Effect of Concomitant Pharmacotherapy on Electroconvulsive Therapy Outcomes

Short-term Efficacy and Adverse Effects

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Context: Medication resistance is the leading indication for use of electroconvulsive therapy (ECT) in major depression. The practice of stopping antidepressant medications prior to ECT derived from studies in the 1960s and 1970s in nonresistant samples. There is also continuing controversy regarding the relative efficacy and adverse effects of right unilateral and bilateral ECT.

Objective: To test the hypotheses that, compared with placebo, concomitant treatment with nortriptyline or venlafaxine during the ECT course enhances short-term efficacy without a meaningful effect on adverse effects and reduces the rate of post-ECT relapse, and to test the hypotheses that high-dose, right-sided, unilateral ECT is equivalent in efficacy to moderate-dosage bilateral ECT and retains advantages with respect to cognitive adverse effects.

Design: Prospective, randomized, triple-masked, placebo-controlled study conducted from 2001 through 2005.

Setting: Three university-based hospitals.

Patients: Of approximately 750 consecutive patients referred for ECT, 319 with a major depressive episode consented, were randomized to pharmacological or ECT treatment conditions, and received at least 1 ECT treatment.

Main Outcome Measures: Scores on the Hamilton Rating Scale for Depression, remission rate following completion of ECT, and selective measures of cognitive adverse effects.

Results: Treatment with nortriptyline enhanced the efficacy and reduced the cognitive adverse effects of ECT relative to placebo. Venlafaxine resulted in a weaker degree of improvement and tended to worsen cognitive adverse effects. High-dosage right unilateral ECT did not differ or was superior to bilateral ECT in efficacy and resulted in less severe amnesia.

Conclusions: The efficacy of ECT is substantially increased by the addition of an antidepressant medication, but such medications may differ in whether they reduce or increase cognitive adverse effects. High-dose, right-sided, unilateral ECT is at least equivalent to moderate-dosage bilateral ECT in efficacy, but retains advantages with respect to cognitive adverse effects.

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ELECTROCONVULSIVE THERAPY (ECT) is widely considered the most effective short-term treatment for major depressive episodes. Nonetheless, remission rates after ECT appear to have declined. At one time, it was expected that approximately 90% of patients with major depression remitted, but this rate is substantially reduced in modern research. This putative decline could be related to several factors including differences over time in assessment methods or ECT administration. Perhaps most important is the shift in patient characteristics. Electroconvulsive therapy was commonly used as a first-line antidepressant treatment, but in recent decades medication resistance has become its primary indication.

There is substantial evidence that the degree of resistance predicts the efficacy of several antidepressant treatments, including pharmacotherapy and ECT. Historically, studies examining the use of concomitant antidepressant medication with ECT had mixed results. Some uncontrolled studies in the 1940s through the 1960s claimed that combining ECT with antidepressant medication resulted in greater likelihood of remission. Randomized placebo-controlled trials from this era failed to demonstrate synergism when ECT was combined with a tricyclic antidepressant or monoamine oxidase inhibitor. A recent study suggested that adding imipramine to ECT resulted in superior efficacy compared with adding paroxetine. During continuation treatment, however, relapse rates were reduced in patients receiving paroxetine relative to imipramine or placebo.
Modern practice often involves use of numerous medications, the effect of which during ECT is unknown. Guidelines vary widely in recommendations regarding concomitant antidepressants.\(^1\) The American Psychiatric Association Task Force on ECT discouraged such combination treatment, given the paucity of findings demonstrating enhanced efficacy and concern about potentiating adverse effects.\(^1\) In contrast, such combination treatment is routine elsewhere.\(^2-4\) Nonetheless, a large proportion of practitioners use BL ECT as their primary intervention.\(^5-6\) The extent findings may have limited generalizability, as much of the literature has used high-dosage BL ECT as the criterion standard treatment condition.\(^5,6\) While this provided a conservative comparison with respect to efficacy, the use of high electrical dosage with BL ECT may have biased previous studies to identify cognitive advantages for RUL ECT. Previous studies also had small samples that underwent substantial medication washout and were studied in specialized research settings.\(^5,6\)

We conducted a multisite, randomized, placebo-controlled, triple-masked trial. Patients were randomized to nortriptyline (NT), venlafaxine (VEN), or placebo (PL) during ECT, as well as high-dosage RUL or moderate-dosage BL ECT. In a second 6-month, triple-masked, continuation therapy trial, patients treated with PL during ECT were randomized to continuation therapy with NT or VEN; those who received active medication during ECT continued taking that medication, and lithium was added in all cases. Here we describe the results of the acute treatment phase.

