Continuation Pharmacotherapy in the Prevention of Relapse Following Electroconvulsive Therapy

A Randomized Controlled Trial

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Context Electroconvulsive therapy (ECT) is highly effective for treatment of major depression, but naturalistic studies show a high rate of relapse after discontinuation of ECT.

Objective To determine the efficacy of continuation pharmacotherapy with nortriptyline hydrochloride or combination nortriptyline and lithium carbonate in preventing post-ECT relapse.

Design Randomized, double-blind, placebo-controlled trial conducted from 1993 to 1998, stratified by medication resistance or presence of psychotic depression in the index episode.

Setting Two university-based hospitals and 1 private psychiatric hospital.

Patients Of 290 patients with unipolar major depression recruited through clinical referral who completed an open ECT treatment phase, 159 patients met remitter criteria; 84 remitting patients were eligible and agreed to participate in the continuation study.

Interventions Patients were randomly assigned to receive continuation treatment for 24 weeks with placebo (n=29), nortriptyline (target steady-state level, 75-125 ng/mL) (n=27), or combination nortriptyline and lithium (target steady-state level, 0.5-0.9 mEq/L) (n=28).

Main Outcome Measure Relapse of major depressive episode, compared among the 3 continuation groups.

Results Nortriptyline-lithium combination therapy had a marked advantage in time to relapse, superior to both placebo and nortriptyline alone. Over the 24-week trial, the relapse rate for placebo was 84% (95% confidence interval [CI], 70%-99%); for nortriptyline, 60% (95% CI, 41%-79%); and for nortriptyline-lithium, 39% (95% CI, 19%-59%). All but 1 instance of relapse with nortriptyline-lithium occurred within 5 weeks of ECT termination, while relapse continued throughout treatment with placebo or nortriptyline alone. Medication-resistant patients, female patients, and those with more severe depressive symptoms following ECT had more rapid relapse.

Conclusions Our study indicates that without active treatment, virtually all remitted patients relapse within 6 months of stopping ECT. Monotherapy with nortriptyline has limited efficacy. The combination of nortriptyline and lithium is more effective, but the relapse rate is still high, particularly during the first month of continuation therapy.

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ELECTROCONVULSIVE THERAPY (ECT) is usually administered to patients with severe and medication-resistant major depression.[1] The number of ECT procedures performed in the United States exceeds coronary bypass, appendectomy, or hernia repair.[2] While the response rate to ECT in major depression is high,[1,3] relapse is a key problem.[4] Naturalistic studies show that the relapse rate during the 6 to 12 months following ECT exceeds 50%.[5-15]

Electroconvulsive therapy is the only somatic treatment in psychiatry that is typically discontinued following response, yet patients untreated following ECT response have high rates of relapse.[16-19] Studies in the 1960s suggested that continuation therapy with a tricyclic antidepressant (TCA) or monoamine oxidase inhibitor markedly reduced the 6-month post-ECT relapse rate.[16-18] Post-ECT monotherapy with antidepressant medication is now standard.[9,20-23] However, the evidence supporting this practice is flawed, and the

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recent naturalistic studies document high relapse rates.

Post-ECT continuation pharmacotherapy has been based on 3 studies conducted in the 1960s.[16-18] A primary goal of those studies was to determine whether concurrent treatment with TCAs or monoamine oxidase inhibitors reduced the number of ECT treatments needed. Following ECT, patients continued taking active medication or placebo or no subsequent treatment. Using 6-month follow-up periods, the findings were consistent. Patients who received a TCA or monoamine oxidase inhibitor during and following ECT had a relapse rate of approximately 20%, compared with 50% in the control groups. There are major concerns about this research.[4,24] At that time, ECT was a treatment of first choice.[25,26] Relevance for continuation therapy in medication-resistant ECT responders is uncertain. Second, some patients likely benefited from the concurrent antidepressant during ECT, and continued to benefit from the medication as continuation therapy. Since use of ECT now centers on medication-resistant patients,[1,21,27] the relevance of this early research is questionable.

We conducted a randomized, double-blind, placebo-controlled trial of continuation pharmacotherapy following ECT response. The treatments were a TCA (nortriptyline hydrochloride), combination treatment with nortriptyline and lithium carbonate, or placebo. A placebo-controlled trial following ECT had never been conducted in the United States. This trial was justified since the relapse rates in recent follow-up studies[5-15] often exceeded those seen with placebo in the controlled investigations from an earlier era.[16-18] A placebo-controlled trial was also justified by our hypothesis that TCA monotherapy, the best documented treatment in post-ECT relapse prevention,[16-18] has limited efficacy. Monotherapy with nortriptyline was tested since (1) early research suggested that TCA continuation therapy was effective in relapse prevention[16-18]; (2) concern that newer agents, such as selective serotonin reuptake inhibitors (SSRIs), may be less effective than TCAs in treatment of the severe episodes characteristic of ECT patients[28-33]; and (3) given the widespread use of SSRIs and other newer agents as first-line treatments, a low probability that ECT responders would have received an adequate TCA trial during the episode.[34] We hypothesized, however, that the nortriptyline-lithium combination would be most efficacious, given the evidence that combined TCA-lithium treatment is particularly effective in medication-resistant major depression,[35-41] and the supposition that regimens effective in the acute treatment of medication-resistant major depression exert protective effects as continuation treatment. Nortriptyline-lithium was also selected since few ECT remitters would have received this treatment during the episode.[34,42]

