Pharmacological Strategies in the Prevention of Relapse After Electroconvulsive Therapy

Joan Prudic, MD, Roger F. Haskett, MD,† W. Vaughn McCall, MD,‡ Keith Isenberg, MD,§ Thomas Cooper, MA,* Peter B. Rosenquist, MD,‡ Benoit H. Mulsant, MD, FRCPC,†|| and Harold A. Sackeim, PhD**

Objective: To determine whether starting antidepressant medication at the start of electroconvulsive therapy (ECT) reduces post-ECT relapse and to determine whether continuation pharmacotherapy with nortriptyline (NT) and lithium (Li) differs in efficacy or adverse effects from continuation pharmacotherapy with venlafaxine (VEN) and Li.

Methods: During an acute ECT phase, 319 patients were randomized to treatment with moderate dosage bilateral ECT or high-dosage right unilateral ECT. They were also randomized to concurrent treatment with placebo, NT, or VEN. Of 181 patients to meet post-ECT remission criteria, 122 (67.4%) participated in a second continuation pharmacotherapy phase. Patients earlier randomized to NT or VEN continued on the antidepressant, whereas patients earlier randomized to placebo were now randomized to NT or VEN. Lithium was added for all patients who were followed until relapse or 6 months.

Results: Starting an antidepressant medication at the beginning of the ECT course did not affect the rate or timing of relapse relative to starting pharmacotherapy after ECT completion. The combination of NT and Li did not differ from VEN and Li in any relapse or adverse effect measure. Older age was strongly associated with lower relapse risk, whereas the type of ECT administered in the acute phase and medication resistance were not predictive. Across sites, 50% of the patients relapsed, 33.6% continued in remission 6 months after ECT, and 16.4% dropped out.

Conclusions: Starting an antidepressant medication during ECT does not affect relapse, and there are concerns about administering Li during an acute ECT course. Nortriptyline and VEN were equally effective in prolonging remission, although relapse rates after ECT are substantial despite intensive pharmacology. As opposed to the usual abrupt cessation of ECT, the impact of an ECT taper should be evaluated.

Key Words: electroconvulsive therapy, relapse prevention, nortriptyline, venlafaxine, lithium

(*J ECT* 2013;29: 3–12)

Relapse is common after successful acute phase treatment with electroconvulsive therapy (ECT). Naturalistic studies[1–4] and randomized controlled trials of alternative continuation therapies[5–7] have documented relapse rates of 40% or greater in the first 6 months after termination of acute phase ECT. Virtually all patients will relapse if no continuation therapy is used, whereas monotherapy with a tricyclic antidepressant, nortriptyline (NT), has a modest beneficial effect.[5] The combination of NT and lithium (Li) and continuation ECT seem to exert equivalent and pronounced benefit, each reducing the relapse rate to approximately 40% to 50%.[5,6]

Electroconvulsive therapy is the only biological treatment in psychiatry that is abruptly discontinued once found to be effective.[8] In the treatment of major depression, the most common strategy has been to use pharmacological interventions as continuation therapy after ECT.[9] Relapse after ECT is heavily skewed toward the period immediately after ECT termination. For example, in an earlier masked randomized trial we conducted, of those who relapsed within 6 months of ECT termination, 67%, 62%, and 89% did so within 8 weeks while receiving placebo (PL), NT alone, or combined NT and Li, respectively.[5] This pattern of early relapse may reflect the fact that antidepressant medications usually show a delay in onset of acute therapeutic action, and this delay may also apply to protection from relapse. Thus, in the period immediately after ECT, patients who are just starting pharmacotherapy may be especially vulnerable to relapse. They are exposed to both the abrupt discontinuation of an effective treatment and the introduction of a new form of treatment with a delay in the onset of therapeutic action.

This study tested the hypothesis that starting antidepressant pharmacotherapy from the onset of ECT, as opposed to after ECT completion, results in a substantial improvement in the relapse rate.[8] During the acute ECT phase, patients were randomized to pharmacological treatment with PL (PL), NT, or venlafaxine (VEN). They were also randomized to receive either high-dosage right unilateral (RUL) or moderate dosage bilateral (BL) ECT. In a second 6-month triple-masked continuation therapy trial, patients treated with PL during the ECT course were randomized to continuation therapy with NT or VEN, those who received active medication during ECT continued on that medication, and Li was added in all cases.

The findings regarding acute phase efficacy and adverse effects have been reported elsewhere.[10] This report focused on the randomized controlled trial of continuation pharmacotherapy after ECT and addressed 2 primary questions: (1) Does starting an antidepressant medication before ECT reduce the post-ECT relapse rate relative to starting the antidepressant medication (and Li) after ECT? and (2) How does the efficacy of VEN-Li compare to NT-Li in relapse prevention after ECT? An alternative to NT could be of special use to patients with a contraindication to treatment with a tricyclic antidepressant.

MATERIALS AND METHODS

Study Site and Study Participation

The study was conducted at the Wake Forest University (WF), Western Psychiatric Institute and Clinic (WPIC), and

From the *New York State Psychiatric Institute and Department of Psychiatry, Columbia University, New York, NY; †Western Psychiatric Institute and Clinic and the Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA; ‡Department of Psychiatry and Behavioral Medicine, Wake Forest University School of Medicine, Winston-Salem, NC; §Department of Psychiatry, Washington University, St. Louis, MO and ||Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada.

Received for publication August 5, 2011; accepted June 27, 2012.

Reprints: Joan Prudic, MD, New York State Psychiatric Institute, 1051 Riverside Dr, New York, NY 10032 (e-mail: jp33@columbia.edu).

This study was supported in part by grants RO1 MH35636 (Dr Sackeim), RO1 MH61609 (Dr Sackeim), RO1 MH61594 (Dr McCall), RO1 MH61621 (Dr Isenberg), and RO1 MH61591 (Dr Haskett) from the US Public Health Service, Rockville, MD. A grant was obtained from Wyeth Pharmaceuticals for the purchase of the medications used in this study. The ECT devices used were loaned by the MECTA Corporation.

The authors have no conflicts of interest or financial disclosures to report.

DOI: 10.1097/YCT.0b013e31826ea8c4

Washington University (WU) in St Louis, MO. The New York State Psychiatric Institute (NYSPI) was the coordinating and monitoring center. Using the Structured Clinical Interview for Axis I *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*—Patient Edition (with Psychotic Screen) disorders,[11] patients who entered phase 1 of the study met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*[12] criteria for major depressive episode (unipolar or bipolar). They also had a pretreatment score of 21 or greater on the Hamilton Rating Scale for Depression (HRSD, 24-item),[13] and treatment with ECT was indicated. Patients were excluded if they had a history of schizophrenia, schizoaffective disorder, non–mood disorder psychosis, neurological illness or insult, 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. Patients with known allergy or medical contraindication to treatment with NT or VEN were also excluded.