**STUDY SITES AND PARTICIPATION**

The study was conducted at Wake Forest University Health Sciences (WF), Western Psychiatric Institute and Clinic (WPIC), and Washington University, St Louis, Missouri (WU). The New York State Psychiatric Institute was the coordinating/monitoring center. Using the Structured Clinical Interview for Axis I DSM-IV Disorders, Patient Edition (with Psychotic Screen, Structured Clinical Interview for DSM Disorders),\(^3\) patients met the DSM-IV\(^3\) criteria for a major depressive episode (unipolar or bipolar). They scored 21 or greater on the Hamilton Rating Scale for Depression (HRSD, 24-item),\(^4\) and treatment with ECT was indicated. Patients were excluded if they had a history of schizophrenia, schizoaffective disorder, non–mood disorder psychosis, neurological illness, alcohol or drug abuse within 6 months, ECT within 6 months, or severe medical illness. Patients were also excluded if they had a known allergy or contraindication to NT or VEN.

Participants at the 3 sites were recruited from approximately 750 consecutive patients referred for ECT, with 340 patients consenting to study participation (Figure 1). Of the 21 patients who did not contribute ECT outcome data, 17 left the study prior to the start of ECT and 4 were dropped owing to identification of an exclusion criterion.

Patients were considered remitters if they had at least a 60% reduction in HRSD scores relative to pre-ECT baseline, with a maximum score of 10 at both an assessment within 2 days of ECT discontinuation and a reassessment 4 to 8 days following ECT termination. Patients were considered completers if they met remission criteria or received at least 8 treatments. Patients pro-
vided 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 the New York State Psychiatric Institute approved the study.

STUDY DESIGN

Patients’ use of psychotropic medications was discontinued, other than lorazepam given as needed (up to 3 mg/d), before starting ECT. Methohexital (0.75-1.0 mg/kg) and succinylcholine (0.75-1.0 mg/kg) were used as anesthetic medications with preadministration of atropine (0.4-0.6 mg) or glycopyrrolate (0.2-0.4 mg). Patients were randomized to RUL ECT administered at 6 times the seizure threshold (6×ST) or BL ECT at 1.5×ST. The RUL and BL ECT were administered using the d’Elia and bifrontaltemporal placements, respectively.1 Seizure threshold was sufficiently elevated in 16 of 155 (10.3%) patients randomized to RUL ECT that the actual dosage administered at the device maximum (576 mC) was below 6×ST. Electroconvulsive therapy was given 3 times per week with a MECTA Spectrum 5000Q device (MECTA Corp, Tualatin, Oregon). Seizure threshold was quantified at the first treatment using the empirical titration procedure.18 Patients in either ECT group who did not show substantial improvement after 8 or more treatments crossed over to high-dose (2.5×ST) B LECT. To be considered adequate, the minimal seizure duration was 20 seconds of motor or 25 seconds of electroencephalogram manifestation. Electroconvulsive therapy was continued as long as clinical progress was observed and terminated after no further improvement for at least 2 treatments.

Patients were also randomized to receive NT, VEN, or PL starting the afternoon following the first ECT treatment. A double-dummy technique was used throughout the acute treatment phase. Each patient received 2 sets of pills, 1 corresponding to VEN or PL in the morning and the other to NT or PL in the evening. A standard-dose escalation schedule was used, differentiating between 2 types of patients based on the clinical judgment of the treating psychiatrist. Patients in class A (healthy, robust) received higher starting doses of the antidepressant and a more rapid escalation than class B (frail) patients. The goal was to achieve therapeutic NT blood levels (100-120 ng/mL) or a minimum daily dose of 225 mg of VEN before discontinuing ECT. Blood samples were obtained weekly to assess NT levels and the presence of VEN. Blood levels were reported to the site for only NT, and a psychopharmacologist at New York State Psychiatric Institute provided fake levels for patients not receiving NT.

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 a permuted blocks, with equal representation within each block of BL and RUL ECT, and a 1:3:1 ratio of PL to either NT or VEN. Randomization was stratified among nonpsychotic patients by the judgment of treating psychiatrist as to whether the patient had received at least 1 adequate antidepressant medication trial in the current episode18 or by the presence of psychosis, based on the Structured Clinical Interview for DSM Disorders. At each site, other than individuals involved in ECT administration (none of whom provided clinical ratings), patients, treatment teams, and outcome assessors were masked to ECT treatment assignment, and, other than the pharmacist, patients and all personnel were masked to pharmacotherapy assignment. Thus, when considering patients, outcome assessors, and treatment providers, the study was triple-masked with respect to pharmacological assignment and double-masked regarding ECT assignment.

ASSSESSMENTS

The Antidepressant Treatment History Form was completed to quantify medication resistance (ie, number of adequate antidepressant trials in the current episode).19 Prior to ECT, twice weekly prior to crossover ECT, and at ECT termination, a clinical rater and a study psychiatrist not involved in ECT administration completed the HRSD.19 Based on videotapes of the clinical rater HRSD interview, a masked, site-independent, expert rater rescored a substantial subset of the HRSD interviews to monitor reliability. The intraclass correlation coefficient at each site exceeded 0.96. The clinical rater also completed the Clinical Global Impression (CGI) scales (CGI-S indicates severity; CGI-I, improvement)30 and the Global Assessment of Function scale32 at the same intervals. Patients completed the Beck Depression Inventory-II19 before and after the ECT course. After ECT, patients and the clinical rater made their best guess as to which of the 3 pharmacological conditions had been administered, whether the patient received RUL or BL ECT, and whether they crossed over to high-dosage BL ECT.

