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)


Objective: To test whether pre–electroconvulsive therapy (ECT) medication resistance is associated with post-ECT relapse rates.

Method: In a post hoc analysis of data from a large multicenter trial of post-ECT relapse prevention strategies (conducted from May 1997 to July 2004), we assessed whether response to antidepressant medications prior to ECT for a unipolar nonpsychotic depressive episode (DSM-IV) was associated with differential relapse rates after remission with ECT. Baseline (i.e., pre-ECT) medication use was assessed with the Antidepressant Treatment History Form. Following remission with ECT that was stable for 1 week, patients were randomly assigned to receive 6 months of treatment with either combination lithium carbonate/nortriptyline or continuation ECT. Relapse was assessed with the 24-item Hamilton Rating Scale for Depression. There were 146 patients followed in the first week after remission (termed the interim week in this study), and 73 in the randomized phase of the study. For the purposes of this trial, medication resistance is defined as not having responded to at least 1 antidepressant medication before ECT.

Results: In the first week after acute remission, 9.8% of patients not having at least 1 antidepressant medication trial met relapse criteria, while 31.4% of medication-resistant patients met relapse criteria, a difference that was statistically significant (p = .026).

In the randomized phase of the study, 34.6% of non–medication-resistant patients relapsed, while 50.0% of medication-resistant patients relapsed, a difference that was not significant (p = .434).

Conclusion: We conclude that nonpsychotic patients who had at least 1 adequate antidepressant medication trial before ECT may be especially prone to early relapse after successful acute remission with ECT.


Depressed patients undergoing a course of electroconvulsive therapy (ECT) have often been treated unsuccessfully with otherwise adequate antidepressant medication trials. Numerous studies have shown lower acute ECT remission rates in medication-resistant patients, while others have found medication-resistant and non–medication-resistant patients to have an equivalent acute remission rate with ECT. We recently completed a large, multicenter study of 2 relapse prevention strategies for depressed patients remitting with ECT. We have already reported that baseline medication resistance did not predict acute ECT outcomes.

Four other studies emanating from 1 group have shown that baseline medication resistance vis-à-vis nonresis-
tance is associated with higher relapse rates in the months after acute remission with ECT. In this report, we assess this finding with data from our own study involving 6 months of follow-up treatment after successful remission with acute ECT.

METHOD

Patients and Assessments

The methodology of the trial has been described in detail elsewhere. Institutional review board approval and written informed consent procedures were undertaken for all clinical sites and all patients, respectively. In brief, the Consortium for Research on Electroconvulsive Therapy (CORE) is a multisite collaboration of investigators conducting trials of ECT efficacy and relapse prevention. In the current trial, conducted from May 1997 to July 2004, depressed patients, including those diagnosed with a unipolar depressive episode, who were referred by their primary psychiatrist for ECT were enrolled. Patients were diagnosed with the Structured Clinical Interview for DSM-IV and were excluded if they had schizophrenia, schizoaffective disorder, bipolar disorder, significant substance use disorders, or neurologic illness. During phase 1 of the trial, the patients received thrice-weekly ECT treatments utilizing standardized techniques including bitemporal electrode placement and electrical stimulus dose titration. The main outcome assessment for depressive severity was the 24-item Hamilton Rating Scale for Depression (HAM-D24), which was conducted at baseline before the first treatment and 24 to 48 hours after each subsequent treatment. Remission was defined as achieving a 60% reduction from baseline in HAM-D24 scores and 2 consecutive scores less than or equal to 10, with no more than a 3-point reduction from 1 rating to the next (the latter to ensure that a plateau in improvement had occurred). Treatments were continued until a patient remitted, dropped out, or had 10 treatments without remission (the latter serving as our definition of nonremission).

Patients meeting remission criteria were assessed for phase 2 of the study after an interval week without treatment to ensure stability of remission before enrolling in phase 2 and also to avoid possible adverse interactions between the medications and the ECT treatments. At the end of the interim week, if remission HAM-D24 scores were sustained at or below 10, the patient was eligible for phase 2, in which randomization to either continuation pharmacotherapy with lithium carbonate/nortriptyline or continuation ECT occurred. Patients were then followed for 6 months. The main goal of the original study was to assess relapse rates in these 2 groups: continuation pharmacotherapy and continuation ECT. Continuation pharmacotherapy dosing was based on attempts to achieve at least a 0.5 mmol/L blood level for lithium and a 60 ng/mL blood level for nortriptyline. For the continuation ECT patients, treatments were given once weekly for 4 weeks, followed by once every 2 weeks for 8 weeks, and then once every 4 weeks for 2 treatments. Continuation pharmacotherapy patients were seen for visits at the same frequency as continuation ECT patients, with blood levels obtained at each visit. In both groups, HAM-D24 scores were obtained at each visit. In brief, there was no difference in relapse rates between the continuation pharmacotherapy and continuation ECT treatment groups.