Participants were recruited from the approximately 750 consecutive patients who were clinically referred for ECT at the 3 sites. Over a 4-year period, 340 patients consented to study participation. Of the 21 patients who did not contribute acute phase 1 outcome data, 17 patients left the study before the start of ECT (diagnostic exclusion identified, n = 7; patient withdrew consent, n = 7; family opposed to participation, n = 3). After starting ECT, 4 additional patients were dropped from the intent-to-treat (ITT) sample owing to identification of an exclusion criterion. The intent-to-treat sample for phase 1 outcomes comprised 319 patients.

Patients were classified as phase 1 remitters if they had 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 after ECT termination. Patients provided separate informed consent for participation in the acute ECT and continuation pharmacotherapy phases, and capacity to consent was assessed at each time point. The institutional review boards at each enrollment site and NYSPI approved the study.

To enter the randomized continuation trial (phase 2), patients had to be classified as remitters after ECT and had no contraindication to treatment with Li. Of the 155 patients who were remitters, 122 patients (79%) participated in the continuation trial. As noted, the criteria for remission required a score of 10 or below on the HRSD and a minimum 60% reduction in score relative to pre-ECT baseline. The threshold of 10 may seem lenient relative to some pharmacological studies, but the criteria are standard in ECT research and are based on use of the 24-item HRSD, whereas a threshold of 7 is commonly used when the 17-item HRSD is administered.

Study Design

In phase 1 of the study,[10] the patients were randomized to receive either RUL administered at 6 times the seizure threshold (ST) (6 × ST) or bilateral (BL) ECT at 1.5 × ST. Electroconvulsive therapy was given 3 times per week with a standard MECTA Spectrum 5000Q device (MECTA Corp, Tualatin, OR). Patients (n = 62) in either ECT group who did not show substantial improvement after 8 or more treatments were crossed over to high dosage (2.5 × ST) BL ECT. Electroconvulsive therapy was continued as long as clinical progress was observed and terminated after no further improvement was observed over at least 2 treatments.

Patients were also randomized to receive NT, VEN, PL starting the afternoon after the first ECT treatment using a "double-dummy" technique to maintain the mask. A standard dose escalation schedule was used, and the goal was to achieve therapeutic blood levels (100-120 ng/mL) of NT or a minimum daily dose of 225 mg of VEN in all patients by the end of the ECT course.

To maintain the mask, the treating psychiatrist prescribed both NT and VEN for each patient. The site pharmacist had access to the randomization code and substituted PL for NT and/or VEN as needed. The randomization to ECT and pharmacological conditions (6 combinations) was based on permuted blocks, with equal representation within each block of BL and RUL ECT, and a 1.5:1 ratio of PL relative to either NT or VEN. At each site, other than the individuals involved in the administration of ECT (none of whom provided clinical ratings), the patients, treatment teams, and outcome assessors were masked to ECT treatment assignment, and, other than the pharmacist, the patients and all personnel were masked to pharmacotherapy assignment.

Eligibility for phase 2 required only that patients be classified as remitters after ECT and all eligible patients were approached for participation. Excessive distance, lack of transportation, and preference to be treated openly by the referring physician were the leading reasons for nonparticipation. The patients who received NT or VEN in phase 1 continued on these medications, whereas the patients who had received PL were randomized to NT or VEN. The mask was maintained for whether the patient was treated with NT or VEN and whether patients received active medication or PL in phase 1. The double-dummy technique was followed for at least 4 weeks or until the patients had been maintained at a steady regimen for at least 2 weeks. At this point, the medication was converted to one set of masked pills (either NT or VEN). All patients also received open continuation treatment with Li. Blood samples were obtained at every visit during phase 2, and dosing of NT was targeted to achieve a steady-state blood level of 100 to 120 ng/mL; dosing of Li was adjusted to achieve a steady-state level of 0.5 to 0.7 mEq/L. The dosing of VEN was targeted for titrating up to 300 mg/d.

Assessments

Information from interviews with the patients, family, and health care providers and from medical records was obtained to complete the antidepressant treatment history form (ATHF) to quantify the extent of medication resistance (ie, number of failed adequate antidepressant trials in the current episode and total number of trials of antidepressant trials).[14] Before ECT, and twice weekly, before crossover ECT, and at ECT termination, a clinical rater (CR) and a study psychiatrist (SP) not involved in ECT administration completed the Hamilton Rating Scale for Depression.[13] The CR also completed the Clinical Global Impression (CGI) scales (severity [CGI-S] and improvement [CGI-I])[15] and the Global Assessment of Function scale[12] at the same intervals. Patients completed the Beck Depression Inventory II (BDI)[16] at, before, and after the ECT course.

During the continuation phase, the patients were followed until relapse or for 6 months. The patients were evaluated at weekly intervals for the first 4 weeks, and at 2-week intervals for the remaining 20 weeks. . same blinded CR and blinded SP that evaluated the patients throughout the ECT course. During the continuation trial, a separate blinded SP assessed adverse effects, vital signs, adjusted medication, or PL dosage based on plasma levels reported by NYSPI and adverse effects. This individual did not complete clinical ratings of symptomatic status.

Time to relapse was the main outcome measure. The criteria for relapse were a mean HRSD score (CR and blinded SP) of at least 16 that was maintained for at least one 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 such that most clinicians would abandon the current treatment in favor of an alternative. Patients could also meet criteria for relapse if they were rated as considerably worse on the CGI by both raters at each of 2 consecutive visits over at least 1 week, and the SP documented that it was in the patients' clinical interest to exit the protocol based on the emergence of suicidal ideation or intent, psychotic symptoms, hypomania or mania, or significant functional impairment (Global Assessment of Function score <50).

Adverse effects were assessed with regard to the frequency of adverse events and serious adverse events and scores on the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale.[17] Adverse events and serious adverse events were defined following standard conventions. The UKU scale was completed by a treating SP at the same intervals as HRSD interviews. The dependent measures were mean and maximal total scores over the continuation pharmacotherapy trial.

Statistical Methods

The sites were compared in remitter rate and phase 2 study participation using χ^2 analyses. Patients who met remitter criteria after 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. Similarly, the 4 treatment groups in the continuation trial were contrasted in these features using analyses of variance (ANOVAs), with each treatment condition representing a different level of the single main effect. Unless otherwise specified, significant main effects in ANOVAs and analyses of covariance (ANCOVAs) were followed by the Tukey honest significant difference (HSD) post hoc test.

The primary analysis testing the key hypotheses 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.[18] Covariates in the regression model were the pharmacological condition in phase 1 (drug vs PL), pharmacological status in phase 2 (NT-Li vs VEN-Li), the interaction of these 2 terms, site (3 levels), number of adequate antidepressant trials in the current episode, HRSD score at the start of the continuation trial, and patient's age. To confirm the findings from the parametric survival analysis regarding treatment group differences, nonparametric estimates of the survival distribution function for each group were computed using the Kaplan-Meier method and contrasted with the log-rank (Mantel-Cox) test.[19]

A second parametric survival analysis was conducted to explore clinical correlates of relapse. In this analysis, the model included effects of site, HRSD score at continuation trial baseline, age, treatment resistance (total number of antidepressant trials in the current episode), psychosis (psychotic vs nonpsychotic depression), polarity (unipolar vs bipolar depression), depression severity (HRSD score at pre-ECT baseline), randomized phase 1 ECT assignment (6 × ST RUL ECT vs 1.5 × ST BL ECT), and total number of ECTs administered.

