# Predictors of Remission After Electroconvulsive Therapy in Unipolar Major Depression

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***Context:*** Electroconvulsive therapy (ECT) is the most effective biological treatment for major depression. However, there is little agreement about clinically useful predictors of acute ECT outcomes.

***Objective:*** To assess whether age, sex, burden of comorbid physical illness, age at onset, history of recurrence, episode duration, chronic depression or comorbid dysthymia, melancholic features, episode severity, and medication resistance are predictors of remission after an acute course of ECT.

***Design:*** We performed an analysis using data gathered prospectively in 328 patients with unipolar major depression (according to Research Diagnostic Criteria) treated with ECT. The study was conducted from 1993 through 1999. Patients had a pretreatment score of 21 or higher on the 24-item Hamilton Rating Scale for Depression (HAM-D). Treatment history was assessed using the Antidepressant Treatment History Form. Remission was defined as a 24-item HAM-D score of 10 or less and a 60% or more relative reduction of the HAM-D score.

***Results:*** On univariate logistic regression, statistically significant predictors of nonremission were chronic depression/dysthymia, medication resistance, longer episode duration, and younger age. On backward elimination logistic regression, only medication resistance (OR = 1.67, 95% CI = 1.05 to 2.67) and chronic depression/dysthymia (OR = 1.84, 95% CI = 1.06 to 3.21) were statistically significant predictors of nonremission.

***Conclusions:*** In patients with major depression, lower rates of remission after acute ECT are associated with medication resistance and chronicity, but not with age or burden of physical illness.

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Beginning in the 1950s, various clinical and demographic characteristics were proposed as predictors of positive response to electroconvulsive therapy (ECT), e.g., "melancholic"[1–4] or "endogenous features," catatonia, somatic delusions, or delusions of guilt.[5] None of these predictors, except for catatonia, were confirmed by later trials.[6–9] As Hamilton[10] pointed out, the study of outcome predictors had added little beyond identifying patients with severe major depression.

Changes in classification and patient population may explain why findings from early studies may not apply to patients receiving treatment during the past 2 decades.[11] Using data gathered prospectively in 328 patients with unipolar major depression treated with ECT, we performed an analysis to broadly examine potential predictors of remission after a course of ECT, including age, sex, burden of comorbid physical illness, age at onset, recurrence, episode duration, chronic depression or comorbid dysthymia, melancholic features, episode severity, and medication resistance. Before the study was initiated, we had hypothesized that participants who had received an adequate antidepressant trial during the index episode prior to ECT would be less likely to respond than those who had not.

## METHOD

The data were obtained in a study whose methods have been described previously.[12–14]

### Participant Recruitment and Eligibility

The study was conducted for 7 years (1993–1999) at 4 sites: the Carrier Foundation (Belle Meade, N.J.), a pri-

vate psychiatric hospital; the university-based psychiatric facilities of the University of Iowa (Iowa City, Iowa); the University of Pittsburgh (Western Psychiatric Institute and Clinic, Pittsburgh, Pa.); and Columbia University (New York State Psychiatric Institute [NYSPI], New York, N.Y.).

Participants were recruited from all patients referred for ECT at the 4 study sites if they (1) met the Research Diagnostic Criteria[58] for major depressive disorder based on the Schedule for Affective Disorders and Schizophrenia (SADS)[59] and (2) had a pretreatment score of 21 or higher on the 24-item Hamilton Rating Scale for Depression (HAM-D).[60] Patients were excluded if they had a history of bipolar disorder, schizophrenia, schizoaffective disorder, other non–mood disorder psychosis, or substance abuse within the past year; had received ECT within the past 6 months; or had a severe medical illness that markedly increased the risks of ECT (e.g., unstable or severe cardiovascular conditions, aneurysm or vascular malformation susceptible to rupture, severe chronic obstructive pulmonary disease). Other exclusion criteria were neurologic illness (other than associated with antipsychotic drug exposure or peripheral neurologic disease), a diagnosis or signs of organic brain syndrome (DSM-III-R), and pregnancy. Written informed consent was obtained prior to the initiation of the study for all participants, following local institutional review board procedures.

### Pre-ECT Assessment and Evaluation of Prior Medication Trials

In addition to the SADS and HAM-D, the assessment included the administration of the Mini-Mental State Examination[61] and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G).[62] Depression was classified as "chronic" if full criteria for a major depressive episode had been met continuously for at least the past 2 years. Treatment history during the index episode was assessed using the Antidepressant Treatment History Form (ATHF).[15,16] Participants with depression without psychotic features with an ATHF score of 3 or more on any medication trial were defined as medication-resistant. In nonpsychotic patients, a score of 3 on the ATHF corresponds to a 4-week trial of an antidepressant medication at an adequate dose (for instance, a tricyclic at 200–299 mg of imipramine equivalent/day, fluoxetine or paroxetine at 20–39 mg/day, bupropion at 300–449 mg/day, or venlafaxine at 150–299 mg/day). In psychotic patients, a score of 3 requires an antidepressant rated as 3 combined with an antipsychotic medication for at least 3 weeks at ≥ 400 mg chlorpromazine equivalent/day.

### Administration of Electroconvulsive Therapy

Psychotropic medications, other than lorazepam, were tapered. At NYSPI, participants were randomly assigned to right unilateral ECT (d'Elia electrode placement) or bilateral ECT (bifrontotemporal placement). At the other 3 sites, clinical judgment determined electrode placement. At all sites, participants who did not show substantial improvement with right unilateral ECT within 5 to 8 treatments were switched to bilateral ECT. ECT was given 2 or 3 times per week with a custom-modified brief-pulse, constant-current MECTA SR1 device (MECTA Corp., Lake Oswego, Ore.) that had double the maximal charge output of commercial devices in the United States. Empirical titration was used to quantify seizure threshold (ST) during the first unilateral or bilateral treatment. For both unilateral and bilateral treatments, subsequent stimulus intensity was set at 150% above threshold (2.5 × ST). ECT course was continued until a participant's HAM-D score was 10 or below, he or she reached a clinical plateau observed over at least 1 week, or he or she decided to discontinue ECT.