Phase 2 relapse was defined as 2 consecutive HAM-D24 scores of 16 or greater and at least a 10-point increase over the phase 2 baseline score. Additionally, if, in the opinion of the attending research clinician, the patient was experiencing a significant clinical relapse, as indicated by suicidal thinking or psychiatric hospitalization, then the patient was removed from the study. Thus, each patient completing phase 1 of the study could belong to 1 of 3 groups during the interim week or during phase 2: (1) sustained remitters—those whose HAM-D24 scores remained below the threshold for relapse, (2) relapers—those who relapsed, and (3) dropouts—those who exited the study prematurely. Relapse in the interim week was defined as failure to maintain a HAM-D24 score at or below 10. This very strict research definition of relapse, which would not be used in clinical practice, was to insure that only stable remitters were enrolled in phase 2.

As part of the baseline assessment prior to entry into the study, patients were administered the Antidepressant Treatment History Form (ATHF), which was developed at Columbia University, New York, N.Y., to document and quantify the degree and strength of antidepressant medication trials a patient has had before entry into a research protocol. In brief, each medication trial a patient has had is rated on a scale from 1 to 5; scores of 3 or greater are considered adequate for research purposes and reflect a sufficient dose for at least a month. For psychotically depressed patients, there must also be concomitant use of an adequate dose of an antipsychotic medication for the overall medication trial to be considered adequate. Utilizing this rating scale, each patient can be dichotomously classified as being medication-resistant if there has been at least 1 adequate medication trial in the index episode of depression or non–medication-resistant if there has not been such a trial (i.e., either they were not prescribed medication or, if they were, it did not meet criteria for adequacy of either dose or duration).

In this report, we carry out post hoc analyses to evaluate the relationship between phase 1 baseline medication resistance status and both interim and phase 2 outcomes. In 1 set of analyses, we consider interim outcomes: relapse during interim, sustained 1-week remission, or interim dropout; in a second set of analyses, we consider phase 2 outcomes: relapse, nonrelapse, or dropout. Because the sample size in phase 2 for psychotically depressed patients was too small for meaningful analyses,
we include data only for nonpsychotically depressed patients in this report. The sample was N = 146 for the interim week and N = 73 for phase 2 (Figure 1).

**Statistical Analysis**

Baseline values for demographic and clinical variables were compared using pooled t tests for continuous variables and \( \chi^2 \) tests for categorical variables for medication-resistant versus non–medication-resistant patients. The categorical outcome variables—outcome of the interim period (sustained remitter, relapser, or dropout) and treatment outcome of phase 2 (sustained remitter, relapser, or dropout)—were compared for medication-resistant versus non–medication-resistant nonpsychotic patients using \( \chi^2 \) tests. Continuous HAM-D_{24} total scores were compared between patients who were medication-resistant and patients who were not medication-resistant at the end of the interim week and at the end of phase 2 using a generalized linear model approach. Unadjusted HAM-D_{24} end-of-period (interim or phase 2) mean scores were compared for the medication-resistant groups using a generalized linear model with medication resistance as the primary independent variable. In a second set of analyses, adjusted HAM-D_{24} mean scores were compared by addition of HAM-D_{24} beginning-of-period score (end of phase 1 for interim or baseline of phase 2), hospital site, and age to the generalized linear model as additional adjustment covariables.

**RESULTS**

No significant differences were found for demographic and clinical phase 1 baseline characteristics for medication-resistant versus non–medication-resistant nonpsychotic patients among those in the interim (Table 1) and those in phase 2 (Table 2).

During the interim week, there were 146 patients for whom an ATHF had been completed; for phase 2, there were 73 patients. The outcome data for the interim and for phase 2 are presented in Tables 3 and 4, respectively.
Comparison of patients in whom an ATHF had been completed and those in whom one had not been completed has been previously reported, and there were no significant differences between these groups on a variety of demographic and clinical variables. Not every patient had an ATHF completed due to constraints on study coordinator time during phase 1 of the study.

As can be seen from Table 3, 9.8% (4 of 41) of non–medication-resistant patients suffered a relapse during the interim week, whereas 31.4% (33 of 105) of the medication-resistant patients suffered a relapse. This difference was significant ($\chi^2 = 7.3, p = .026$). Analyses of individual medication classes (i.e., selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, venlafaxine, bupropion, nefazodone, and mirtazapine) revealed no association between resistance to a specific drug and higher relapse during the interim week, whereas 31.4% (33 of 105) of the medication-resistant patients suffered a relapse. This difference was significant ($\chi^2 = 7.3, p = .026$). Analyses of individual medication classes (i.e., selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, venlafaxine, bupropion, nefazodone, and mirtazapine) revealed no association between resistance to a specific drug and higher relapse during the interim week.
relapsed, whereas 53.1% (26 of 49) of the medication-resistant patients relapsed. This difference did not reach statistical significance, however ($\chi^2 = 1.6, p = .434$).

Mean HAM-D$_{24}$ scores at the end of the interim phase were significantly higher for the medication-resistant group for both the unadjusted and the adjusted models ($p = .032$ and $p = .049$, respectively). At the end of phase 2, the difference in mean HAM-D$_{24}$ scores for the resistant versus nonresistant group was not significant (unadjusted $p = .644$, adjusted $p = .708$) (Table 5).