The phase 2 treatment groups were contrasted in adverse effects, examining mean, and maximum UKU scores during the continuation trial. Analyses of covariance were conducted on these measures, modeling phase 1 medication condition (drug vs PL) and phase 2 medication condition (NT-Li vs VEN-Li) as main effects, the interaction of these 2 terms, and the main effect of site, and using age as a covariate. Additional ANOVAs examined the effects of phase 2 clinical outcome on UKU scores, with site and phase 2 outcome (relapse, dropout, and complete without relapse) as main effects.

Analyses of covariance were conducted on the mean and maximum oral dosages of NT, VEN, and Li and the mean and maximum blood levels of NT and Li. For patients not receiving a medication, the oral dosage that was believed to be administered was substituted, as was the dummy blood level (for NT) that was reported. The between-subject factors included phase 1 and phase 2 medication conditions, their interaction, and site, with age serving as a covariate. Parametric survival analyses were conducted separately for patients treated with NT-Li and VEN-Li to examine relations between oral dosage, blood levels, and relapse.

RESULTS

Sample Characteristics

Of 319 patients who received at least one treatment with ECT, as described elsewhere,[10] 181 patients (56.7%) were remitters (Table 1). The remission rate was higher in the patients randomized to RUL relative to BL ECT and in the patients randomized to receive NT during the ECT course and, to a lesser extent, VEN in comparison to PL. The sites differed in remitter rate: $\chi^2_2 = 12.36$, $P = 0.002$ (Table 1). The remission rate was highest at WPIC, lowest at WU, and intermediate at WF.

Of 181 remitters, 122 patients (67.4%) entered the randomized, double-masked, continuation pharmacotherapy trial. The principal reasons for nonparticipation in the continuation trial were travel limitations and preference to be treated openly by their referring physician. The rate of participation in the continuation trial among remitters differed among the sites; ($\chi^2_2 = 7.11$, $P = 0.03$; Table 1), with the participation rate at WPIC (77.4%) higher than at WF (59.0%) and WU (58.3%).

Demographic and clinical characteristics of the continuation trial participants are presented in Table 2. Remitters who did or did not enter the continuation trial were contrasted in the features listed in Table 2. There were no significant differences. The 4 treatment groups in the continuation trial, defined by whether they received an antidepressant or PL during ECT and NT-Li or VEN-Li as post-ECT continuation therapy, were contrasted in these clinical features. For the continuous measures, the 4 continuation therapy groups differed in years of education

TABLE 1. Number of Patients at Each Site Who Started ECT, Remitted with ECT, and Entered and Completed the Continuation Trial

Site	Started ECT	ECT Remitter	Entered Continuation Trial	Continuation Trial	
				Dropout	Relapse
Wake Forest University	106	61	36	12	12
Washington University	86	36	21	3	14
Western Psychiatric Clinic and Institute	127	84	65	5	35
Total	319	181	122	20	61

TABLE 2. Demographic and Clinical Features of the Total Continuation Trial Sample and for Each of the 4 Randomized Treatment Groups

			Phase 1: Placebo				Phase 1: NT		Phase 1: VEN	
	Total Continuation Sample		Phase 2: NT-Li		Phase 2: VEN-Li		Phase 2: NT-Li		Phase 2: VEN-Li	
	n = 122		n = 20		n = 24		n = 39		n = 39	
Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age, yrs	48.90	15.01	48.30	16.76	45.50	9.86	47.08	16.79	53.13	14.38
Sex, % female	64.75		65.00		58.33		58.97		74.36	
Education, yrs	13.92	2.68	15.30	3.31	13.29	1.71	14.13	3.00	13.38	2.24
Pre-ECT HRSD	29.80	5.80	30.30	5.71	28.17	5.25	31.36	6.49	28.97	5.19
Pre-ECT CGI-S	5.30	0.71	5.30	0.47	5.33	0.70	5.49	0.60	5.10	0.88
Pre-ECT BDI	37.24	10.60	39.75	8.80	34.92	10.02	40.33	10.68	34.28	10.88
Psychotic, %	25.41		20.00		16.67		30.77		28.21	
Polarity, % bipolar	19.67		30.00		20.83		28.21		5.13	
Episode duration, wks§	38.09	34.39	28.1	23.17	36.04	34.18	39.76	35.43	43.13	38.32
No. adequate antidepressant treatment trials, current episode	1.21	1.29	1.45	1.00	1.54	1.69	0.95	1.05	1.15	1.33
No. total antidepressant treatment trials, current episode	5.52	3.98	4.85	2.37	7.04	6.00	5.15	3.69	5.31	3.21
Medication resistant, %	75.41		85.00		75.00		71.79		74.36	
Total no. ECTs	8.27	3.46	8.20	2.95	8.58	3.55	8.59	3.41	7.79	3.77
Post-ECT HRSD	5.43	2.78	6.50	2.86	5.25	2.27	5.18	2.99	5.23	2.79
Post-ECT CGI-S	1.82	0.83	1.90	1.02	1.97	0.81	1.58	0.74	1.94	0.80
Post-ECT CGI-I	1.59	0.65	1.60	0.68	1.50	0.59	1.51	0.54	1.71	0.75
Post-ECT BDI	9.94	8.49	11.98	8.59	8.73	5.54	11.12	10.15	8.46	8.03

Adequacy of each medication trial given during the index episode before ECT was evaluated with the Antidepressant Treatment History Form.[14] Each trial was rated on a scale ranging from zero 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, for example, 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 at least 400 mg/d chlorpromazine equivalents.

An upper limit of 104 weeks was imposed.

($F_{[3,118]} = 2.94$, $P = 0.04$) and pre-ECT BDI score ($F_{[3,118]} = 3.02$, $P = 0.03$). Post hoc comparisons (Tukey HSD) indicated that the group that received PL during ECT followed by NT-Li continuation therapy had more years of education (15.30 ± 3.31) compared to the patients treated with VEN during ECT and followed by VEN-Li (13.38 ± 2.24). Post hoc comparisons revealed no significant pairwise differences among the groups in pre-ECT BDI scores. In the discrete variables, the 4 continuation therapy groups differed only in the representation of bipolar disorder: $\chi^2_3 = 8.39$, $P = 0.04$. The rates were highest for those who received PL during ECT followed by NT-Li (30.00%) compared to the patients who received VEN during ECT followed by VEN-Li (5.13%). Overall, it seemed that the randomizations were successful in creating groups with comparable demographic and clinical features.