Adverse effects were assessed in terms of the frequency of adverse and serious adverse events, scores on the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale,20 and primary cognitive outcome measures from a neuropsychological battery. Adverse events and serious adverse events were defined following standard conventions. The UKU scale was completed by a treating psychiatrist at the same interval as the HRSD rating. A battery of cognitive tests was administered before starting ECT, before crossover ECT, and 1 to 4 days following all ECT. Four tests provided primary cognitive outcome measures: total score on the modified Mini-Mental State Examination (MMSE),31 accuracy (d’) on the N-Back test,30 total recall of unrelated words across 6 trials of the Buschke Selective Reminding Test (SRT),41 and score on the Autobiographical Memory Interview, Short Form (AMI-SF).30,42 The MMSE assessed global cognitive status, the N-Back assessed working memory, the SRT assessed anterograde amnesia for verbal information, and the AMI-SF assessed retrograde amnesia for autobiographical information. The computer-administered N-Back required identification of matching 4-digit numbers that were 2 or 3 earlier in a sequence. Alternate versions of each test were randomized to assessment occasion. We hypothesized an advantage for RUL relative to BL ECT on the MMSE, SRT, and AMI-SF. Effects of the pharmacological conditions on cognitive measures were considered exploratory.

STATISTICAL ANALYSIS

The sites were compared in demographic and clinical features with 1-way analyses of variance for continuous measures and χ² analyses for dichotomous variables. The randomized treatment conditions were compared in baseline variables using fully factorial 3 (PL vs NT vs VEN) × 2 (BL vs RUL ECT) analyses of variance or log-linear analyses. The Tukey honest significant difference test and χ² analyses were used for post hoc pairwise analyses of continuous and dichotomous variables, respectively.

Analyses of covariance (ANCOVAs) were conducted on ECT and pharmacological treatment parameters to detect differences among the randomized treatment conditions. The models included pharmacological and ECT assignments as fully crossed factors, the main effect of site, and age as a covariate. For ECT administration, the variables examined were seizure threshold at the first treatment (charge), charge, dynamic impedance, and motor and electroencephalogram seizure duration, averaged across all treatments. For pharmacological treatment parameters, the variables examined were average and maximum doses of VEN or its PL and NT or its PL.

The primary efficacy analyses were conducted in the intent-to-treat (ITT) sample (n=319). The a priori primary outcome measures were the HRSD scores 4 to 8 days following completion of
all ECT and the rate of remission. Secondary outcome measures were the CGI-S and Beck Depression Inventory-II scores following completion of ECT and the rate of response on the CGI-I, defined as a post-ECT score of 1 or 2. For continuous variables, ANCOVAs were performed by modeling the main effects and interaction of the randomized pharmacological, ECT conditions, main effect of site age, number of adequate antidepressant trials in the current episode, and baseline score on the continuous outcome measure as covariates. For the dichotomous outcome measures, log-linear analyses were conducted with all of the same terms and with the baseline HRSD score serving as a covariate.

Secondary efficacy analyses were conducted in 2 other samples. The 2 primary outcome measures were examined following completion of all ECT in a sample restricted to completers, ie, those who remitted or received at least 8 treatments. To determine whether the choice of 8 treatments as a cutoff for nonremitting completers biased the results, the log-linear analyses on remission were reanalyzed for samples in which completers status was defined by remission or receiving at least 1, 2, 4, 6, or 8 treatments. Because outcomes following completion of ECT included 60 patients whose regimen changed to high-dose BL ECT (Figure 1), the analyses of the 2 primary outcome measures were also conducted in the ITT sample after completion of the original randomized ECT assignment and before crossover.

Analyses of covariance were conducted on the 4 cognitive measures, log-linear analyses on remission were reanalyzed for samples in which completers status was defined by remission or receiving at least 1, 2, 4, 6, or 8 treatments. Because outcomes following completion of ECT included 60 patients whose regimen changed to high-dose BL ECT (Figure 1), the analyses of the 2 primary outcome measures were also conducted in the ITT sample after completion of the original randomized ECT assignment and before crossover.

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## RESULTS

The sites varied in clinical and demographic characteristics (Table 1), with significant differences in age ($F_{2,316} = 6.45; P = .002$), duration of current episode ($F_{2,289} = 3.66; P = .004$), HRSD score ($F_{2,316} = 13.91; P < .001$), Global Assessment of Function score ($F_{2,316} = 29.31; P < .001$), Beck Depression Inventory-II score ($F_{2,316} = 4.57, P = .01$), and number of treatment trials in the current episode ($F_{2,316} = 3.92; P = .02$) as well as the distributions of sex ($\chi^2 = 6.44, P = .04$) and psychotic depression ($\chi^2 = 17.37, P < .001$). However, the analyses contrasting the randomized treatment conditions in baseline characteristics (Table 1) yielded no effects.

