Antidepressant Medication Treatment Failure Does Not Predict Lower Remission With ECT for Major Depressive Disorder: A Report From the Consortium for Research in Electroconvulsive Therapy

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Objective: To test whether antidepressant medication treatment failure predicts differential remission with electroconvulsive therapy (ECT) in nonpsychotic unipolar depression.

Method: Depressed patients diagnosed with the Structured Clinical Interview for DSM-IV receiving ECT were assessed for medication use with the Antidepressant Treatment History Form (ATHF) (N = 345). Response to ECT was assessed with the 24-item Hamilton Rating Scale for Depression. Baseline medication treatment failure was analyzed as a possible predictor of remission status. Dates of study enrollment were from May 1997 to July 2004.

Results: Resistance to antidepressant medication as assessed by the ATHF, either taken as a whole or for any individual class of medication, was not predictive of acute remission status with ECT.

Conclusion: Treatment failure with antidepressant medication does not predict acute remission status with ECT for nonpsychotically depressed patients.

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Failure to respond to antidepressant medication is one of the indications for electroconvulsive therapy (ECT).[1] However, some research has indicated that depressed patients who have been exposed to at least 1 adequate antidepressant trial without benefit have markedly lower remission rates with ECT relative to those patients who have not had such a trial.[2–10] Other studies have found that medication-refractory and -nonrefractory patients have the same antidepressant response with ECT.[11–17] If in fact medication-refractory patients have lower remission rates with ECT, then this factor would have implications for clinical ECT practice.

The Consortium for Research in Electroconvulsive Therapy (CORE) recently undertook a large trial of post-ECT relapse prevention strategies. As part of baseline data collection before ECT, we recorded detailed information about all psychotropic medications used during the index depressive episode, allowing us to analyze whether medication use at baseline was associated with response to ECT. We report our results herein. The relationship between baseline medication use and post-ECT relapse rates will be reported in a separate article.

MATERIALS AND METHOD

Patients

The trial received institutional review board approval at all sites, and each patient provided written informed consent to participate. Methodology of the CORE trial has been published previously.[18] In brief, patients with Structured Clinical Interview for DSM-IV[19]–defined unipolar major depressive disorder already referred by their primary psychiatrist for ECT were enrolled in the trial (May 1997–July 2004). Patients were excluded if they had recent substance abuse/dependence, schizophrenia or schizoaffective disorder, coarse brain disease (e.g., Parkinson's disease, epilepsy, multiple sclerosis), dementia, delirium, or a primary anxiety disorder or did not

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provide their own written consent for ECT. Previous course of ECT was not an exclusion criterion unless performed during the current depressive episode.

The 24-item Hamilton Rating Scale for Depression (HAM-D-24)[20] scores were obtained at pre-ECT baseline and 1 day after each treatment or on the morning immediately prior to the following treatment. The interviews were performed by trained personnel with coratings conducted by study psychiatrists at key points in the study (e.g., at baseline and with impending remission). An intensive longitudinal quality assurance program was instituted to maintain good interrater agreement.[21] Remission was defined as an at least 60% reduction of baseline scores, 2 consecutive ratings of less than or equal to 10, and no more than a 3-point drop between the last 2 ratings. The reason for the latter requirement was to ensure that patients' HAM-D-24 scores had reached a plateau. Nonremission was defined as not meeting remission criteria and having had at least 10 ECT treatments. Exiting the study before either of these criteria were met was defined as a premature exit (dropout). Patients who remitted with the index course of ECT and who sustained the remission for an interim week without treatment were offered enrollment into the randomized phase of the trial, which consisted of 6 months of continuation treatment with either maintenance ECT or combination nortriptyline/lithium medication.

ECT Technique

Patients were treated thrice weekly with bitemporal electrode placement utilizing the Thymatron DGx ECT device (Somatics, Inc., Lake Bluff, Ill.). Baseline psychotropic medications were tapered off before ECT commenced; however, there was no minimum interval from the last administration of such agents until the first ECT treatment. The first (baseline) HAM-D-24 interview was usually conducted the morning of the first ECT treatment. As-needed lorazepam (up to 3 mg/day) or diphenhydramine (up to 50 mg/day) were allowed during index ECT for agitation or insomnia. At the first session, a stimulus titration was utilized to determine seizure threshold, and the dosage at all subsequent treatments was 1.5 times the threshold.[18] Seizure duration was monitored via the cuff technique and with a left fronto-mastoid electroencephalographic channel. Anesthetic medications consisted of glycopyrrolate, methohexital, and succinylcholine. Oxygenation was maintained with positive pressure ventilation from the onset of apnea until the resumption of spontaneous respirations after seizure termination. Pulse oximetry, electrocardiographic rhythm, and blood pressure were monitored throughout the procedure.