Hypothesis Testing

The findings from the parametric survival analysis of the relapse-time data are presented in Table 3. There was no indication that beginning an antidepressant agent at the start of ECT affected relapse relative to receiving PL during the ECT course: $\chi^2_1 = 1.41$, $P = 0.23$. The Kaplan-Meier survival plot for this comparison is presented in Figure 1. Likewise, in the parametric survival analysis, there was no indication that treatment with NT-Li differed in relapse from treatment with VEN-Li: $\chi^2_1 = 0.36$, $P = 0.55$. The Kaplan-Meier survival plot for this comparison is presented in Figure 2. In the parametric survival analysis, there was also no indication of an interaction between the phase 1 and phase 2 medication conditions: $\chi^2_1 = 0.01$, $P = 0.93$. The Kaplan-Meier survival plot representing the 4 groups individually is presented in Figure 3. Nonparametric tests of each of these comparisons, as represented in Figures 1 to 3, all failed to approach significance (all P's > 0.61). Thus, there was no evidence that early start of an antidepressant or use of NT relative to VEN had any impact on relapse.

TABLE 3. Parametric Survival Analysis on Relapse-Time Data

Source	DF	χ^2	P
Site	2	6.13	0.047
Phase 1 medication condition (PL vs drug)	1	1.41	0.23
Phase 2 medication condition (NT-Li vs VEN-Li)	1	0.36	0.55
Phase 1 × phase 2 medication condition	1	0.01	0.93
No. adequate treatment trials, current episode	1	2.06	0.15
HRSD at continuation trial baseline	1	2.62	0.11
Age	1	14.90	0.0001

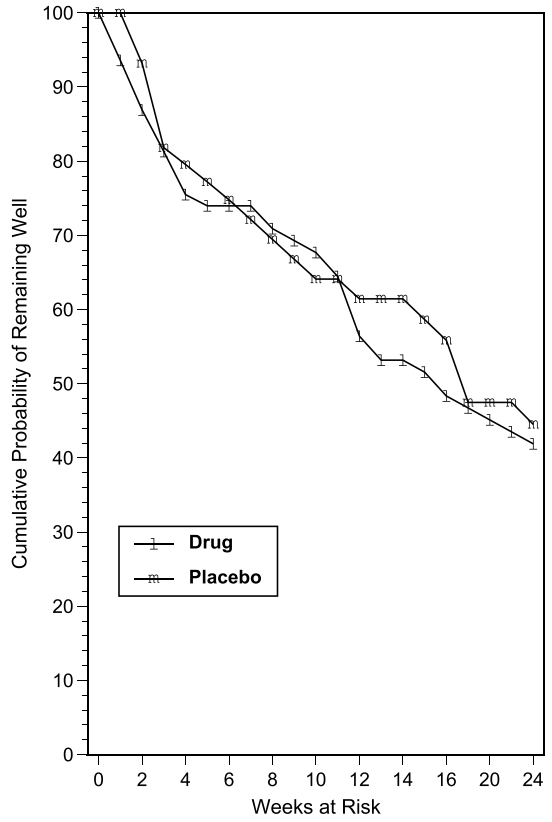

FIGURE 1. Kaplan-Meier estimates of the proportion of patients who remained well during the continuation pharmacotherapy trial for patients randomized to treatment with PL or antidepressant medication (NT or VEN) during the ECT course.

Overall, the risk of relapse was substantial. Of the 122 patients to enter the trial, 61 patients (50.0%) relapsed during the 6-month follow-up period, 41 patients (33.6%) completed without relapse, and 20 patients (16.4%) dropped out. There was a narrow range of relapse rates among the 4 treatment groups. As seen in Figure 3, the probability of remaining well at trial termination ranged from 37.8% (NT during ECT followed by NT-Li) to 46.1% (VEN during ECT followed by VEN-Li).

Correlates of Relapse

As seen in Table 3, the parametric analysis indicated that the sites differed in relapse: $\chi^2_1 = 6.13$, $P = 0.047$. The nonparametric test of this effect only yielded a trend: $\chi^2_1 = 5.10$, $P = 0.08$. Likelihood of survival was somewhat lower at WU than at the other 2 sites.

As also seen in Table 3, there was a strong association between patient age and relapse: $\chi^2_1 = 14.90$, $P < 0.0001$. The patients who completed without relapse (54.78 ± 14.17) were on average nearly 10 years older than the patients who relapsed (44.89 ± 14.05), with patients who dropped out being intermediate (49.10 ± 16.21). A one-way ANOVA indicated that the 3 groups differed in age ($F_{[2,119]} = 5.75$, $P = 0.004$) and Tukey HSD indicated that the patients who relapsed were significantly younger than those who completed.

In previous research, degree of treatment resistance, as quantified by the ATHF, has been a potent predictor of post-ECT relapse.[1,3–5] However, in this study, the term in the parametric model representing treatment resistance, the number of adequate failed treatment trials in the current episode, only had a weak nonsignificant relationship to relapse: $\chi^2_1 = 2.06$, $P = 0.15$ (Table 3). It is widely known that adequate treatment trials constitute a relatively small proportion of the total attempts at antidepressant treatment. Indeed, in this study, on average, patients received more than 4.5 times as many attempts at antidepressant treatment (5.52 ± 3.98) compared to the number of adequate trials they received (1.21 ± 1.29; Table 2). The parametric survival analysis summarized in Table 3 was repeated using the total number of treatment trials as the term representing treatment resistance. The previously observed effects of site and age were essentially unchanged. There was also a strong relationship between the total number of antidepressant treatment trials and relapse: $\chi^2_1 = 6.81$, $P = 0.009$. No other effects emerged.

A one-way ANOVA conducted on the total number of antidepressant trials contrasting patients who relapsed (6.26 ± 5.00), completed (4.59 ± 2.51), or dropped out (5.20 ± 2.19) yielded only an effect at a trend level: $F_{(2, 119)} = 2.31$, $P = 0.10$. However, a t test indicated that patients who relapsed had received more antidepressant trials than patients who completed without relapse: $t(93.65) = 2.33$, $P < 0.03$. In all subsequent analyses, the total number of antidepressant trials was retained in the parametric survival model as the term representing treatment resistance.

A parametric survival analysis was conducted to explore other factors that may be associated with relapse risk. As seen in Table 4, a new model was applied that included terms representing

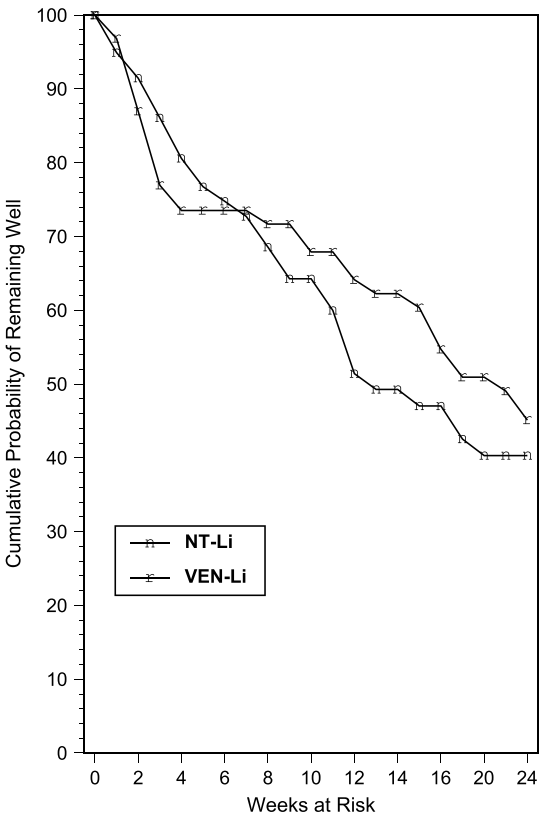

FIGURE 2. Kaplan-Meier estimates of the proportion of patients who remained well during the continuation trial for patients randomized to treatment with NT-Li or VEN-Li as continuation pharmacotherapy.