METHODS

Study Site and Study Participation

The study was conducted at the Carrier Foundation (Belle Meade, NJ), a private psychiatric hospital, and at university-based psychiatric facilities of the University of Iowa (Iowa City) and Western Psychiatric Institute and Clinic (WPIC; Pittsburgh, Pa). The New York State Psychiatric Institute (NYSPI; New York) was the coordinating and monitoring center. Using the *Schedule for Affective Disorders and Schizophrenia*,[43] patients met the research diagnostic criteria[44] for major depressive disorder. They had a pretreatment score of 21 or higher on the Hamilton Rating Scale for Depression (HRSD; 24-item scale).[45] Patients were excluded if they had a history of bipolar disorder, schizophrenia, schizoaffective disorder, nonmood disorder psychosis, neurological illness, alcohol or drug abuse within the past year, ECT within the past 6 months, or severe medical illness that markedly increased the risks of ECT (eg, unstable or severe cardiovascular conditions, aneurysm or vascular malformation susceptible to rupture, severe chronic obstructive pulmonary disease).

Participants were recruited from those clinically referred for ECT. Over a 6-year period (1993-1998), 349 patients consented and participated in the pre-ECT screening (FIGURE 1). Patients who met inclusion/exclusion criteria for the open ECT phase were completers if they received at least 5 treatments or ended ECT earlier due to response and did not receive any psychotropic medication during the ECT course other than lorazepam (≤3 mg/d). Of the 59 patients who did not contribute to ECT outcome data, 17 patients were dropped before ECT due to diagnostic exclusions; 14 patients could not be withdrawn from psychotropics before (n=7) or during (n=7) ECT; 12 patients terminated ECT against medical advice prior to the fifth treatment; 9 developed an intercurrent illness so ECT was not initiated (n=2) or was interrupted (n=7) (all before the fifth treatment); 6 patients withdrew consent before ECT; and 1 dropped below the inclusion threshold (HRSD score of 21) before starting ECT. Only 2 of 59 dropouts (prohibited medications) should have contributed to ECT efficacy analyses, but end point evaluations were not obtained.

To enter the continuation trial, patients had to achieve at least a 60% reduction in HRSD scores relative to pre-ECT baseline, with a maximum score of 10 both at an assessment within 2 days of ECT discontinuation and reassessment 4 to 8 days following ECT termination, while free of psychotropic medication. Since the extent of residual symptoms is predictive of relapse following antidepressant treatment,[46,47] the remitter criteria were particularly stringent. These criteria required both a substantial symptomatic reduction and a low absolute score both immediately and 4 to 8 days following ECT. Patients with medical contraindications to nortriptyline or lithium were excluded. Patients provided separate informed consent for participation in the ECT and continuation pharmacotherapy phases, and capacity to consent was assessed at each time point. The institutional review boards at each enrollment site and the NYSPI approved the study. Assuming a relapse rate of 50% with placebo, the goal was to enroll at least 25 patients in each randomized treatment condition to have

at least an 80% probability of detecting a significant advantage in relapse time for an active treatment in a primary, intent-to-treat, parametric survival analysis.