### TREATMENT PARAMETERS

The ANCOVAs indicated that the randomized pharmacological conditions did not differ in ECT treatment parameters (Table 2). There were also no effects of ECT electrode placement condition on motor or electroencephalogram seizure duration measures. The mean (SD) initial seizure threshold was higher with BL (127.9 [76.0] mC) than RUL ECT (92.0 [66.6] mC; $F_{1,289} = 34.99; P < .001$), a well-replicated finding. Also in line with previous results, the mean (SD) dynamic impedance was higher with RUL (218.6 [35.1] Ω) than BL ECT (202.7 [28.7] Ω; $F_{1,289} = 19.98; P < .001$). Given the dosing strategies used, the mean (SD) charge per treatment was substantially greater with RUL (367.0 [140.8] mC) than BL ECT (219.6 [118.2] mC; $F_{1,289} = 111.23; P < .001$). One patient who received BL ECT was dropped because adequate seizures could not be elicited at maximal device settings (protocol deviation).

The randomized pharmacological and ECT conditions did not differ in any of the pharmacological treatment parameters (Table 2). The methods used to adjust dosage of NT and VEN resulted in equivalent average and maximum dosage prescriptions of NT and VEN or their matched placebos in the randomized groups. The ANCOVAs yielded main effects of site for the average ($F_{2,289} = 16.59; P < .001$) and maximum ($F_{2,289} = 64.38; F < .001$) dose of VEN and maximum dose of NT ($F_{2,289} = 4.41; P = .01$). The average and maximum doses of VEN were higher at WPIC than WU, and the doses at WU were higher than at WF. In contrast, the maximum NT dose was higher at WU than at both WPIC and WF, which

### Table 1. Clinical and Demographic Characteristics of the Sample as a Function of Study Site

<table>
<thead>
<tr>
<th>Variable</th>
<th>WF (n=106)</th>
<th>WPIC (n=127)</th>
<th>WU (n=86)</th>
<th>Total (n=319)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53.4 (16.2)</td>
<td>46.5 (15.4)</td>
<td>47.3 (14.7)</td>
<td>49.0 (15.7)</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>75.0 (70.8)</td>
<td>82.0 (64.6)</td>
<td>46.0 (53.9)</td>
<td>203.0 (63.6)</td>
</tr>
<tr>
<td>Education, y</td>
<td>13.5 (3.2)</td>
<td>13.8 (2.6)</td>
<td>13.7 (2.8)</td>
<td>13.6 (2.9)</td>
</tr>
<tr>
<td>Bipolar, No. (%)</td>
<td>16.0 (15.1)</td>
<td>29.0 (22.8)</td>
<td>21.0 (24.4)</td>
<td>66.0 (20.7)</td>
</tr>
<tr>
<td>Psychotic depression, No. (%)</td>
<td>19.0 (17.9)</td>
<td>38.0 (29.9)</td>
<td>6.0 (7.0)</td>
<td>63.0 (19.8)</td>
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<tr>
<td>Duration of current episode, wk</td>
<td>30.1 (27.4)</td>
<td>38.0 (35.1)</td>
<td>47.1 (37.5)</td>
<td>37.9 (34.0)</td>
</tr>
<tr>
<td>Pre-ECT HRSD score</td>
<td>29.3 (5.2)</td>
<td>30.8 (6.3)</td>
<td>33.7 (7.2)</td>
<td>31.1 (6.5)</td>
</tr>
<tr>
<td>Clinical Global Impression, severity score</td>
<td>5.3 (0.7)</td>
<td>5.3 (0.7)</td>
<td>5.2 (0.8)</td>
<td>5.3 (0.7)</td>
</tr>
<tr>
<td>Global Assessment of Function score</td>
<td>34.7 (7.6)</td>
<td>33.2 (10.0)</td>
<td>42.7 (10.0)</td>
<td>36.2 (10.1)</td>
</tr>
<tr>
<td>Beck Depression Inventory score</td>
<td>37.8 (11.7)</td>
<td>40.1 (8.1)</td>
<td>35.8 (10.6)</td>
<td>38.2 (10.4)</td>
</tr>
<tr>
<td>Total medication trials, No.</td>
<td>5.6 (3.7)</td>
<td>5.4 (3.3)</td>
<td>4.3 (3.1)</td>
<td>5.2 (3.5)</td>
</tr>
<tr>
<td>Total adequate medication trials, No.</td>
<td>1.1 (1.3)</td>
<td>1.4 (1.4)</td>
<td>1.2 (1.2)</td>
<td>1.3 (1.3)</td>
</tr>
</tbody>
</table>

Abbreviations: ECT, electroconvulsive therapy; HRSD, Hamilton Rating Scale for Depression; WF, Wake Forest University; WPIC, Western Psychiatric Institute and Clinic; WU, Washington University.

$^{a}$Values differed significantly from those with a footnote $b$ in pairwise post hoc comparisons.

$^{b}$Values differed significantly from those with a footnote $a$ in pairwise post hoc comparisons.

$^{c}$Values did not differ significantly from those with a footnote $a$ or $b$ in pairwise post hoc comparisons.