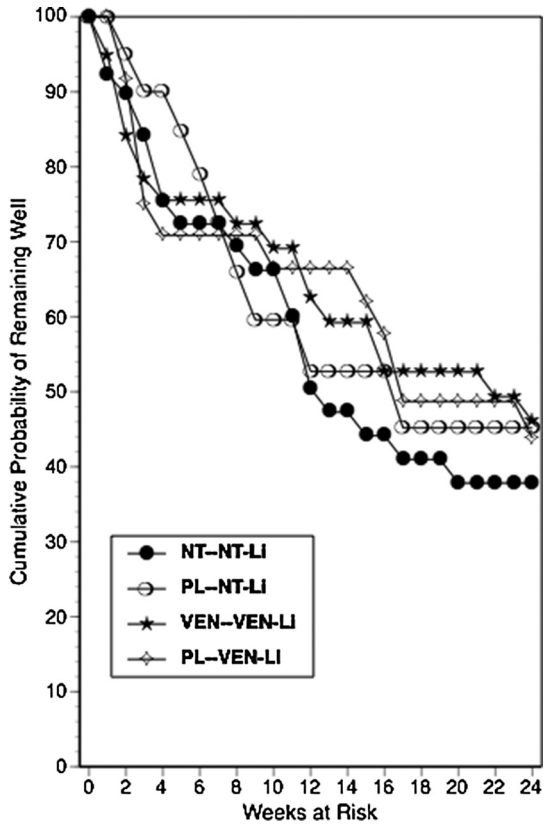

FIGURE 3. Kaplan-Meier estimates of the proportion of patients who remained well during the continuation trial for patients randomized to the 4 treatment conditions: PL or drug (NT or VEN) during ECT and, during continuation pharmacotherapy, NT-Li or VEN-Li as continuation pharmacotherapy.

psychosis, unipolar versus bipolar depression, severity of depression (HRSD score) at pre-ECT baseline, duration of current episode, randomization to RUL versus BL ECT, and total number of ECT. The effects of site, age, and total number of antidepressant trials remained significant, whereas the effect of HRSD score at continuation trial baseline approached significance: $\chi^2_1 = 2.88$, $P = 0.09$. There were no other effects. In particular, there was no evidence that the distinction between psychotic and nonpsychotic depression, depression severity at pre-ECT baseline, receipt of BL versus RUL ECT, or total number of ECTs were related to risk of relapse.

TABLE 4. Parametric Survival Analysis of Clinical Predictors of Relapse-Time Data

Source	DF	χ^2	*P*
Site	2	9.76	0.0078
HRSD at continuation trial baseline	1	3.38	0.07
Age	1	11.56	0.0007
Total no. antidepressant trials, current episode	1	5.52	0.02
Psychosis, yes/no	1	0.11	0.74
Unipolar vs bipolar	1	2.47	0.12
HRSD at pre-ECT study entry	1	0.02	0.88
ECT assignment (BL vs RUL)	1	0.01	0.91
Total no. ECTs	1	1.29	0.26

Adverse Effects and Adverse Events

Analyses of covariance were conducted on the mean UKU score during the continuation trial as well as on the maximum score during the trial. In both cases, there was no main effect of phase 1 or phase 2 medication status, or their interaction. Thus, there was no impact on adverse effect burden whether patients received active medication or PL in phase 1 and whether patients received NT-Li or VEN-Li in phase 2. There were no effects of age in either ANCOVA. However, there was a main effect of site in the ANCOVA on mean UKU score ($F_{[2,107]} = 5.74$, $P = 0.004$) and maximum UKU score ($F_{[2,107]} = 3.81$, $P = 0.025$). In both cases, post hoc comparisons (Tukey HSD) indicated that UKU scores were significantly higher at WU than at WPIC, with WF intermediate.

Previously, we noted that UKU scores in the total phase 1 sample decreased markedly from pre-ECT baseline, an effect linked to the extent of clinical improvement.[10] This was also true in the subsample of 111 patients who had at least one UKU score at pre-ECT baseline during the ECT course and during the continuation trial. Mean ± SD UKU scores declined from 19.90 ± 8.36 at pre-ECT to 10.64 ± 5.01 during ECT: $t(110) = 15.40$, $P < 0.0001$. In contrast, there was a small but significant rise in mean ± SD UKU scores during the continuation trial: 12.33 ± 7.17, $t(110) = 2.28$, $P = 0.02$. Thus, reports of adverse effects were somewhat lower during the ECT than the continuation pharmacotherapy phase of this study. However, the maximum UKU score during the ECT course, 17.30 ± 7.12 did not differ from the maximum score during the continuation trial: 17.66 ± 7.36, $t(110) = 0.45$, $P = 0.66$.

Analyses of variance were conducted on mean and maximum UKU scores during the continuation trial with site and phase 2 outcome (completed without relapse, with relapse, and dropout) as between-subject terms. In both analyses, the effect of site was significant, as described earlier. There was also a significant effect of phase 2 outcome for both the mean UKU score ($F_{[2,109]} = 18.26$, $P < 0.0001$) and the maximum UKU score ($F_{[2,109]} = 14.56$, $P < 0.0001$). Post hoc comparisons (Tukey HSD) indicated that patients who relapsed had substantially higher mean and maximum UKU scores than either patients who completed or dropped out (Table 5). Thus, clinical status seemed to exert a powerful effect on UKU scores in both phases 1 and 2.

Seven patients experienced single AEs, one patient had 2 AEs, one patient had 2 AEs and one SAE, and one patient had a single SAE. The number of events was too small to examine relationships with treatment conditions or outcome. The 11 adverse events included orthostasis (n = 2), falls (n = 2), emergence of mania, hypertension, rash, seizure-like attack, nausea, dizziness and slowed movement, and multiple symptoms related to high NT blood levels. The 2 SAEs included a patient with an

TABLE 5. Mean and Maximum UKU Score During the Continuation Trial as a Function of Clinical Outcome

	Mean UKU Score		Maximum UKU Score	
Phase 2 Outcome	**Mean**	**SD**	**Mean**	**SD**
Completed without relapse (n = 40)	7.73	3.83	13.53	5.35
Relapse (n = 59)	15.69	7.28	20.93	7.04
Dropout (n = 15)	11.76	6.82	15.80	7.40

Udvalg for Kliniske Undersogelser data were not obtained in 8 patients.

acute subdural hematoma after a fall that was evacuated in neurosurgery, and a suicide attempt by overdose.