Study Design

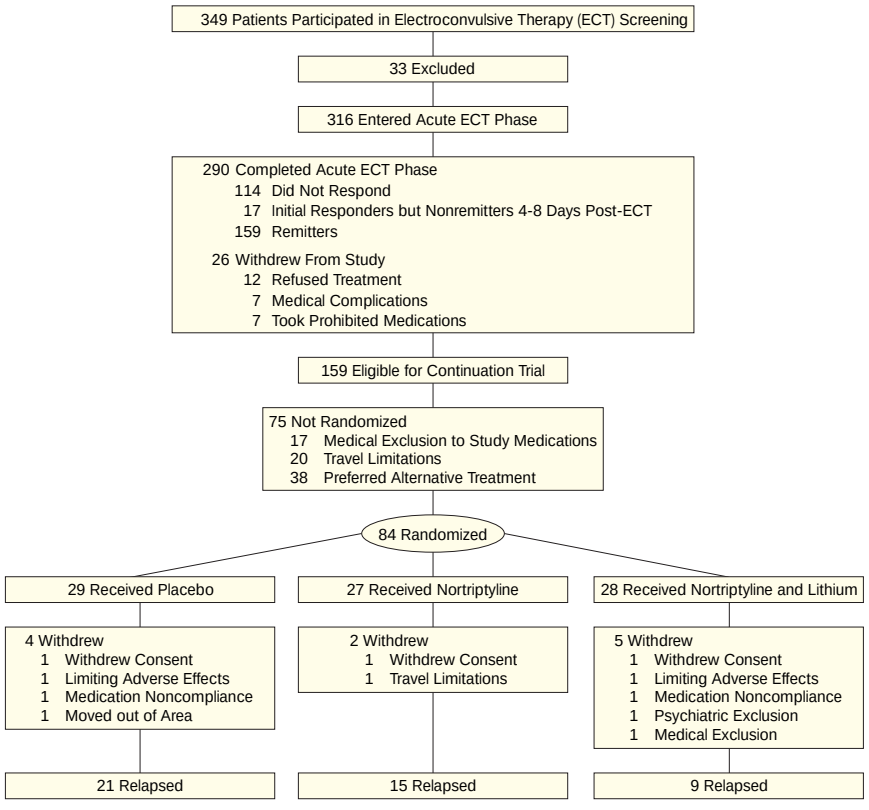
Patients were withdrawn from psychotropic medications, other than lorazepam (up to 3 mg/d) as needed, before starting ECT. Methohexital (0.75-1.0 mg/kg) and succinylcholine chloride (0.75-1.0 mg/kg) were the anesthetic medications, with preadministration of an anticholinergic agent (0.4-6 mg of atropine or 0.2-4 mg of glycopyrrolate). Based on clinical judgment, patients received either right unilateral or bilateral ECT, using the d'Elia[48] or bifrontotemporal[21] placements, respectively. Electroconvulsive therapy was given 3 times per week with a customized MECTA SR1 device (MECTA Corp, Lake Oswego, Ore), which had double the maximal charge output of commercial devices in the United States. Seizure threshold was quantified at the first treatment using empirical titration.[49] For right unilateral ECT, dosage at subsequent treatments exceeded initial threshold by at least 150%. Patients who did not show substantial improvement to right unilateral ECT within 5 to 8 treatments were switched to bilateral ECT. To be considered adequate, minimal seizure duration was 20 seconds of motor or 25 seconds of electroencephalogram manifestation.[21] Length of the ECT course was determined on clinical grounds.

The ECT remitters were randomized to 3 continuation pharmacotherapy groups, stratified by classification of the index episode as psychotic depression; medication-resistant nonpsychotic depression; and nonpsychotic depression without medication resistance. Medication resistance was rated using the Antidepressant Treatment History Form.[8,34,50] Medication-resistant nonpsychotic patients had to have received at least 1 adequate antidepressant trial prior to ECT. Patients with psychotic depression were not further stratified by resistance classification since only 4 (4.3%) of 92 such patients received an adequate combination antidepressant-antipsychotic trial during the episode.[42]

Using a randomly permuted block procedure consisting of blocks of 6 patients (within site and the 3 strata), each treatment condition was equally represented. The study psychiatrist who completed the Antidepressant Treatment History Form communicated the patient classification to the pharmacist who assigned the next available patient number within the stratum. Only the site pharmacist, the study coordinator at NYSPI, and the NYSPI laboratory conducting plasma level assays had access to the randomization code. The randomization code was generated by the study coordinator at NYSPI based on the randomization tables provided by Fleiss.[51] Treatment teams, outcome assessors, and data analysts were blind to treatment assignment.

Medication was administered in sealed capsules containing 25 mg of nortriptyline, 300 mg of lithium, or microcrystalline cellulose (placebo). The capsules containing nortriptyline or lithium were distinct in appearance, and each was matched with placebo capsules identical in size, weight, appearance, and taste. Each patient was given 2 sets of pills. On the first study day, 50 mg of nortriptyline or its placebo and 600 mg of lithium or its placebo were administered. Blood samples were obtained 24 hours later and estimates were determined for the oral dose needed to produce steady-state levels of 100 ng/mL of nortriptyline and 0.7 mEq/L of lithium.[52-54] On days 3 and 4, depending on the estimate, oral doses were adjusted and maintained until plasma levels were again taken on days 9 through 11. The goal was to maintain nortriptyline levels between 75 and 125 ng/mL and lithium levels between 0.5 and 0.9 mEq/L. During the 24-week trial, plasma levels were determined on 10 occasions. A yoked-control procedure was used, with a

Figure 1. Participant Flow



psychiatrist at NYSPI reporting simulated nortriptyline and lithium values for patients receiving placebo, based on matching by sex, age, and weight with patients who were receiving active medication.