$^{d}$Capped at 104 weeks.

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did not differ. The ANCOVAs also indicated that age was negatively associated with average and maximum doses of both NT and VEN (all \( P < .001 \)). The mean (SD) blood level of NT during the acute ECT phase in the NT pharmacological group was 82.1 (51.2) ng/mL and the mean (SD) maximum level achieved was 99.9 (58.7) ng/mL. There was no difference among the pharmacological or ECT conditions in the index episode (\( P > .1 \)). Compared with patients who were considered non-completers, completers had higher average (\( t_{298} = 5.33; P < .001 \)) and maximum (\( t_{298} = 6.93; P < .001 \)) doses of VEN and higher maximum doses of NT (\( t_{298} = 2.36; P = .02 \)).

**EFFICACY**

**ITT Sample**

The ANCOVA on post-ECT HRSD scores yielded main effects of pharmacological condition (\( F_{2,308} = 3.44; P = .03 \)), site (\( F_{2,308} = 3.98; P = .02 \)), pre-ECT HRSD score (\( F_{1,308} = 25.84; P < .001 \)), and number of adequate treatment trials (\( F_{1,308} = 4.11; P = .04 \)). Post hoc comparisons indicated that clinical outcome was superior in patients receiving NT relative to PL. Venlafaxine did not differ from the other conditions (Table 3). Final HRSD scores were higher at WU than WPIC, and a greater number of adequate treatment trials were associated with poorer outcome. The log-linear analysis on remission rates yielded main effects of pharmacological condition (\( \chi^2 = 6.32; P = .04 \)), ECT electrode placement (\( \chi^2 = 4.64; P = .03 \)), site (\( \chi^2 = 10.38; P = .006 \)), pre-ECT HRSD score (\( \chi^2 = 11.25; P < .001 \)), and number of adequate treatment trials in the index episode (\( \chi^2 = 4.68; P = .03 \)). Remission rates were higher with NT than PL and higher in patients randomized to RUL than to BLECT (Table 3). Remission rates were higher at WPIC than WU. Greater treatment resistance was associated with lower remission rates. Thus, both primary clinical outcome measures demonstrated superior efficacy in pa-

### Table 2. Pharmacological Treatment Parameters and ECT in the Intent-to-Treat Sample as a Function of Randomized Pharmacological and ECT Conditions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n=135)</th>
<th>Nortriptyline (n=93)</th>
<th>Venlafaxine (n=91)</th>
<th>Bilateral (n=164)</th>
<th>Right Unilateral (n=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECT treatment parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial seizure threshold, mC</td>
<td>112.4 (82.8)</td>
<td>110.7 (68.2)</td>
<td>107.1 (68.8)</td>
<td>127.9 (78.0)</td>
<td>92.0 (66.6)</td>
</tr>
<tr>
<td>Average electrical dose, mC</td>
<td>280.3 (148.3)</td>
<td>302.6 (153.2)</td>
<td>296.3 (146.4)</td>
<td>219.6 (118.2)</td>
<td>367.0 (140.8)</td>
</tr>
<tr>
<td>Average dynamic impedance, ( \Omega )</td>
<td>206.2 (32.6)</td>
<td>210.5 (33.3)</td>
<td>216.6 (32.2)</td>
<td>202.7 (28.7)</td>
<td>218.6 (35.1)</td>
</tr>
<tr>
<td>Motor seizure duration, s</td>
<td>40.4 (15.1)</td>
<td>37.5 (12.5)</td>
<td>38.1 (14.4)</td>
<td>38.6 (15.2)</td>
<td>38.2 (13.0)</td>
</tr>
<tr>
<td>EEG seizure duration, s</td>
<td>61.9 (24.0)</td>
<td>59.5 (23.1)</td>
<td>59.1 (22.1)</td>
<td>60.9 (24.6)</td>
<td>59.9 (21.8)</td>
</tr>
<tr>
<td>Pharmacological treatment parameters, mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average dose of NT or its PL</td>
<td>65.9 (16.3)</td>
<td>67.4 (18.4)</td>
<td>67.6 (15.3)</td>
<td>66.6 (16.8)</td>
<td>67.0 (16.5)</td>
</tr>
<tr>
<td>Maximum dose of NT or its PL</td>
<td>78.3 (18.7)</td>
<td>79.9 (26.8)</td>
<td>76.2 (15.6)</td>
<td>77.5 (19.9)</td>
<td>78.9 (21.3)</td>
</tr>
<tr>
<td>Average dose of VEN or its PL</td>
<td>179.1 (49.3)</td>
<td>176.9 (55.3)</td>
<td>187.4 (51.2)</td>
<td>183.7 (50.1)</td>
<td>177.9 (53.1)</td>
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<tr>
<td>Maximum dose of VEN or its PL</td>
<td>246.1 (61.0)</td>
<td>243.8 (69.9)</td>
<td>256.6 (58.7)</td>
<td>250.9 (62.1)</td>
<td>245.8 (64.2)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ECT, electroconvulsive therapy; EEG, electroencephalogram; NT, nortriptyline; PL, placebo; VEN, venlafaxine.