Psychotropic Medication Use Assessment

Baseline psychotropic medication use was quantified with the Antidepressant Treatment History Form (ATHF) developed by the Columbia University group.[5,22] On the ATHF, each psychotropic medication used by the patient in the current episode of depression is recorded along with respective dose and duration. The strength of an antidepressant trial is rated on a 5-point scale. In order to be considered adequate, a trial of antidepressant must be of sufficient dose (defined for each medication) and at least 4 weeks in duration.

For nonpsychotic patients, a level 1 trial is one in which the duration is less than 4 weeks. A level 2 trial is one in which the duration is at least 4 weeks, but the dose is below adequacy. A level 3 trial is one in which the duration is at least 4 weeks and the dose is adequate. A level 4 trial is similar to level 3 except the dose is at a higher level (defined for each medication) than for level 3. A level 5 trial is similar to a level 4 trial except that lithium augmentation for at least 2 weeks is used. Additionally, if lithium is used and the trial is otherwise a level 3, then it is considered a level 4 trial. A lithium trial cannot elevate a level 1 or 2 trial to a higher level. Arbitrarily, a level 3 trial is considered "adequate" for the purposes of the ATHF.

For psychotic patients, levels 1 through 5 are similar to above except that for levels 3 through 5, an adequate dose (defined for each medication) of antipsychotic agent must accompany the antidepressant for at least 3 weeks. Thus, the strength of each trial can be considered dichotomously as "adequate" or "inadequate," or it can be considered continuously on a scale from 1 to 5.

As this trial involved only unipolar depressed patients, use of lithium alone did not constitute an antidepressant trial. Use of adjunctive agents, such as benzodiazepines, buspirone, thyroid hormone as a psychotropic, stimulants, and anticonvulsants, was recorded but did not enter into ratings of medication resistance. Of note, the source of information for the ATHF was patient self-report, chart information, and occasionally pharmacy printouts. No formal assessment of compliance entered into the scoring, but if the patient's reliability was questioned, that ATHF score was not used.

Statistical Analysis

The demographic, clinical, and treatment characteristics for the total sample and for the subset of patients having usable ATHF scores were described using standard descriptive statistics (mean and standard deviation for continuous variables and proportions for categorical variables). Two sample t tests (or Wilcoxon rank sum test) for continuous variables and χ^2 tests for categorical variables were used to determine if there were significant differences between the subsets of patients who did/did not have valid ATHF scores.

Analyses of the relationship between treatment-resistance status (which was dichotomized as "resistant" vs. "not resistant") and acute treatment outcome were restricted to nonpsychotic depressed patients because the

number of psychotic patients evaluated as treatment resistant was too small to allow valid analyses. The relationship between acute treatment outcome and overall medication resistance, as well as resistance to individual antidepressants, was modeled using logistic regression analysis, with the dependent variable, treatment outcome, dichotomized as remit/not remit by considering all dropouts as nonremitters. For primary univariate regression analyses modeling the unadjusted relationship between remission and resistance status (labeled model 1), treatment resistance status was used as the single independent variable. In additional multivariable analyses, age, gender, severity of depression, number of prior episodes, length of current episode, and clinical center were added to the model to evaluate the effect of medication resistance (overall and individual) on treatment outcome adjusted for the added covariables (adjusted models, labeled model 2).

Odds ratios obtained from these models, along with their 95% confidence limits, are reported as measures of the strength of association between treatment resistance category and treatment outcome. For the set of analyses considering resistance to individual antidepressants, both nonadjusted and Bonferroni-corrected p values were determined. The Bonferroni-corrected p values were determined using a multiplier of 6 to account for the 6 different individual medication classifications. In a final set of exploratory analyses, we evaluated the effect modification of demographic and clinical variables on the relationship between resistance category and treatment outcome by addition of a putative effect modifier by resistance status interaction term in the logistic model. For example, a significant length of current episode by resistance status interaction term would indicate that episode duration moderates the relationship of resistance status to outcome. Each of the covariables listed above was considered as a potential effect modifier.