Patients were evaluated at weekly intervals for the first 4 weeks, at 2-week intervals for the next 8 weeks, and at 4-week intervals for the remaining 12 weeks. They were contacted by telephone at weekly intervals between visits. Clinical ratings during the continuation phase were obtained by the same blinded evaluator (continuous rater) who evaluated patients throughout the ECT course. During the continuation trial, a blinded study psychiatrist assessed adverse effects and vital signs, adjusted medication or placebo dosage (based on plasma levels reported by NYSPI and adverse effects), and completed clinical ratings. To evaluate the adequacy of the blinding, patients guessed their treatment assignment as placebo, nortriptyline, or nortriptyline-lithium at study exit. Patients who dropped out of the study or relapsed were offered clinical care by a psychiatrist at the research site not affiliated with the study or the follow-up evaluation of the particular patient.

Time to relapse was the main outcome measure. The criteria for relapse were a mean HRSD score (continuous rater and study psychiatrist) of at least 16 that was maintained for at least 1 week (over 2 consecutive visits) and a mean absolute increase of at least 10 points at 2 consecutive visits relative to continuation trial baseline. These criteria reflected a clinical worsening for which most clinicians would abandon the current treatment in favor of an alternative.

At the pre-ECT evaluation, a research nurse completed ratings on the Cumulative Illness Rating Scale[55] to assess medical comorbidity. At all major time points (pre-ECT, post-ECT, start of continuation trial [day 0], week 12, week 24, and relapse), the HRSD, Clinical Global Impression,[56] and Global Assessment Scale[43] scores were completed by the continuous rater and the study psychiatrist. At each site, intraclass correlation coefficients for the 2 raters exceeded 0.97, 0.93, and 0.90 for HRSD, Clinical Global Impression, and Global Assessment Scale scores, respectively. A site-independent, time-blind clinician at NYSPI rated 239 videotapes of continuous rater interviews conducted at random intervals during the ECT and continuation phases. The intraclass correlation coefficients were 0.97, 0.96, and 0.95 for HRSD, Clinical Global Impression, and Global Assessment Scale scores, respectively. The HRSD, Clinical Global Impression, and Global Assessment Scale scores reported below are the continuous rater evaluations.

At each visit in the continuation phase, a blinded study psychiatrist completed the Treatment Emergent Symptom Scale.[56] Forty-eight possible adverse effects were rated for severity, relationship to study medication, and action taken. Clinically significant adverse effects were defined as those rated as moderate in severity, possibly related to study medication, and, at minimum, those requiring increased surveillance.

Statistical Methods

Patients who met remitter criteria following ECT and who did or did not participate in the continuation trial were compared in demographic, clinical, and previous treatment features with *t* tests for continuous measures and χ^2 analyses for dichotomous variables. The randomized continuation pharmacotherapy groups were compared on baseline variables using analyses of variance or χ^2 analyses.

The primary analysis of the continuation trial used survival analysis for right-censored failure-time data. A simultaneous regression model was fit to the relapse-time data using the Weibull distribution.[10,15] Covariates in the regression model were the randomized treatment condition (3 levels), strata (3 levels), sex, and HRSD score at the start of the trial. In a secondary analysis, ECT treatment modality (right unilateral only vs right unilateral and bilateral ECT vs bilateral ECT only) and number of ECT treatments were added as additional covariates. To confirm the findings from the parametric analysis regarding treatment group differences, nonparametric estimates of the survival distribution function for each group were computed, using the Kaplan-Meier method[57] and contrasted with the log-rank test (Mantel-Cox).[58]

Early in the study, 1 site (Carrier Foundation) was closed when the hospital discontinued its research division, so another site (University of Iowa) was added late. These 2 sites entered 21 patients in the continuation trial compared with 63 patients at WPIC. To determine whether the effects were not unique to WPIC, the Carrier Foundation and the University of Iowa were pooled for analysis. A site term (WPIC vs Carrier Foundation and University of Iowa) was entered into both secondary parametric and nonparametric survival analyses.

To assess the adequacy of pharmacotherapy, separate analyses of variances were conducted on the last plasma levels for nortriptyline and lithium obtained in completers (24-week or time of relapse), using the assayed values for active medication and the simulated values for placebo, and treatment group (3 levels) and relapse status as between-subject factors. A logistic regression was conducted on the patients' guess of treatment condition with relapse status and actual treatment assignment as predictors.

RESULTS

Of the 290 patients who completed the ECT phase, 159 (54.8%) patients were remitters (TABLE 1 and Figure 1). There was no difference among the sites in remitter rate (χ^2_2=3.75, *P*=.15). Immediately following ECT, 17 patients (5.9%) met initial remitter criteria, but not at the 4- to 8-day reassessment. The remitter rate may have been negatively influenced by the stringency of the remission criteria and the fact that 262 patients (90.3%) started with right unilateral ECT, with the minimum dosage only 150% above seizure thresh-

old. Subsequent research has shown that the efficacy of right unilateral ECT improves at a higher dosage relative to seizure threshold.[15,59]

Of the 159 remitters, 84 (52.8%) patients entered the randomized continuation trial. Of the 75 remitters who did not participate, 22.7% had medical exclusions for nortriptyline or lithium; 26.7% had travel limitations; and 50.7% preferred treatment by their referring physician, were receiving other medications or ECT, or were unwilling to receive placebo.