### Table 3. Clinical Outcome Measures as a Function of Randomized Pharmacological and ECT Conditions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Nortriptyline</th>
<th>Venlafaxine</th>
<th>Bilateral</th>
<th>Right Unilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-treat sample (n=319)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-ECT HRSD score</td>
<td>14.6 (10.7)</td>
<td>11.6 (10.0)</td>
<td>12.2 (10.2)</td>
<td>13.5 (10.4)</td>
<td>12.5 (10.4)</td>
</tr>
<tr>
<td>Remission rate, %</td>
<td>48.9</td>
<td>63.4</td>
<td>60.2</td>
<td>51.8</td>
<td>61.3</td>
</tr>
<tr>
<td>Post-ECT CGI-S score</td>
<td>3.1 (1.5)</td>
<td>2.6 (1.4)</td>
<td>2.6 (1.4)</td>
<td>2.9 (1.5)</td>
<td>2.8 (1.4)</td>
</tr>
<tr>
<td>CGI-I response rate, %</td>
<td>51.1</td>
<td>64.5</td>
<td>61.5</td>
<td>52.4</td>
<td>63.9</td>
</tr>
<tr>
<td>Post-ECT BDI score</td>
<td>18.4 (12.9)</td>
<td>16.8 (11.6)</td>
<td>14.9 (12.0)</td>
<td>17.9 (12.7)</td>
<td>15.9 (11.8)</td>
</tr>
<tr>
<td>ECT treatments, No.</td>
<td>8.4 (4.3)</td>
<td>7.9 (3.9)</td>
<td>7.9 (4.98)</td>
<td>8.1 (4.3)</td>
<td>8.1 (4.5)</td>
</tr>
<tr>
<td>Completer sample (n=252)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-ECT HRSD score</td>
<td>11.7 (9.3)</td>
<td>8.8 (8.1)</td>
<td>9.8 (9.4)</td>
<td>11.0 (9.6)</td>
<td>9.6 (8.5)</td>
</tr>
<tr>
<td>Remission rate, No.</td>
<td>62.3</td>
<td>79.7</td>
<td>76.7</td>
<td>67.2</td>
<td>76.0</td>
</tr>
<tr>
<td>Intent-to-treat sample prior to crossover (n=319)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-ECT HRSD Score</td>
<td>15.9 (10.7)</td>
<td>12.6 (9.8)</td>
<td>13.0 (9.7)</td>
<td>14.4 (10.1)</td>
<td>13.8 (10.4)</td>
</tr>
<tr>
<td>Remission rate, No.</td>
<td>41.4</td>
<td>54.8</td>
<td>52.8</td>
<td>45.7</td>
<td>48.6</td>
</tr>
</tbody>
</table>

**Abbreviations:** BDI, Beck Depression Inventory; CGI-I, Clinical Global Impression improvement scores; CGI-S, Clinical Global Impression severity scores; ECT, electroconvulsive therapy; HRSD, Hamilton Rating Scale for Depression.

* Treatment groups within the pharmacological and ECT conditions that differed significantly in post hoc comparisons not shown.
adequate trials ($F_{1,308}=5.01; P=.03$), and pre-ECT Beck Depression Inventory-II score ($F_{1,308}=21.32; P<.001$).

The advantages that the NT and RUL ECT conditions showed in efficacy were not attributable to longer courses of ECT (Table 3). The ANCOVA on total number of ECT treatments yielded an interaction between the pharmacological and ECT assignments ($F_{2,308}=6.07; P=.003$). Patients who received NT and BL ECT were administered the fewest treatments (mean [SD], 6.9 [3.8]) but only differed significantly from patients who received PL and BL ECT (mean [SD], 9.3 [4.0]). There was also a main effect of site ($F_{2,308}=21.70; P<.001$). A substantially greater number of treatments were given at WPIC than at both other sites.

**Completer Sample**

Of the 319 patients in the ITT sample, 66 (20.7%) were considered noncompleters (Figure 1). The log-linear analysis on completer rate yielded only a main effect of site ($\chi^2=7.12; P=.03$). This rate was higher at WPIC (86.6%) than at WF (72.6%), with WU (76.7%) having an intermediate rate. When restricting the sample to completers, the ANCOVA on post-ECT HRSD scores produced a trend for a main effect of pharmacological condition ($F_{2,242}=2.88; P=.06$), significant effects of site ($F_{2,242}=3.64; P=.03$), number of adequate treatment trials ($F_{1,242}=3.91; P<.05$), and baseline HRSD score ($F_{1,242}=13.93; P<.001$). Post hoc comparisons indicated that the final HRSD score was lower in the NT than the PL group, with VEN not differing from either group. Similarly, the other effects mirrored the findings for this variable in the full ITT sample. The log-linear analysis on remission rate produced significant effects of pharmacological condition ($\chi^2=7.77; P=.02$), site ($\chi^2=8.92; P=.01$), number of adequate medication trials ($\chi^2=5.70; P=.02$), and baseline HRSD score ($\chi^2=4.99; P=.03$). Among completers, significant differences in efficacy between the ECT electrode placement conditions were not observed (Table 3). Otherwise, the findings for the 2 primary outcome measures were consonant between the ITT and completer samples.