All significance tests were 2-sided with a significance level of $p < .05$ and were carried out using SAS version 8 (SAS Institute, Cary, N.C.).

RESULTS

There were 345 usable ATHFs on a total sample of 531 patients who signed consent forms for the trial. The reason for an incomplete set of ATHFs was due to time constraints on the study coordinators at the clinical sites as well as lack of available data in some cases. There were no significant differences between those patients with and those without ATHFs completed in age, gender, psychosis status, or episode duration, suggesting that there were no systematic biases influencing which patients had this instrument completed. However, black patients were less likely to have had an ATHF completed. The small number of such patients in the trial makes it unlikely that this factor had any effect on our conclusions. Of the 345 patients with a completed ATHF, 69.6% (240/345) were female, with a mean ± SD age of 54.5 ± 17.1 years. Of all nonpsychotic patients, 66.4% (158/238) had been given at least 1 adequate antidepressant trial, which was operationally defined as "medication resistance" for the purposes of this article. Only 3.7% (4/107) of psychotic patients met criteria for medication resistance, similar to another large ECT trial.[23] Therefore, meaningful statistical analyses were not possible to explore relationships to ECT outcome in that population. In this report, we provide analyses for nonpsychotic patients only, who were divided into "resistant" versus "not resistant" groups.

Table 1. Number of Adequate Trials in Nonpsychotic Patients

No. of Adequate Trials	Patients, % (N/N)
0	26.9 (58/216)
1	41.2 (89/216)
2	20.4 (44/216)
3	5.6 (12/216)
4	3.2 (7/216)
5	2.8 (6/216)

The mean ± SD number of adequate medication trials per patient for the nonpsychotic patients was 1.26 ± 1.17. Table 1 presents the distribution of number of adequate trials in that sample. As can be seen, most of the medication-resistant patients had 1 or 2 adequate trials. Of note, the number of patients for whom complete medication data were available to compute number of adequate trials was 216, which is slightly less than the sample for the statistical modeling (N = 226). This difference is because some patients could be classified as resistant, and thus entered into the statistical modeling, based on having had at least 1 adequate trial of a particular medication, but the data on the ATHF for other medications used were insufficient for the purpose of classifying adequacy, and thus, total number of adequate trials could not be assessed.

Table 2 presents the results of the statistical modeling and Table 3 presents the sample sizes for the relationship between medication resistance and remission status for acute-phase ECT. In the unadjusted models (model 1), giving the odds of remitting for those patients resistant to medication compared with those not resistant to medication, no statistically significant relationships were observed between remission status and either overall resistance or resistance to individual antidepressant classes. In an effort to check for possible moderating effects of demographic and clinical history factors, model 2 adjusted for age, severity of illness at baseline, gender, number of prior episodes, length of current episode, and clinical center. In this model, a statistically significant relationship between remission and resistance status was found for only 1 antidepressant class: venlafaxine treatment failure was significantly associated with lower remission rates than nontreatment failure with venlafaxine (OR = 0.09,

Table 2. Relationship of Medication Resistance Status to Phase 1 Outcome (remission status)[a]

Model[b]	Odds Ratio	95% Confidence Limits for Odds Ratio	p Value[c]
Overall medication resistance			
Model 1 (unadjusted)[d]	0.69	0.362, 1.32	.262
Model 2 (adjusted)[e]	0.48	0.191, 1.19	.112
SSRI resistance			
Model 1 (unadjusted)	1.34	0.664, 2.71	.412
Model 2 (adjusted)	1.13	0.414, 3.08	.812
TCA resistance			
Model 1 (unadjusted)	0.61	0.186, 1.99	.411
Model 2 (adjusted)	0.42	0.077, 2.32	.320
Mirtazapine resistance			
Model 1 (unadjusted)	0.90	0.270, 3.02	.867
Model 2 (adjusted)	3.87	0.274, 54.87	.317
Venlafaxine resistance			
Model 1 (unadjusted)	0.44	0.166, 1.17	.101
Model 2 (adjusted)	0.09	0.012, 0.68	.019
Nefazodone resistance			
Model 1 (unadjusted)	1.67	0.443, 6.31	.449
Model 2 (adjusted)	3.40	0.188, 61.25	.407
Bupropion resistance			
Model 1 (unadjusted)	0.70	0.250, 1.94	.145
Model 2 (adjusted)	0.45	0.079, 2.54	.364