Comparisons of remitters who did or did not enter the continuation trial yielded no differences in pre- or post-ECT HRSD, Clinical Global Impression, or Global Assessment Scale scores, number of episodes, duration of current episode, number of ECT treatments, strength of the most potent antidepressant trial during the index episode, sum or average potency of all trials, number of trials, or number of adequate trials. The groups also did not differ in sex, race, history of previous ECT, use of right unilateral or bilateral ECT, or classification of medication resistance. Trial participants were younger (mean [SD], 57.4 [17.2] years) than nonparticipants (64.2 [16.3] years) (t_{157}=2.54; P=.01); had more previous psychiatric hospitalizations (2.4 [2.6]) than nonparticipants (1.5 [1.6]) (t_{157}=2.82; P=.005); a higher rate of psychotic depression (41.7% vs 16.0%) (χ^2_1=12.54, P <.001); and less total medical burden (Cumulative Illness Rating Scale score, 6.1 [4.2] vs 8.0 [3.9]) (t_{157}=2.91; P=.004). The medical exclusions for the continuation trial and travel limitations likely accounted for the higher age and greater medical burden of nonparticipants.

The continuation treatment groups were compared in demographic and clinical features (TABLE 2). There were no significant differences.

Eleven (13.1%) of the 84 patients dropped out of the trial before completing 24 weeks or meeting relapse criteria. The reasons for noncompletion are described in Figure 1. Dropout rates were evenly distributed among the 3 treatment groups (4 placebo, 2 nortriptyline, and 5 nortriptyline-lithium).

The overall model in the parametric analysis on survival time was significant (likelihood ratio, χ^2_6=27.3; P<.001) (TABLE 3). The treatment groups differed markedly (P<.001). Both nortriptyline alone (P=.01) and nortriptyline-lithium (P<.001) were superior to placebo in survival time, and nortriptyline-lithium was superior to nortriptyline alone (P=.04).

The Kaplan-Meier survival function was computed for each treatment group (FIGURE 2). Across the sample, 45 (61.6%) of 73 completers relapsed. This confirmatory nonparametric analysis yielded a log-rank χ^2_2 of 9.12 (P=.01).

Table 1. Number of Patients at Each Site Who Completed Electroconvulsive Therapy (ECT), Remitted With ECT, and Entered and Completed the Continuation Trial

Site	ECT Completer	ECT Remitter	Entered Continuation Trial	Continuation Trial	
				Dropout	Relapse
Carrier Foundation	66	43	16	3	8
University of Iowa	22	12	5	0	2
Western Psychiatric Clinic and Institute	202	104	63	8	35
Total	**290**	**159**	**84**	**11**	**45**

Table 2. Patient Characteristics for Continuation Treatment Groups*

Variable	Placebo Only (n = 29)	Nortriptyline and Placebo (n = 27)	Nortriptyline and Lithium Carbonate (n = 28)
Age, mean (SD), y	55.8 (13.6)	57.2 (19.8)	59.2 (18.3)
Women, %	69.0	70.4	60.7
Pre-ECT Hamilton Rating Scale for Depression, mean (SD)	34.9 (8.4)	36.1 (8.2)	34.9 (8.5)
Psychotic, %	44.8	37.0	42.9
Medication resistant, %†	48.3	44.4	50.0
Selective serotonin reuptake inhibitor	31.0	33.3	37.0
Tricyclic antidepressant	17.2	11.1	18.5
Monoamine oxidase inhibitor	10.3	0	0
Other antidepressant	3.4	14.8	11.1
Tricyclic antidepressant lithium carbonate	6.9	0	0
Cumulative Illness Rating Scale, mean (SD) total	4.8 (3.4)	7.3 (4.4)	6.3 (4.6)
Episode duration, median, wk	31.0	24.0	25.0
No. (%) of previous episodes‡	2.3 (2.6)	2.4 (2.0)	2.8 (2.2)
History of previous ECT, %	41.4	48.1	46.4
Age at onset, mean (SD), y	40.7 (18.1)	38.1 (17.3)	38.0 (17.4)
Total ECT treatments, mean (SD)	10.2 (2.9)	10.8 (5.2)	10.7 (3.5)
Total right unilateral ECT treatments, mean (SD)	7.7 (3.0)	7.4 (3.4)	6.6 (2.9)
Hamilton Rating Scale for Depression, mean (SD)§	5.0 (2.7)	5.6 (3.1)	6.0 (3.1)
Clinical Global Impression severity, mean (SD)§	1.6 (0.6)	1.7 (0.6)	1.8 (0.6)
Global Assessment Scale, mean (SD)§	74.8 (6.1)	73.2 (7.1)	73.2 (6.5)