Oral Dosage and Medication Levels

Analyses of covariance were conducted on the mean and maximum oral dosages of NT, VEN, and Li and the mean and maximum blood levels of NT and Li. The between-subject terms were phase 1 and phase 2 medication conditions, their interaction, and site; and age was the covariate. Table 6 presents the descriptive statistics for the patients randomized in phase 2 to either NT-Li or VEN-Li. Values for patient groups not receiving a medication (eg, NT values for patients treated with VEN-Li) reflect the oral dosage that was believed to be administered or the dummy blood level reported to the treating physician.

In the ANCOVAs, there was no effect involving phase 1 medication condition. Thus, whether patients received a PL in phase1 and started an antidepressant in phase 2 or continued on the same antidepressant in phase 2 had no impact on the mean or maximum oral dosage or blood levels of medication in phase 2. Similarly, with but one exception, there was no effect involving phase 2 medication condition. The exception was that patients treated with NT-Li had higher maximum blood levels of NT during the continuation trial than the maximum dummy levels reported for the patients treated with VEN-Li ($F_{[1,109]} = 14.56$, $P = 0.004$; Table 6), despite the fact that the 2 groups were nearly equivalent in mean NT levels. This effect was caused by abnormally high NT blood levels (≥ 200 ng/ml) occurring exclusively among patients actually receiving NT (n = 12), presumably reflecting slow metabolism of the medication. In hindsight, this threat to maintenance of the blind could have been eliminated by including a small number of very high dummy values in the reports given to the treating physicians. Other than this, there were no effects of the randomized phase 1 or phase 2 medication conditions on oral doses and blood levels, strongly supporting the integrity of the study.

TABLE 6. Oral Dosage and Blood Levels of Continuation Pharmacotherapy Medications by Treatment Condition

	Continuation Pharmacotherapy Group			
	NT-Li		VEN-Li	
	Mean	SD	Mean	SD
Mean oral dose, mg				
NT	87.63	27.78	86.51*	21.18
VEN	286.74*	29.60	275.20	37.42
Li	686.91	219.19	664.08	242.10
Maximum oral dose, mg				
NT	99.11	30.88	93.85*	23.57
VEN	294.64*	24.17	291.39	30.92
Li	816.96	285.92	784.43	300.49
Mean blood level				
NT, ng/mL	107.99	45.68	104.80*	30.06
Li, mEq/L	0.51	0.16	0.48	0.17
Maximum blood level				
NT, ng/mL	154.60	69.93	122.77*	33.22
Li, mEq/L	0.71	0.23	0.68	0.27

*For patients not receiving a medication (eg, NT for patients treated with VEN-Li), oral dosage reflects the dosage believed to be administered, and blood levels reflect dummy values reported to the treating physician.

There were effects of site in the ANCOVAs on the mean ($F_{(2,107)} = 4.75$, $P = 0.01$) and maximum ($F_{(2,107)} = 4.38$, $P = 0.01$) Li blood level. Post hoc comparisons indicated that WPIC had higher mean and maximum Li levels than either WF or WU. Indeed, these values, on average, were more than 25% higher at WPIC than either WF or WU. Despite the higher Li levels at WPIC, as noted earlier, the relapse rate was essentially equivalent at WF and WPIC. There were also effects of site on the mean ($F_{[2,110]} = 7.02$, $P = 0.001$) and maximum, ($F_{[2,110]} = 3.37$, $P = 0.04$), oral VEN dosage. Post hoc comparisons indicated that oral VEN dose (across the VEN-Li and NT-Li groups) was higher at WPIC than WF, with WU being intermediate. The magnitudes of these site differences were small.

Age exerted a significant effect in the ANCOVAs on oral mean and maximum dosages of NT, VEN, and Li (all P's ≤ 0.02). In each case, older patients received smaller oral dosages. However, there was no effect of age on blood levels of NT or Li (all P's > 0.21). Thus, it seemed that the sites successfully adjusted oral dosage of NT and Li to produce substantial equivalence in blood levels. Older patients had a substantial advantage in this trial of relapse rate. This effect could not be attributed to differences in age groups in blood levels of the medications. Overall mean oral dosage (VEN) and blood levels (NT and Li) were within the ranges targeted.

Finally, parametric survival analyses on survival time data were conducted separately for patients treated with NT-Li or VEN-Li in phase 2, with phase 1 medication condition, site, and age as predictors. In separate analyses, mean blood level of NT, mean blood level of Li, and mean oral dosage of VEN were added as predictors. In none of the 6 analyses was there an effect of phase 1 medication condition (medication vs PL). In all 6 analyses, there was a significant effect of age (all P's ≤ 0.02), indicating that the protective effect of age on relapse was significantly manifested in both phase 2 treatment conditions. In no case was the oral dosage (VEN) or blood level (NT or Li) related to relapse.

DISCUSSION

In this study, despite aggressive continuation pharmacotherapy, the overall relapse rate in the 6 months after remission of a depressive episode with ECT was 50%. The size of the patient sample makes it one of the larger randomized ECT data sets in the modern literature. This geographically diverse sample included unipolar and bipolar depressed patients and was representative of the severely depressed, often treatment-resistant, patients who are common in modern ECT practice. One site reported significantly higher relapse rates than the others, and, of course, these data contributed to raising the overall relapse rate observed in the study as a whole. Other than the overall relapse rate, however, this difference did not change the major findings of the study, which were the same whether the site was included in the analyses or not, mirroring a similar set of findings in the report of the outcomes in the acute phase of ECT treatment.[10]

The first aim of this study was to determine whether starting an antidepressant medication at the start of ECT resulted in a reduction in relapse compared to the standard practice of starting continuation pharmacotherapy only once ECT is completed. There was no evidence in this trial that the early start of an antidepressant medication had any effect on post-ECT relapse (Fig. 1). The second aim of this study was to determine whether there was a difference in the efficacy or safety of post-ECT continuation therapy with NT-Li compared to VEN-Li. There was no evidence in this trial for a difference between the

post-ECT continuation therapy regimens in relapse or adverse effects. These findings were consistent across the sites.

It was surprising that we failed to observe any benefit of the earlier start of antidepressant medication on relapse rate. As seen in Figures 1 to 3, relapse in this trial and in previous prospective studies[1–6] was most common in the period immediately after completion of the ECT course. When designing this trial, it seemed commonsensical that an earlier start of antidepressant treatment would prove beneficial, especially given the view that antidepressant treatment is associated with a substantial delay in onset of therapeutic benefit. However, the findings of this trial were clearly not supportive of this hypothesis. It should be recognized, of course, that this trial only tested the potential benefit of starting early the antidepressant component of the combined treatment with Li. Owing to the potential of a negative interaction between Li and ECT, Li treatment is typically discontinued during the acute ECT course.[20–22] In our previous multicenter, prospective trial, monotherapy with NT was distinctly inferior in relapse prevention compared to combination NT-Li. Thus, it seems that Li contributes important protection from relapse and that starting an antidepressant alone before the completion of ECT does not contribute to relapse prevention.