[a]Phase 1 (acute electroconvulsive therapy) outcome: remitter vs. nonremitter/dropout.
[b]Model 1 contains only the respective medication resistance (overall, SSRI); model 2 contains the respective medication resistance (overall, SSRI), age, baseline HAM-D-24 total score, gender, number of prior episodes, length of current episode, and clinical center.
[c]Bonferroni-corrected p values are obtained by multiplying reported p values by a factor of 6.
[d]Odds ratio (overall resistance–unadjusted): the odds of remitting for those resistant to medication compared with those not resistant to medication.
[e]Odds ratio (overall resistance–adjusted): the odds of remitting for those resistant to medication compared with those not resistant to medication adjusted for age, baseline HAM-D-24 total score, gender, number of prior episodes, length of current episode, and clinical center.
Abbreviations: HAM-D-24 = 24-item Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

95% confidence limit (CL) = 0.012, 0.68; p = .019). Following Bonferroni correction for multiple outcomes, this association became nonsignificant (Bonferroni-corrected p value = .11). As can be appreciated from Table 2, the confidence limits are wide for several of the analyses, which probably reflects low statistical power.

Further adjustment of the logistic models adding interaction terms to evaluate effect modification found that overall medication resistance (i.e., failure to respond to at least 1 antidepressant medication trial regardless of class) was associated with lower acute ECT remission rates if the current episode was 1 to 15 weeks in duration (OR = 0.09, 95% CL = 0.013, 0.65; p = .017) but not if the length of current episode was greater than that (16–40 weeks: OR = 0.27, 95% CL = 0.03, 2.4; p = .239; > 40 weeks: OR = 1.21, 95% CL = 0.241, 5.08; p = .816). However, after Bonferroni correction for multiple outcome comparisons, this association of remission to resistance status in the 1 to 15 weeks' duration group also became nonsignificant (p = .10).

An attempt was made to explore the relationship between number of adequate trials and remission rates to see if patients resistant to more than 1 trial had lower remission rates than those with only 1 trial. The remission rates for those patients with 1, 2, or more than 2 adequate antidepressant medication trials was 65.2%, 63.6%, and 60.0%, respectively. These rates were not significantly different by χ^2 analysis ($\chi^2 = 6.45$, df = 6, p = .374).

DISCUSSION

In our large sample of unipolar depressed patients receiving ECT, strength of baseline medication use did not predict remission rates. Several investigators have reported ECT outcomes in open-label samples of medication-resistant patients and have generally found 50% to over 90% success rates.[24–31] These studies are limited in their generalizability because of the lack of non–medication-resistant control patients.

In contrast, numerous studies have compared the ECT response in medication-resistant to non–medication-resistant patients. Overall, the literature is relatively evenly split on whether the response/remission rates of these 2 groups are equal[11–17] or lower for the medication-resistant patients.[2–10] There are no studies in which medication-resistant patients have a superior response.

The ideal study would include 3 features: (1) use of diagnostic criteria for the population of patients studied, (2) precise definition of medication resistance to include criteria for adequate trials of each medication, and (3) reliable quantification of ECT outcome using standardized rating scales. Many of the above-referenced articles vio-

Table 3. Sample Sizes Used in Logistic Regression Models

		Resistant, N		Not Resistant, N	
Model	Total, N	Remitter	Nonremitter + Dropout	Remitter	Nonremitter + Dropout
Overall medication resistance					
Model 1	226	105	63	41	17
Model 2	149	69	39	33	8
SSRI resistance					
Model 1	167	78	46	24	19
Model 2	110	54	30	17	9
TCA resistance					
Model 1	53	37	16	23	8
Model 2	40	11	6	18	5
Mirtazapine resistance					
Model 1	48	12	7	19	10
Model 2	31	9	2	13	7
Venlafaxine resistance					
Model 1	79	21	14	34	10
Model 2	50	11	9	27	3
Nefazodone resistance					
Model 1	41	13	5	14	9
Model 2	22	7	1	8	6
Bupropion resistance					
Model 1	63	12	12	23	16
Model 2	39	9	6	17	7

Abbreviations: SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

late one or more of these criteria by using impressionistic approaches to diagnosis (e.g., reporting patients simply as "depressed" without further specification), having no criteria for medication resistance in terms of proper dose or duration of therapy, or by classifying outcome through general clinical impression and not with structured rating scales.