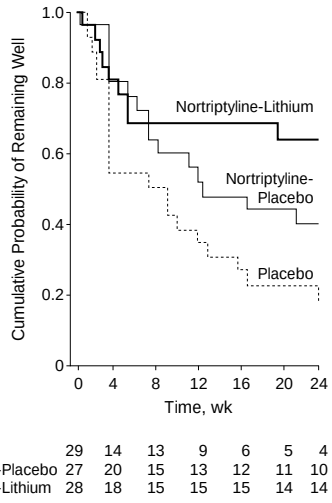
*ECT indicates electroconvulsive therapy.
†Adequacy of each medication trial given during the index episode before ECT was evaluated with the Antidepressant Treatment History Form. Each trial was rated on a scale ranging from 0 to 5, with a score of 3 the threshold for classification as medication resistant. To be considered an adequate trial, the threshold for sufficient dosage corresponded to a minimum of 200 mg/d imipramine equivalents for tricyclic antidepressants and 20 mg/d for fluoxetine. The threshold for sufficient duration was a minimum of 4 weeks at or above the threshold for sufficient dosage. To be classified as resistant, patients with psychotic depression had to receive an adequate antidepressant trial and at least 3 weeks of concurrent treatment with an antipsychotic medication, with a dosage of at least 400 mg/d chlorpromazine equivalents.
‡An upper limit of 10 episodes was used.
§Measured at day zero, which was the start of the continuation trial.

Table 3. Parametric Survival Analysis on Time to Relapse*

	Coefficient (SE)	*df*	χ^2	*P* Value
Treatment group				
Nortriptyline	0.96 (0.39)	1	6.18	.01
Nortriptyline and lithium carbonate	1.75 (0.47)	1	13.67	<.001
Total		2	14.74	<.001
Medication resistance/psychosis				
Psychotic depression	0.79 (0.37)	1	4.57	.03
Nonpsychotic nonresistant	0.34 (0.56)	1	0.37	.54
Total		2	4.59	.10
Sex†	−0.98 (0.43)	1	5.23	.02
Hamilton Rating Scale for Depression‡	−0.15 (0.06)	1	5.40	.02

*Within the treatment groups, the statistical comparisons for the nortriptyline alone and combined nortriptyline-lithium treatment conditions are against the placebo condition. Within the subgroup strata, the tests for psychotic depression and nonpsychotic depression, nonresistant subgroups are against the nonpsychotic, medication-resistant subgroup.
†Values are 1 for men and 2 for women.
‡Measured at day zero.

Figure 2. Kaplan-Meier Estimates



Proportion of patients who remained well during the continuation trial, for patients randomized to treatment with placebo (n=29), nortriptyline alone (n=27), and combination nortriptyline and lithium carbonate (n=28).

The relapse rates for completers were 84.0% (21/25) for placebo (95% confidence interval [CI], 70%-99%); 60.0% (15/25) for nortriptyline (95% CI, 41%-79%); and 39.1% (9/23) for nortriptyline-lithium (95% CI, 19%-59%). Only 1 patient relapsed while taking nortriptyline-lithium after 5 weeks, while relapse steadily continued with placebo and nortriptyline throughout the 24-week trial (Figure 2). Nonparametric survival analyses comparing each active treatment condition with placebo yielded a significant effect for nortriptyline-lithium (χ^2_1=8.52; *P*=.004), but only a trend for nortriptyline (χ^2_1=3.33; *P*=.07).

The parametric survival analysis indicated that across the treatment conditions, medication-resistant nonpsychotic patients had a higher relapse rate than patients with psychotic depression. The relapse rates were 50.0% for psychotic patients (n=28), 55.6% for nonpsychotic patients without medication resistance (n=9), and 72.2% for nonpsychotic medication-resistant patients (n=36). The significant effect of sex was due to a higher relapse rate among women (77.8%) than men (53.6%). Patients who relapsed had higher mean (SD) HRSD scores at trial entry (6.0 [3.1]) than patients who did not relapse (5.0 [2.8]). There were no additional significant effects in the parametric survival analysis when treatment with right unilateral, right unilateral and bilateral, or bilateral ECT (*P*=.89), and number of ECT treatments (*P*=.96) were entered as additional terms.

Study site (WPIC vs combined Carrier Foundation and University of Iowa) was entered as a term in both the parametric and nonparametric survival analyses. There were no site effects. The relapse rates at WPIC for placebo, nortriptyline, and nortriptyline-lithium were 88.9%, 60.0%, and 41.2%, respectively, and for the combined Carrier Foundation and University of Iowa they were 71.4%, 60.0%, and 33.3%, respectively.

The high rate of relapse across the treatments could have been due to excessively sensitive relapse criteria. Clinical ratings at continuation trial entry and end point were compared as a function of relapse status (TABLE 4). Relapsed patients showed marked symptomatic worsening. Fifteen (33%) of the 45 relapsed patients were hospitalized and received ECT, 6 patients (13%) received outpatient ECT, and all other relapsed patients (53%) were switched to other pharmacotherapies. The severity of relapse did not differ among the continuation treatments.

