-ECT group was 9.1 ± 7.0 weeks compared with 6.7 ± 4.7 weeks for the C-Pharm group ($t_{61}=-1.53$; $P=.13$); median times to re-

lapse were 5.5 and 4.0 weeks for the C-ECT and C-Pharm groups, respectively (Wilcoxon rank sum test $P=.22$), indicating that 50% of relapses in both groups occurred within the first 4 (C-Pharm) to 6 (C-ECT) weeks.

In the primary Cox proportional hazards model regression analyses (**Table 2**), the relapse rates for the C-ECT and C-Pharm groups were not significantly different (unadjusted hazard ratio for C-ECT compared with C-Pharm (reference group), 1.1; 95% CI, 0.7-1.9; $P=.63$). After adjustment for clinical center, psychosis status, age, and sex, the relapse rate for C-ECT compared with C-Pharm (hazard ratio) was also not statistically significantly different between the treatment groups (adjusted hazard ratio, 1.2; 95% CI, 0.7-1.9; $P=.53$). None of the evaluated covariables (psychosis, age, sex, center) were found to significantly moderate the effect of treatment on relapse as indicated by nonstatistically significant interaction terms (treatment by putative moderating variable) added individually to the full model, although failure to find a moderating effect may be attributable to low power to detect these effects. Specifically, we found no statistical evidence that the treatment affected relapse rate differentially in, for example, patients with vs without psychoses. These analyses focused on a priori hypothesized moderating variables. An extensive exploration of predictors and moderators or mediators of relapse in these data will be reported elsewhere.

In a study with an almost identical design to that of this one, Sackeim et al¹³ reported a 84% relapse among a placebo group ($n=29$; 95% CI, 70%-99%). In comparison with this historical placebo control, both the C-ECT group and the C-Pharm groups had significantly

Table 2. Survival Analysis Results From Cox Proportional Hazards Regression Model*

Model	Hazard Ratio (95% CI)	P Value
Model 1		
Treatment†	1.13 (0.69-1.36)	.62
Model 2		
Treatment†	1.18 (0.71-1.94)	.53
Psychosis‡	0.56 (0.32-1.00)	.05
Age§	0.99 (0.97-1.00)	.13
Sex	0.63 (0.37-1.08)	.09

Abbreviations: C-ECT, continuation electroconvulsive therapy; C-Pharm, combination of lithium carbonate plus nortriptyline hydrochloride; CI, confidence interval.

*Results are presented for 2 Cox proportional hazards regression models. Model 1 contained treatment, and model 2 (adjusted model) contained treatment, psychosis, age, and sex. Model 2 also contained clinical center as a covariate.

†Reference category was C-Pharm; hazard ratio of relapse for C-ECT compared with C-Pharm. The C-ECT group was 1.2 times more likely to relapse than C-Pharm group.

‡Reference category was no psychosis; hazard ratio of relapse for psychosis compared with no-psychosis group. A patient with psychotic features is 0.56 times less likely to relapse than a patient without psychotic features, after adjustment for treatment, age, sex, and center.

§Age was entered as a continuous variable; hazard ratio represents the change in the hazard of relapse for every 1-year increment (decrement) in age. As age increases by 1 year, the estimated hazard ratio is decreased (since the parameter estimate is negative) 0.99 times.

||Reference category was male; hazard ratio of relapse for female compared with male group. A female patient is 0.63 times less likely to relapse than a male patient after adjustment for treatment, age, psychosis, and clinical center.

lower relapse rates (χ^2 ; $P < .001$ for both comparisons). Significant differences with the historical placebo group held even when assuming that all dropouts in the C-ECT and C-Pharm groups were relapsers (χ^2 ; C-ECT vs placebo: $P = .006$; C-Pharm vs placebo: $P = .005$).

The mean \pm SE mMMSE scores were not statistically significantly different for C-Pharm compared with C-ECT at phase 2 baseline (C-ECT: 46.2 ± 0.8 ; C-Pharm: 47.7 ± 0.7 ; $t_{172} = 1.57$; $P = .12$). Among those who had not relapsed or dropped out at 3 months, the baseline and center adjusted mean \pm SE mMMSE scores were 47.7 ± 0.5 for the C-ECT group and 49.4 ± 0.5 for the C-Pharm group ($t_{93} = 2.59$; Bonferroni corrected $P = .02$). The adjusted mean mMMSE scores for C-Pharm vs C-ECT were not significantly different at study end (6 months) among those who had not relapsed or dropped out (C-ECT: 48.4 ± 0.5 ; C-Pharm: 49.1 ± 0.5 ; $t_{73} = 1.11$; Bonferroni corrected $P = .54$). The mMMSE scores for both groups improved, on average, during the 6-month period, with a mean change from baseline not significantly different for the C-ECT and C-Pharm groups. Among the 15 patients in the C-ECT group who exited early, 8 indicated that they no longer wanted ECT (largely because they experienced the treatment as unpleasant), and 2 exited because of adverse events (headache and memory loss). In the C-Pharm group, 13 patients exited early because of adverse events from the medications. As expected, the most common adverse events in the C-Pharm group were dry mouth (27.4%), tremor (17.9%), drowsiness and fatigue (14.7%), and constipation (13.7%).