There are 9 studies that do meet the 3 criteria.[5–10,15–17] Of these, 5 emanate from 1 group at Columbia University.[5,6,8–10] The methodology is the same for these reports, in which unipolar depressed patients diagnosed through structured interviews according to research criteria were enrolled in one of this group's studies comparing electrode placements and stimulus intensities in ECT. Outcome was assessed with the HAM-D-24. Remission was defined as an at least 60% reduction in baseline score with a final score of 10 or less after the last treatment and sustained for up to a week without treatment. Medication resistance was assessed with the ATHF, which was developed by that group. In all of these reports, medication-resistant patients had significantly lower remission rates with ECT than did the nonresistant patients. Of the other 4 studies cited above, which meet the 3 criteria for rigorous methodology, only 1 found that baseline medication-resistance status predicted lower response rates with ECT,[7] while the others found no difference in response rates between groups.[15–17] Another factor that might explain the difference in findings among studies is use of unilateral electrode placement in some of the studies that did find a relationship between medication failure and ECT outcomes,[5,6,8–10] while in our study, we used bitemporal placement. It is possible that, in the face of medication failure, electrode placement is relevant to acute outcomes.

In several reports, resistance specifically to tricyclic antidepressants, vis-a-vis resistance to other antidepressant medications, was predictive of lower remission rates.[2–4,6] However, other studies in addition to our own reported here have found no particular association between tricyclic resistance and lowered ECT remission.[14,15,17]

One factor that separates these otherwise very similar studies is the definition of remission. The Columbia group has consistently used a HAM-D-24 score less than 10 sustained for approximately 1 week as the measure of remission, while other groups,[15–17] including ours, use the score obtained the day after the last treatment, which is a less rigorous definition. If some patients relapse within the week after the first rating of less than 10 but before the next rating, then that patient would count as a remitter in our study but not in the Columbia studies. In fact, in one of the latter studies,[5] data are presented for HAM-D-24 ratings the day after the last treatment and approximately 1 week later, and there is not a significant difference between resistant and nonresistant patients the day after the last treatment. Thus, baseline medication resistance may not necessarily predict differential acute remission with ECT but rather tendency toward early relapse after remission. This latter hypothesis will be explored in a later article when we analyze our postremission continuation data.

There are several limitations to our data. First, not all of the enrolled patients had an ATHF completed, due as mentioned above to limitations on study coordinator time and lack of available data in some cases. Thus, the sample of patients who did have the ATHF completed may not have been truly representative of the entire sample, though there were no significant differences in several demographic variables between the 2 groups. A second limitation is the

arbitrary definition of *treatment resistance*, a term that has been used quite variably in the psychiatric literature. It is possible that a different definition of adequacy of dosage and duration for the various antidepressant medications could have led to different results. A third limitation is reliance on patients to provide their own information on doses and durations of medications used, along with chart data, which may not be wholly reliable. Still, one would expect that if strength of medication use does predict lower remission rates, in a sample of several hundred patients, there should have been a signal to this effect even though the information obtained was from patient recall. Another limitation concerns the reason why a particular "adequate" medication trial failed. That is, whether the patient never responded to the medication or initially responded with subsequent relapse is not distinguished in our dataset, and these 2 scenarios may have different implications for ECT response.

In conclusion, in the largest sample yet of unipolar depressed patients diagnosed with structured scales receiving ECT in whom detailed information about baseline psychotropic medication use was obtained along with quantified rating scales measuring clinical outcome, we found no significant association between treatment failure with antidepressant medication use and acute remission rates. This finding would imply that if the usual psychopathologic features indicating ECT are present, antidepressant medication resistance should not sway the clinician from prescribing this modality.

Drug names: bupropion (Wellbutrin and others), diphenhydramine (Benadryl and others), glycopyrrolate (Robinul and others), lithium (Lithobid, Eskalith, and others), lorazepam (Ativan and others), methohexital (Brevital sodium), mirtazapine (Remeron and others), nortriptyline (Pamelor and others), succinylcholine (Quelicin and Anectine), venlafaxine (Effexor and others).

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