No effects approached significance in the analyses of variances of nortriptyline and lithium levels on final visit. At final visit, the mean (SD) nortriptyline level was 89.9 (38.2) ng/mL for the nortriptyline group, 89.2 (32.2) ng/mL for the nortriptyline-lithium group, and the simulated levels reported for the placebo group averaged 93.0 (27.5) ng/mL. For lithium, the levels were 0.59 (0.2) mEq/L for the nortriptyline-lithium group, with simulated levels of 0.54 (0.2) mEq/L and 0.62 (0.2) mEq/L for the nortriptyline and placebo groups, respectively. Relapse was not associated with nortriptyline or lithium plasma levels.

A 1-way analysis of variance indicated that the treatment groups did not differ in the average number of clinically significant adverse effects ($F_{2,80}$=0.13; *P*=.88). For the placebo, nortriptyline, and nortriptyline-lithium groups, the mean (SD) number of significant adverse effects per patient was 1.24 (1.8), 1.42 (1.7), and 1.21 (1.3), respectively. An analysis of variance in the completer sample (with treatment group and relapse status as between-subject factors) yielded no significant effects. The mean (SD) number of significant adverse effects among patients who relapsed (1.48 [1.7]) did not differ from nonrelapsed patients (1.32 [1.6]) (t_{70}=0.39; *P*=.70). TABLE 5 presents the clinically significant adverse effects experienced by at least 3 patients.

At study exit, 63 of the 73 completers guessed their treatment assignment. The logistic regression analysis

yielded a modest association between the treatment assignment and the patients' guesses (χ^2_4=9.68; P=.05) and a more robust association with relapse status (χ^2_2=8.17; P=.02). Only 1 (4%) of the 25 patients who did not relapse believed he/she was treated with placebo, while this was true of 16 (42.1%) of the 38 patients who did relapse. Of the patients treated with placebo, 50% believed they received only placebo, while 31.8% and 18.2% believed that they had received nortriptyline and nortriptyline-lithium, respectively. For the nortriptyline group, the guesses were 29.4% for placebo, 23.8% for nortriptyline, and 52.4% for nortriptyline-lithium. For nortriptyline-lithium, these guesses were 5.0%, 30.0%, and 65.0%, respectively. While the patient blinding was imperfect, relapse status was a more powerful determinant of the guesses. The distributions overlapped considerably among patients treated with nortriptyline and nortriptyline-lithium.

Table 4. Clinical Ratings as a Function of Relapse Status

	Mean (SD) Nonrelapse (n = 28)		Mean (SD) Relapse (n = 45)	
	Baseline	End Point	Baseline	End Point
Hamilton Rating Scale for Depression	5.0 (2.8)	4.8 (3.8)	6.0 (3.1)	24.1 (6.8)
Clinical Global Impression	1.6 (0.5)	1.4 (0.7)	1.7 (0.6)	4.1 (0.6)
Global Assessment Scale	74.5 (6.3)	77.9 (8.7)	73.3 (6.4)	49.3 (9.2)

Table 5. Clinically Significant Adverse Effects for the Continuation Treatment Groups*

	No. (%)			
Adverse Effect	Total Sample (N = 84)	Placebo Only (n = 29)	Nortriptyline and Placebo (n = 27)	Nortriptyline and Lithium Carbonate (n = 28)
Drowsiness/tiredness	19 (22.6)	5 (17.2)	8 (29.6)	6 (21.4)
Insomnia	10 (11.9)	5 (17.2)	3 (11.1)	2 (7.1)
Constipation	7 (8.3)	0 (0)	5 (18.5)	2.(7.1)
Anorexia/decreased appetite	6 (7.1)	4 (13.8)	0 (0)	2 (7.1)
Depressive affect	6 (7.1)	2 (6.9)	3 (11.1)	1 (3.6)
Syncope/dizziness	6 (7.1)	2 (6.9)	3 (11.1)	1 (3.6)
Dry mouth	5 (6.0)	2 (6.9)	3 (11.1)	0 (0)
Nausea/vomiting	5 (6.0)	2 (6.9)	1 (3.7)	2 (7.1)
Hypotension	4 (4.8)	1 (3.4)	0 (0)	3 (10.7)
Dermatologic	3 (3.6)	1 (3.4)	1 (3.7)	1 (3.6)
Diarrhea	3 (3.6)	1 (3.4)	1 (3.7)	1 (3.6)
Headache	3 (3.6)	1 (3.4)	1 (3.7)	1 (3.6)
Nasal congestion	3 (3.6)	0 (0)	3 (11.1)	0 (0)
Peripheral edema	3 (3.6)	0 (0)	0 (0)	3 (10.7)

*Clinically significant adverse effects were defined as those rated by the study psychiatrist on the Treatment Emergent Symptoms Scale as at least moderate in severity, at least possibly related to study medications, and as requiring at minimum greater surveillance or a dosage change. Data are presented for the clinically significant adverse effects experienced by at least 3 of the 84 patients.