Practically, the implications of this negative finding regarding the timing of antidepressant administration should be considered in tandem with the earlier findings of this study.[10] The short-term efficacy of ECT was improved by the concomitant administration of NT or VEN compared to PL. This effect was substantial, corresponding to an approximately 15% improvement in remission rate. There was also suggestive evidence that NT may have a protective effect on aspects of neuropsychological function. Thus, the overall results of this trial provide evidence of benefit for the coadministration of ECT and antidepressant medications. The benefit, perhaps surprisingly, is reflected in short-term ECT outcome and not in the prevention of relapse.

This study had careful standardization of medication management procedures. As a result, NT levels averaged close to the target of 100 ng/mL, and mean VEN oral dosage was near the target of 300 mg/d. Lithium levels were typically approximately 0.5 mEq/L. Perhaps owing to the adequacy of dosing and medication management, no relationship was seen between oral dose or blood level of medications and relapse. Of note, older patients were able to maintain similar blood levels compared to younger patients, once again providing assurance as to the feasibility of adequate administration of these medication regimens in the elderly.

The second aim of this study was to contrast NT-Li and VEN-Li as continuation therapies. Similar maintenance of remission was obtained whether NT or VEN was used as the antidepressant medication in the combination treatment. This finding confirms that a second-generation antidepressant with both serotonergic and noradrenergic effects can be used as the antidepressant component of a pharmacologic relapse prevention strategy. This may be of special import for patients who have a contraindication to the use of NT. Both treatments were well tolerated, apparently equally, and there was no difference in adverse effect burden whether NT-Li or VEN-Li was used. The presumed better tolerability of a second-generation agent did not materialize in the quantitative analyses of adverse effects.

A variety of demographic and clinical variables were examined as potential predictors of relapse. Across the analyses, and confirmed within each of the 2 pharmacological continuation treatments, patients' age was a robust and consistent predictor of relapse. Older patients were substantially less likely to relapse than younger patients, replicating an effect we first reported in our earlier multisite, post-ECT randomized, continuation pharmacological trial.[5] This effect was not statistically significant ($P = 0.13$) in the recent multisite comparison of continuation ECT and NT-Li.[6] Of note, approximately half the acute ECT trials that examined an association between patients' age and short-term efficacy reported a positive relationship,[23] including a large recent multisite study.[24] Thus, it would seem that older patients have an advantage in both short-term and longer-term clinical outcome after ECT. It is very unusual in medicine for therapeutic benefit for a treatment to increase with aging. The fact that the benefit pertains to both acute efficacy and freedom from relapse provides justification for the preferential use of this intervention in late-life depression. At a mechanistic level, the aspect of aging responsible for these associations is unknown.

Treatment resistance has been a predictor of ECT short-term outcome in many,[2–4,25,26] but not all,[27] studies. Indeed, treatment resistance, as indexed by the number of failed adequate antidepressant treatment trials in the current episode, was a consistent predictor of short-term ECT clinical outcome in this prospective multisite study.[10] Similarly, in a number of studies, treatment resistance has been a potent predictor of post-ECT relapse.[1,3–5,28] However, in this study, the traditional measure of treatment resistance, the number of failed adequate trials, was a significant predictor of acute ECT outcome but had only a weak nonsignificant relationship with relapse. Secondary analyses demonstrated that another measure of treatment resistance, the total number of antidepressant trials in the current episode (regardless of adequacy), had a robust relationship with relapse. Inconsistency among studies in the relations of ATHF measures of treatment resistance to ECT outcomes may be related to the effort required to query sources about past treatment trials and the limited reliability in determining the adequacy of treatments given incomplete information regarding dose, duration, and compliance. In this study, the measure that showed robust relations with relapse, the total number of trials, has significant practical advantages. Its determination only requires knowledge of what trials were attempted in the current episode, without requiring knowledge of the determinants of adequacy. Determining which measures of treatment resistance are most predictive of ECT outcomes may have broad ramifications. Assessment of treatment resistance has become common in defining samples in antidepressant trials, and treatment resistance has shown strong predictive value of antidepressant outcomes for other brain stimulation interventions[29,30] and for pharmacological treatment of major depression.[31,32]

Also of consequence were the clinical features and treatment parameters that were unrelated to relapse. Polarity of depression, the presence or absence of psychosis, the severity of depressive symptoms at pre-ECT baseline, and current episode duration (data not shown) had no relations with relapse. These negative findings may help rule out some alternative explanations for the link of age or treatment resistance with relapse. Of note, however, Axis II comorbidity was not assessed, and there is substantial evidence that the short- and long-term efficacy of antidepressant treatment may be influenced by this dimension.[33–35] It is also noteworthy that the number of ECTs received in the acute treatment phase and randomization to high-dosage RUL ECT or low-dosage BL ECT had no impact on relapse. Indeed, to our knowledge, no study has ever found vulnerability to relapse after ECT to be related to ECT technique. Indeed, in several prospective trials in which patients were randomized to ECT modalities that often differed markedly in efficacy, there was no indication that forms of ECT differed in relapse potential.[2–4,10] In other words, it may be safely concluded that how one achieves remission with ECT

(number of treatments and form of ECT administered) is independent of the likelihood of relapse.

Although we did not find a difference between the 2 pharmacological continuation therapies in adverse effect burden, these scores were strongly related to clinical outcome during the follow-up period. Patients who relapsed reported more severe adverse effects during the trial than those who completed without relapse. In the earlier phase of the study, we found that adverse effect (UKU) scores dropped markedly during ECT compared to pre-ECT baseline and that the magnitude of this change was associated with the change in HRSD scores.[10] Thus, in both phases of this study, clinical outcome was strongly related to adverse effect scores. This pattern may not be surprising given the overlap between depressive symptoms and some systemic adverse effects. Regardless, our findings indicate that the reports of adverse effects were more influenced by clinical state than the forms of treatment received (ECT or pharmacology).

Each the 3 recent large multisite, prospective, randomized trials of post-ECT continuation therapy (including this study) found relapse rates in the order of 40% to 50% for optimal forms of continuation pharmacotherapy or continuation therapy with BL ECT.[5,6] These are underestimates because some patients drop out before relapse can be established. Thus, even with aggressive continuation ECT or continuation pharmacotherapy, it seems that 50% or more of remitted patients will relapse within 6 months of ECT completion, with the bulk of relapse skewed to the early weeks after ECT. Two factors might be weighed when considering this conclusion. First, it is possible that the methods used in these trials to declare "relapse" are too sensitive and that a number of patients may experience worsening a few weeks after ECT that is transient. This account is speculative. In this study, we required a substantial increase in the symptoms that was maintained for at least a week to designate relapse. We had no information on the duration of symptomatic worsening in patients who were declared relapsed, and this might be a subject of future investigation. Second, although a 50% relapse rate after ECT is high and worrisome, it may not compare unfavorably with the relapse rate reported in treatment-resistant patients who achieve remission with pharmacological agents. It has long been thought that continuing the pharmacological strategy that achieved remission was key to relapse prevention after a short-term response to antidepressant medication.[36] The findings of the STAR*D trial indicate that relapse after remission increases at greater levels of treatment resistance and are comparable to the rates found here.[31,32]

Due to unexpected low collection of cognitive data, analyses of cognitive outcomes were not possible, and represent a limitation of the study.