The choice of 8 treatments as the cutoff to identify noncompleters was based on a judgment of the minimum number of treatments necessary to consider an ECT trial adequate given nonremission. However, the higher this number, the more likely dropout due to lack of efficacy contributes to noncompletion. Therefore, remission rates were contrasted for the randomized treatment conditions using no cutoff (ie, ITT sample that received at least 1 treatment) and requiring 2, 4, 6, or 8 treatments to identify noncompleters. The numerical advantage of NT and VEN relative to PL held across all cutoffs, and for NT ranged from an improvement in remission rate of 12.5% to 17.5% and for VEN from 9.2% to 14.6% (Figure 2). In recontrolling the log-linear analyses, the main effect of pharmacological condition was significant for all cutoffs, except 4 or more treatments, where a trend was obtained ($P=.06$). The numerical advantage for RUL relative to BL ECT in remission rate held across the cutoffs, ranging from 8.5% to 13.2%. This effect was significant in the 1 treatment cutoff (full ITT sample), as was observed at a trend level (all $P \leq .1$) for the 2-, 4-, and 6-treatment thresholds.
Excluding Crossover Treatment

The foregoing analyses examined clinical outcomes following completion of acute-phase ECT treatment and included outcomes for 60 patients after crossover to high-dosage (2.5 × ST) BL ECT. Because an efficacy difference favoring RUL ECT was obtained, it was important to test efficacy when treatment was restricted to the original randomized electrode placement conditions. Of the 164 patients randomized to BL ECT, 29 (17.7%) received crossover treatment. This was true of 31 of the 155 (20.0%) patients randomized to RUL ECT. This rate was somewhat higher in the PL (22.2%) than NT (15.1%) and VEN (17.6%) conditions, but a log-linear analysis indicated that there were no significant differences among the randomized conditions. The ANCOVA on HRSD scores yielded effects of pharmacological condition (F_{1,284} = 4.45; \( P < .01 \)) and baseline HRSD score (F_{1,284} = 22.58; \( P < .001 \)), with a trend for number of adequate trials (F_{1,284} = 3.98; \( P = .06 \)). The outcome was superior with NT relative to PL, with VEN not differing from the other 2 conditions (Table 3). Similarly, the log-linear analysis on remission rate yielded a trend for pharmacological condition (\( \chi^2 = 5.41; \ P = .07 \)), significant effects of number of adequate trials (\( \chi^2 = 4.31; \ P = .04 \)), and baseline HRSD score (\( \chi^2 = 7.20; \ P = .007 \)). The absence of significant effects of electrode placement suggested that the group randomized to RUL ECT benefited particularly from the crossover to high-dose BL ECT. Of 31 RUL patients, 15 (48.4%) were remitters after crossover, while this held for 11 of 29 (37.9%) BL ECT patients.

Adverse Effects

Adverse Events. A single adverse event was experienced by 22 patients, 5 had 2 adverse events, 9 had a serious adverse event, and 2 experienced both an adverse event and a serious adverse event. The most common adverse event was a cardiac complication (n = 13), typically manifesting as sustained tachycardia and/or hypertension after seizure termination, and managed with a beta-blocker medication. The most common serious adverse events were suicide attempt (n = 3), delirium (n = 2), and an intercurrent illness requiring hospitalization (n = 2). Analyses of covariance did not reveal any difference among the randomized treatment conditions in number of adverse events and/or serious adverse events.

UKU Scores. The ANCOVA on average UKU scores during and immediately following the ECT course yielded effects of site (F_{1,271} = 5.24; \( P = .006 \)) and pre-ECT UKU score (F_{1,271} = 130.82; \( P < .001 \)) and a trend for age (F_{1,271} = 3.14; \( P = .08 \)). When the ANCOVA was conducted on the maximal UKU score there were effects of site (F_{1,274} = 13.61; \( P < .001 \)), pre-ECT UKU score (F_{1,274} = 119.92; \( P < .001 \)), and number of ECT treatments (F_{1,274} = 23.89; \( P < .001 \)). A greater number of treatments was associated with a higher maximal score. Paired comparisons demonstrated that, relative to pre-ECT baseline, the average (t_{284} = 21.59; \( P < .001 \)) and maximal (t_{284} = 6.91; \( P < .001 \)) UKU scores decreased significantly. Adding the final HRSD to the foregoing ANCOVAs yielded significant effects for this term (both P ≤ .001). Greater clinical improvement was associated with lower UKU scores. Nonetheless, the differences among the randomized conditions still did not approach significance.

Cognitive Adverse Effects. While post-ECT deficits were observed with all 4 primary measures (Figure 3), the magnitude was substantially greater for the AMI-SF. There was a significant effect of pharmacological condition for 3 of the 4 measures (Table 4), all reflecting a superiority of NT compared with either VEN (MMSE, SRT) or PL (N-Back). The RUL ECT resulted in less severe amnesia than BL ECT on the AMI-SF and SRT. The site effects reflected superior cognitive outcomes compared with bilateral ECT on the Buschke SRT and the Columbia University Autobiographical Memory Interview, Short Form (AMI-SF).