**DISCUSSION**

There has been intense focus in recent years on factors associated with relapse and recurrence in depressive illness. It would make intuitive sense if degree of resistance to antidepressant medications during the index depressive episode were associated with higher relapse rates in the first few months after remission. Such an association has been documented in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, in which the number of medication trials needed to achieve remission was inversely related to the chances of sustaining that remission for 1 year.  

Previous work with the ATHF has shown that baseline medication resistance was associated with twice the relapse rate during a long-term follow-up period. In our sample, relapse was much higher for the medication-resistant group in the months postremission, although this was only statistically significant for the first week. For the subsequent 6 months of phase 2, even though relapse rates were twice as high in the medication-resistant group, this was not statistically significant, probably due to the small sample sizes in that phase of the study (which also precluded analysis of the continuation medication and ECT groups separately). Even though this effect did not reach statistical significance, it is intriguing that the differential relapse rates of resistant and nonresistant patients during our 6-month phase 2 were virtually identical to those of the previous trial alluded to.  

There are several limitations to our data set. Our decision to delay the initiation of the medications in the continuation pharmacotherapy group for a week after remission was probably overly cautious. Perhaps if these patients had received their first doses the day after the last treatment, some relapses could have been avoided. However, initiating the medication without a break may not have affected the fundamental conclusion of this communication, namely, that baseline medication resistance was associated with higher initial relapse rates.  

Our criteria for remission and relapse were necessarily arbitrary but in line with other similarly designed studies.  

A particular concern was how to define relapse for the interim week after acute remission with ECT. On the one hand, a HAM-D$_{24}$ score of 11 or higher would not normally be considered a relapse in routine clinical care. However, we wanted to be strict at this stage so that patients who might be having impending full relapses could have any available option for their management at their psychiatrists’ disposal. Thus, we acknowledge that scores of 12 do not constitute full relapses, but the same criterion was used for medication-resistant and non–medication-resistant patients, so a difference between these 2 groups is still a significant finding regarding relapse potential in the first week after ECT.  

A more significant limitation was our lack of statistical power due to the small sample size. This was caused by 2 main factors. First, of all patients enrolled in the study at phase 1 baseline, a majority did not enter phase 2 of the study because of nonremission and dropouts with index ECT and relapses and dropouts during the interim. Additionally, we were not able to complete ATHF’s on all patients during the acute phase of the study because of the large number of assessments performed on the patients and constraints on study coordinator time. Further, the small sample sizes in these post hoc analyses were not based on a priori power calculations designed to provide a sufficient likelihood of detecting clinically meaningful differences. As a result, failure to detect statistical significance may be the result of low power rather than an indication that true differences in corresponding population parameters do not exist. Therefore, conclusions should be taken as hypothesis-generating rather than hypothesis-confirming. Further large studies would be needed to confirm the results.

Another limitation is the arbitrary nature of the ATHF criteria for adequacy of a trial. On the ATHF, a trial must meet criteria for dosage, which varies by medication (e.g., 225 mg/day for venlafaxine, 20 mg/day for fluoxetine) and duration, which must be 4 weeks of continuous usage. Other criteria sets may differ. Furthermore, we completed our ATHFs when patients were acutely depressed and might not have accurately recalled their medications. The other source of information we used, namely, the patients’ records, might not have contained all available information. Thus, some of our non–medication-resistant patients may have had adequate trials that were not recalled by the patient or recorded on the chart. A final note on methodology concerns use of the term adequate to describe antidepressant medication trials. This is purely a research term to quantify strength of medication usage and does not pertain to adequacy of patient care. For example, there are several reasons why a medication trial might not reach research criteria for adequacy: lack of patient willingness to take the medication at “adequate” doses, patient’s quitting of medication use before criteria for dose or duration are met, intolerance of medication due to side effects, and disagreement among prescribers over what constitutes an adequate dose of medication. Furthermore, in our data set, we did not discriminate between a patient’s originally
responding to a medication and then relapsing and a patient’s not responding to an adequate dose or duration from the beginning: both were classified as medication-resistant but may in fact be quite different in relapse potential and neurobiological factors.

In summary, in a multisite trial of ECT in which patients had precise assessments of depressive severity and baseline medication usage, we found that medication-resistant patients initially remitted with ECT at the same rate as nonresistant patients, but it appears that this remission was less stable than in those patients who were not medication-resistant, particularly in the first week after remission. This does in fact replicate the findings of Prudic et al., who provided data on acute results after the last ECT treatment and 1 week later; they found, like us, that baseline medication-resistant patients had acute remission rates the same as nonresistant patients when assessed the day after the last treatment but had higher relapse rates during the first week after remission. Their data and ours underscore the sometimes fragile nature of ECT-induced remissions in previously medication-resistant patients and the need for aggressive relapse prevention strategies.

**Drug names:** bupropion (Aplenzin, Wellbutrin, and others), fluoxetine (Prozac and others), lithium ( Eskaliat, Lithobid, and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), venlafaxine (Effexor and others).

**REFERENCES**