In summary, this study confirmed that use of Li in combination with 2 different antidepressants provides moderate protection against relapse. This study also broadened the choice of antidepressant to include a second-generation compound in common use, VEN. A recent study also found similar outcomes using a fixed schedule of continuation ECT without use of concurrent psychotropics.[6] Along with the skewing of relapse to the first several weeks after ECT, these observations suggest exploration of other strategies to maintain remission. One strategy is to taper ECT over a few weeks, thereby providing coverage while medication regimens are being put in place. A second approach common in community practice is to augment pharmacological continuation therapy with ECT scheduled according to symptomatic exacerbations. Alternatively, the first phase of this study demonstrated augmentation of acute response to ECT by concomitant antidepressant pharmacotherapy.[10] This would suggest that the combination of complete courses of continuation pharmacotherapy with continuation ECT should be more effective than alone. Using other forms of brain stimulation to maintain remission is also worthy of exploration, although repetitive transcranial magnetic stimulation seems most useful for less treatment-resistant depression,[29,30] and vagus nerve stimulation, the only other brain stimulation treatment labeled for use in depression and with evidence of long-term benefit,[37] is generally not covered by insurers. Study of other antidepressants and mood stabilizers may also be warranted, and there is justification to test agents with novel mechanisms. There remains an urgent need for treatments that will improve on current practice options to maintain the still superior recovery from depression that is achieved with ECT.

REFERENCES

1. Sackeim HA, Prudic J, Devanand DP, et al. The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. *J Clin Psychopharmacol*. 1990;10:96–104.
2. Sackeim HA, Prudic J, Devanand DP, et al. Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *N Engl J Med*. 1993;328:839–846.
3. Sackeim HA, Prudic J, Devanand DP, et al. A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Arch Gen Psychiatry*. 2000;57:425–434.
4. Sackeim HA, Prudic J, Nobler MS, et al. Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *Brain Stimulation*. 2008;1:71–83.
5. Sackeim HA, Haskett RF, Mulsant BH, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *JAMA*. 2001;285:1299–1307.
6. Kellner CH, Knapp RG, Petrides G, et al. Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: a multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE). *Arch Gen Psychiatry*. 2006;63:1337–1344.
7. Lauritzen L, Odgaard K, Clemmesen L, et al. Relapse prevention by means of paroxetine in ECT-treated patients with major depression: a comparison with imipramine and placebo in medium-term continuation therapy. *Acta Psychiatr Scand*. 1996;94:241–251.
8. Sackeim HA. Continuation therapy following ECT: directions for future research. *Psychopharmacol Bull*. 1994;30:501–521.
9. Prudic J, Olfson M, Sackeim HA. Electro-convulsive therapy practices in the community. *Psychol Med*. 2001;31:929–934.
10. Sackeim HA, Dillingham EM, Prudic J, et al. Effect of concomitant pharmacotherapy on electroconvulsive therapy outcomes: short-term efficacy and adverse effects. *Arch Gen Psychiatry*. 2009;66:729–737.
11. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for Axis I DSM-IV Disorders—Patient Edition (with Psychotic Screen) (SCID-I/P)*. New York, NY: Biometrics Research Department, New York State Psychiatric Institute; 1996.
12. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
13. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. 1967;6:278–296.
14. Sackeim HA. The definition and meaning of treatment-resistant depression. *J Clin Psychiatry*. 2001;62(suppl 16):10–17.

15. Guy W. *ECDEU Assessment Manual for Psychopharmacology.* Washington, DC: Superintendent of Documents, U.S. Government Printing Office, U.S. Department of Health, Education, and Welfare Publication, No. 76–338; 1976.
16. Beck AT, Steer RA, Brown GK. *Beck Depression Inventory Manual*.2nd ed. San Antonio, TX: Psychological Corporation; 1996.
17. Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand Suppl*. 1987;334:1–100.
18. Kalbfleisch JD, Prentice RL. *Survival Models and Data Analysis*. New York, NY: John Wiley; 1980.
19. Peto R, Peto J. Asymptomatically efficient rank invariant procedure. *J R Stat Soc Ser A*. 1972;135:185–207.
20. Weiner RD, Whanger AD, Erwin CW, et al. Prolonged confusional state and EEG seizure activity following concurrent ECT and lithium use. *Am J Psychiatry.* 1980;137:1452–1453.
21. American Psychiatric Association. *The Practice of ECT: Recommendations for Treatment, Training and Privileging*. 2nd ed. Washington, D.C.: American Psychiatric Press; 2001.
22. Small JG, Milstein V. Lithium interactions: lithium and electroconvulsive therapy. *J Clin Psychopharmacol*. 1990;10:346–350.
23. Sackeim HA. Electroconvulsive therapy in late-life depression. In: Roose SP, Sackeim HA, eds. *Late-Life Depression*. New York, NY: Oxford University Press; 2004:241–278.
24. O'Connor MK, Knapp R, Husain M, et al. The influence of age on the response of major depression to electroconvulsive therapy: a C.O.R.E. Report. *Am J Geriatr Psychiatry.* 2001;9:382–390.
25. Prudic J, Sackeim HA, Devanand DP. Medication resistance and clinical response to electroconvulsive therapy. *Psychiatry Res*. 1990;31:287–296.
26. Prudic J, Haskett RF, Mulsant B, et al. Resistance to antidepressant medications and short-term clinical response to ECT. *Am J Psychiatry.* 1996;153:985–992.
27. Kellner CH, Fink M. The efficacy of ECT and "treatment resistance". *J ECT.* 2002;18:1–2.
28. Rasmussen KG, Mueller M, Rummans TA, et al. Is baseline medication resistance associated with potential for relapse after successful remission of a depressive episode with ECT? Data from the Consortium for Research on Electroconvulsive Therapy (CORE). *J Clin Psychiatry.* 2009;70:232–237.
29. Lisanby SH, Husain MM, Rosenquist PB, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology.* 2009;34:522–534.
30. George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry.* 2010;67:507–516.
31. Rush AJ. STAR*D: what have we learned? *Am J Psychiatry.* 2007;164:201–204.
32. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry.* 2006;163:1905–1917.
33. DeBattista C, Mueller K. Is electroconvulsive therapy effective for the depressed patient with comorbid borderline personality disorder? *J ECT.* 2001;17:91–98.
34. Feske U, Mulsant BH, Pilkonis PA, et al. Clinical outcome of ECT in patients with major depression and comorbid borderline personality disorder. *Am J Psychiatry.* 2004;161:2073–2080.
35. Thase ME. The role of Axis II comorbidity in the management of patients with treatment-resistant depression. *Psychiatr Clin North Am.* 1996;19:287–309.
36. Klein D, Gittelman R, Quitkin F, et al. *Diagnosis and Drug Treatment of Psychiatric Disorders: Adults and Children*. Baltimore, MD: Williams and Wilkins; 1980.
37. Sackeim HA, Brannan SK, John Rush A, et al. Durability of antidepressant response to vagus nerve stimulation (VNSTM). *Int J Neuropsychopharmacol*. 2007;10:817–826.