COMMENT

Early research, based on first-choice use of ECT for major depression, indicated that half of the patients remain well in the 6 months following response without continuation therapy.[16-18] We found that the relapse rate for placebo-treated patients was 84%. This suggests that the prognosis following ECT is more guarded today. Given the shift in use of ECT for severe, recurrent, and medication-resistant patients with higher risk of relapse,[8,15,60] almost universal relapse should be expected without effective continuation therapy.

The early research suggested that continuation monotherapy with a TCA reduced the relapse rate to approximately 20%.[16-18] We found that the relapse rate with nortriptyline continuation monotherapy was 60%, above the original projections for placebo. While TCAs are believed to be among the most effective antidepressant agents,[27,30,33] our findings indicate that the efficacy of post-ECT TCA continuation monotherapy is not acceptable. Similarly, in a naturalistic study, Flint and Rifat[61] found that continuation monotherapy with a TCA was ineffective in preventing relapse in psychotically depressed patients who responded to ECT.

The relapse rate for the combination of nortriptyline-lithium was 39.1%, which was superior to placebo and nortriptyline monotherapy. Similar results were reported in a naturalistic study at NYSPI, in which relapse rates over 1 year were markedly lower among ECT remitters who received TCA-lithium continuation therapy (35.3%) compared with patients who received continuation treatment with other pharmacological regimens (67.9%).[15] It was noteworthy that the lithium levels in the present study were at the low end of what is considered the therapeutic range for acute or maintenance treatment (0.5-1.2 mEq/L).[62,63] This suggests that in combination with nortriptyline, lithium levels may only need to be greater than 0.5 mEq/L to prevent post-ECT relapse.

This study could not determine whether the advantage of the TCA-lithium combination was due to lithium alone or the synergism of lithium with the TCA. The only placebo-controlled trial of lithium following ECT in unipolar patients found that lithium did not have protective effects during the first 6 months following ECT.[64,65] Thus, it is likely that the advantage of nortriptyline-lithium was due to additive or synergistic effects and not lithium alone. Our findings encourage the use of nortriptyline-lithium as post-ECT continuation therapy. It is unknown whether similar protective effects would be obtained with a mood stabilizer other than lithium or antidepressants other than nortriptyline (in combination with

lithium). This issue is important since SSRIs and other newer antidepressant agents have better tolerability than TCAs and are now more commonly used.

Patients with higher HRSD scores at the start of the continuation trial had shorter survival time. This is consistent with several studies of relapse during continuation pharmacotherapy following response to antidepressant medications[46,47] or ECT.[8] Thus, concerted attempts should be made to maximize symptomatic improvement in patients receiving ECT. Women were more prone to relapse during the continuation phase. There is inconsistent evidence from naturalistic studies of a higher relapse/recurrence rate among women.[14,66-70] Studies of patients with psychotic depression suggested a high post-ECT relapse rate.[6,7] However, regardless of the treatment producing remission, no previous controlled study has compared relapse rates in psychotic and nonpsychotic depressed patients. We found that psychotically depressed patients had a lower relapse rate than medication-resistant nonpsychotic patients. Several studies have shown that medication resistance is especially predictive of post-ECT relapse.[8,15,60] It is also possible that compared with medication-resistant nonpsychotic patients, patients with psychotic depression had less Axis II (personality disorder) pathology and better interepisode function. There is evidence that the post-ECT course is poorer in patients with significant Axis II pathology.[71,72]

The major finding was that treatment with the nortriptyline-lithium combination produced a substantially lower relapse rate than treatment with placebo or nortriptyline alone. Nonetheless, the relapse with nortriptyline-lithium was high (39.1%). Two alternative strategies, which are not mutually exclusive, should be tested.[4] Both strategies are suggested by the observations that relapse is heavily skewed to the period immediately following ECT. During the acute treatment phase, there is a several week delay before antidepressant and mood stabilizing agents exert therapeutic effects.[73] Further, the abrupt discontinuation of effective somatic treatment is associated with potentiation of relapse,[74-76] which is standard in terminating an ECT course. One strategy is to taper ECT over a few weeks, as is commonly done with pharmacological treatments, providing symptom suppression during the most vulnerable period. Second, the antidepressant medication used in continuation therapy may be started during the course of ECT, followed by post-ECT addition of lithium. All controlled studies in which ECT was combined with an antidepressant medication focused on whether response to ECT was improved,[16-19] and not whether this strategy reduced post-ECT relapse. Nonetheless, a low post-ECT relapse rate was seen in studies in which patients began taking an antidepressant at the start of the ECT course.[16-19] Thus, these 2 adjunctive strategies raise the possibility that the advantage seen with the nortriptyline-lithium therapy may be further improved and that the problem of the high rate of early relapse with continuation pharmacotherapy following ECT could be resolved.

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