This study is the first randomized controlled clinical trial, to our knowledge, to assess the efficacy and tolerability of C-ECT as a relapse prevention strategy in unipolar major depression. We found no statistical evidence to suggest that one treatment arm had greater efficacy in relapse prevention than the other. Our C-Pharm results are comparable to those of Sackeim et al,¹³ who have shown a nearly identical relapse rate in a cohort of similar patients given the identical pharmacotherapy regimen in a study comparing post-ECT relapse rates among placebo, nortriptyline alone, and nortriptyline and lithium in combination. The relapse rates in the C-ECT and C-Pharm arms are also markedly superior to the relapse rates with either placebo or monotherapy with nortriptyline reported by Sackeim et al.¹³ Although both C-ECT and C-Pharm were shown to be modestly effective in preventing depressive relapse, an important interpretation of these data is that relapse or treatment discontinuation rates after successful ECT remain unacceptably high with standard treatment regimens. Such high rates were also documented in an effectiveness study of ECT in community settings in the United States²⁰ and in a smaller, observational study in the Netherlands.²¹ In general, relapse rates after episodes of major depression treated with any modality of continuation therapy are unacceptably high.^{22,23}

We observed that most relapses occurred early in continuation treatment, a finding also consistent with that of Sackeim et al.¹³ However, the definition of relapse in our study is a strict one, and many patients who were declared to have disease relapse were substantially improved clinically compared with phase 1 baseline measurements.

Both treatments were well tolerated. The adverse effect profile of ECT includes cognitive effects and common but generally minor adverse effects on treatment days of headache, nausea, and muscle aches. The adverse effects of nortriptyline and lithium are well known and include anticholinergic and lithium-specific effects. The adverse effect profiles of the 2 treatments are markedly different, and it is possible that patients may prefer one treatment over the other based on individual assessments of tolerability.

On the basis of the mMMSE as a measure of cognitive effects, both groups improved, on average, over all time points. This was anticipated, given the well-known short-term effects of ECT on cognition and their documented trajectory of improvement over time.^{24,25} A more comprehensive assessment of the cognitive effects of these 2 treatments is deferred to a report that will include analysis of the full neuropsychological test battery data.

A strength of the study is the size of the patient sample, making it one of the largest randomized ECT data sets in the modern literature. The sample is also geographically diverse and represents typical, severely depressed, often treatment-refractory patients, who are not uncommon in contemporary practice. Other strengths of the study are the careful standardization of the ECT and medication management procedures and the innovative approach to the

standardization of assessments, given the constraints of a nonblinded primary efficacy outcome measure.

Limitations of the study include the lack of blindness of the raters for the HRSD₂₄ ratings (although measures were taken to minimize and assess rater bias through comparison with an independent blind rater) and the lack of flexibility in the C-ECT schedule. In real-world practice, continuation and maintenance ECT schedules are more individualized to each patient's requirements based on patterns of historical and current symptom recurrence. Such flexibility could potentially decrease the likelihood of relapse. The design feature of offering C-ECT to all acute ECT remitters might be criticized as not reflective of real-world practice, limiting the generalizability of our results. In fact, contemporary ECT practice is to offer at least a brief period of C-ECT to a much higher percentage of patients than in the past. Thus, the design of our study is actually more consistent with contemporary practice than practice of 5 to 10 years ago, in which multiple post-ECT pharmacotherapy regimens would have to fail for the patient to be eligible for continuation or maintenance ECT. The study design feature of the interim week was intended to ensure stable remission, but delaying pharmacotherapy for 1 week after remission with short-term ECT might have weakened the C-Pharm arm. On the other hand, it may have strengthened both arms by "weeding out" patients prone to early relapse. The interim week may limit generalizability of our results to patients whose acute remission is robust enough to be completely sustained without treatment for 1 week. Additionally, the blood level for lithium is lower than optimally targeted (but similar to that of the study by Sackeim et al¹³), suggesting that lack of compliance and tolerability issues may have weakened the arms in both studies. The specific medications in the pharmacotherapy arm, although carefully chosen to represent those medications about which the most published relapse prevention data were available, might be criticized as outmoded, given the variety of currently available antidepressants and anticonvulsant mood stabilizers. Further study of different medication combinations (such as a selective serotonin reuptake inhibitor and an anticonvulsant) is warranted. We acknowledge the potential bias produced by use of patients who tolerated and responded to ECT (enriched design); however, the aim of the study was to evaluate relapse strategies after successful ECT with the target population for inference represented by the sample randomized in this study. Use of the modified ITT sample, which did not include the 17 patients from whom no postbaseline data were obtained, limits generalizability to those patients who are willing to accept or can tolerate either treatment modality. Failure of the study to find statistically significant differences for both efficacy and safety outcomes cannot be taken to mean that the outcomes in the 2 groups are equal. For the primary efficacy outcome, although the study was designed to have adequate power to detect clinically meaningful effects, failure to find statistically significant differences cannot be interpreted to mean that relapse rates for the 2 groups are exactly equal in the populations of inference. Lack of statistically significant differences could be the result of low statistical power. The small number

of minority patients in the sample (which reflects the demographics of patients who receive ECT in the United States)²⁶ is a further limitation of the study.

In summary, our data demonstrate moderate protection against depressive relapse by both C-Pharm and C-ECT and provide no statistical evidence to suggest that one treatment arm had greater efficacy in relapse prevention than the other. Physicians and patients need to select 1 of the 2 treatment options based on judgments about tolerability for the individual patient and patient preference. Further research is needed to explore individual patient characteristics (either historical or potential biomarkers) that can be used to predict which patients will do best with which treatment. Most important, our study begs the question of how much better relapse prevention strategies might be with combined modalities, that is, concurrent use of continuation or maintenance ECT and multidrug pharmacotherapy regimens. Such studies will allow optimized therapy algorithms for depressed patients in whom medication and psychotherapy treatments have failed. There is an urgent need for treatments that will further decrease the unacceptably high relapse rates after recovery from an episode of major depression.

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