Integrity of the Mask. The \( \chi^2 \) analyses indicated that there was no association between the best guesses of either patients or clinical raters and actual treatment conditions. Thus, the mask was effectively maintained.

Combining ECT with NT resulted in a clinical outcome superior to combining ECT with PL. This was observed in the ITT sample, completor sample, and ITT sample restricted to clinical evaluations prior to crossover. The improvement, due to the concomitant administration of NT, was approximately a 15% increase in remission rate, a clini-
cally important effect. Concomitant administration of VEN also resulted in improved clinical outcomes, though of lesser magnitude.

Neither the concomitant administration of NT or VEN resulted in increased adverse events and/or serious adverse events. However, cognitive adverse effects on all but the measure of retrograde amnesia were reduced by NT and were basically unchanged or worsened by VEN. The cognitive protection afforded by the concomitant administration of a tricyclic antidepressant may have been due to its effects on noradrenergic transmission. Electroconvulsive therapy results in substantial downregulation of the β2-adrenergic receptor, and animal studies have repeatedly shown that enhancement of noradrenergic transmission following ECT ameliorates adverse cognitive effects. Thus, it appears that an agent like NT has the capacity to both improve therapeutic outcome and ameliorate cognitive disturbance. The adrenergic effects of VEN are thought to be triggered at higher dosage levels than were generally achieved during the acute ECT phase. Given this, it might be assumed that the pharmacological actions of VEN resembled a selective serotonin reuptake inhibitor. There are no controlled data on the effect of selective serotonin reuptake inhibitors on ECT outcomes. The pattern observed with VEN suggested enhancement of efficacy, though less robust than NT, and either no effect or a modest deleterious effect on cognitive outcomes.

The findings clearly demonstrated that high-dose RUL ECT is not inferior in clinical outcome to BL ECT given at a moderate dose. Efficacy differences due to electrode placement were observed principally in the ITT sample and not the completer sample. These differences favored RUL ECT and were attributable, in part, to a higher rate of early dropout in patients treated with BL ECT. Despite high dose, RUL ECT retained an advantage over BL ECT in the severity of anterograde and retrograde amnesia following the ECT course.

The major findings have implications for practice and are particularly noteworthy given their consistency across multiple clinically diverse sites and the fact that the mask was effectively maintained. The recommendation that antidepressant medications not be combined with ECT requires reconsideration. The findings with NT indicate that such a combination may have superior therapeutic effects than ECT alone, strongly improving the remission rate. The findings also indicate that high-dose RUL ECT has a superior adverse effect profile, and at least equivalent efficacy to a common form of BL ECT. A limitation was that cognitive and all other outcomes were only examined immediately following the ECT course. Nonetheless, recent naturalistic and randomized controlled studies have demonstrated long-term cognitive effects of ECT that were consistent with the patterns observed immediately following the treatment course. Therefore, this study underscores the superior risk: benefit ratio of RUL relative to BL ECT when RUL ECT is administered at high dosage, and the possibility that combining ECT with a tricyclic antidepressant results in a substantial improvement in remission rate with minimal or beneficial effect on cognitive adverse effects.

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Table 4. Results of Analyses of Covariance on Primary Cognitive Outcome Measures

<table>
<thead>
<tr>
<th>Term</th>
<th>MMSE (n=187)</th>
<th>N-Back d’ (n=134)</th>
<th>Buschke SRT (n=179)</th>
<th>AMI-SF (n=177)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>P Value</td>
<td>F</td>
<td>P Value</td>
</tr>
<tr>
<td>Pharmacological condition</td>
<td>6.57</td>
<td>.002</td>
<td>3.56</td>
<td>.03</td>
</tr>
<tr>
<td>ECT electrode placement</td>
<td>2.05</td>
<td>.15</td>
<td>0.97</td>
<td>.79</td>
</tr>
<tr>
<td>Pharmacological condition × ECT electrode placement</td>
<td>1.20</td>
<td>.30</td>
<td>0.65</td>
<td>.52</td>
</tr>
<tr>
<td>Site</td>
<td>8.93</td>
<td>&lt;.001</td>
<td>6.92</td>
<td>.001</td>
</tr>
<tr>
<td>Age, y</td>
<td>4.53</td>
<td>&lt;.001</td>
<td>4.97</td>
<td>.03</td>
</tr>
<tr>
<td>Treatments, No.</td>
<td>1.80</td>
<td>.18</td>
<td>0.32</td>
<td>.57</td>
</tr>
<tr>
<td>Baseline cognitive score</td>
<td>65.33</td>
<td>&lt;.001</td>
<td>12.90</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: AMI-SF, Columbia University Autobiographical Memory Interview, Short Form; ECT, electroconvulsive therapy; MMSE, Mini-Mental State Examination; SRT, Selective Reminding Test.
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