### Post-ECT Evaluation and Criteria for Response and Remission

Participants were assessed twice, 1 to 2 days and 4 to 8 days after completion of ECT. For this analysis, remission was defined as a 24-item HAM-D score of 10 or less and a 60% or more relative reduction of the HAM-D score at both post-ECT evaluations.

### Participant Flow

To be included in this outcome analysis, participants had to receive at least 5 treatments (or end ECT earlier due to response) and complete the post-ECT assessment; this analysis includes 328 participants. Forty participants were recruited and treated at NYSPI. In addition, a total of 349 patients at the other 3 sites consented to participate in the study and underwent baseline assessment; 61 of these participants did not contribute to these outcome data because 17 were dropped before initiation of ECT due to diagnostic exclusions, 14 could not be withdrawn from psychotropic medications, 12 terminated ECT against medical advice prior to the fifth treatment, 9 developed an intercurrent illness so ECT was not initiated (N = 2) or was interrupted (N = 7) (all before the fifth treatment), 6 withdrew consent before ECT, 1 had a HAM-D score below 21 before starting ECT, and data were not available for 2. After these exclusions, the number of participants at the 3 sites was as follows: Carrier Foundation, 64 participants; Western Psychiatric Institute and Clinic, 202 participants; and University of Iowa, 22 participants.

### Statistical Methods

First, univariate logistic regression was used to identify variables associated with nonremission. Then, backward elimination logistic regression was used to identify unique predictors of nonremission. Clinical characteristics and outcomes were compared among patients with and with-

**Table 1. Demographic and Clinical Characteristics of Participants (N = 328)**

| Characteristic | Mean/% | SD | Median | Min | Max |
|---|---|---|---|---|---|
| Age, mean, y | 57.4 | 18.3 | 56.8 | 19.7 | 93.2 |
| Female, % | 68.0 | ... | ... | ... | ... |
| CIRS-G, mean, total score | 6.4 | 4.6 | 6 | 0 | 20 |
| Duration of current episode, mean, wk | 59.7 | 79.2 | 30.0 | 2 | 480 |
| Age at onset, mean, y | 39.8 | 18.7 | 37.0 | 4 | 85 |
| Recurrent depression, % | 77.1 | ... | ... | ... | ... |
| No. previous episodes, mean | 2.4 | 2.3 | 2 | 0 | 10 |
| Chronic depression/dysthymia, % | 22.6 | ... | ... | ... | ... |
| Severe depression, % | 87.2 | ... | ... | ... | ... |
| Melancholic features, % | 81.7 | ... | ... | ... | ... |
| Psychotic features, % | 28.4 | ... | ... | ... | ... |
| Medication-resistant, % | 54.3 | ... | ... | ... | ... |
| HAM-D pre-ECT, mean, score | 34.5 | 7.8 | 34.5 | 20.5 | 56 |
| HAM-D post-ECT, mean, score | 11.8 | 9.1 | 9 | 0 | 46 |
| No. ECT treatments, mean | 11.2 | 4.7 | 10 | 5 | 32 |

Abbreviations: CIRS-G = Cumulative Illness Rating Scale for Geriatrics, ECT = electroconvulsive therapy, HAM-D = Hamilton Rating Scale for Depression, Min = minimum, Max = maximum.
Symbol: ... = not applicable.

**Table 2. Predictors of Nonremission After Acute Electroconvulsive Therapy**

| Characteristic | Remitters (N = 183) | Nonremitters (N = 145) | Odds Ratio | 95% CI | p Value |
|---|---|---|---|---|---|
| Univariate logistic regression[a] | | | | | |
| Age, mean (SD), y | 59.8 (17.2) | 54.5 (19.3) | 0.98 | 0.97 to 1.00 | .01 |
| Duration of episode, mean (SD), wk[b] | 49.3 (63.1) | 72.9 (94.4) | 1.23 | 1.02 to 1.47 | .03 |
| CIRS-G, mean (SD), total score[c] | 6.4 (4.4) | 6.4 (4.9) | 0.96 | 0.78 to 1.19 | .73 |
| Female, % (N) | 68.3 (125) | 67.6 (98) | 0.97 | 0.61 to 1.54 | .89 |
| Recurrent depression, % (N) | 76.0 (139) | 78.6 (114) | 1.16 | 0.69 to 1.96 | .57 |
| Melancholic features, % (N) | 84.2 (154) | 78.6 (114) | 0.69 | 0.40 to 1.21 | .20 |
| Chronic depression/dysthymia, % (N) | 16.4 (30) | 30.3 (44) | 2.22 | 1.31 to 3.77 | .003 |
| Medication-resistant, % (N) | 47.0 (86) | 63.5 (92) | 1.96 | 1.25 to 3.06 | .003 |
| Severe depression, % (N) | 84.7 (155) | 90.3 (131) | 1.69 | 0.85 to 3.34 | .13 |
| Psychotic features, % (N) | 30.6 (56) | 25.5 (37) | 0.77 | 0.48 to 1.27 | .31 |
| Backward elimination logistic regression | | | | | |
| Chronic depression/dysthymia, % (N) | 16.4 (30) | 30.3 (44) | 1.84 | 1.06 to 3.21 | .03 |
| Medication-resistant, % (N) | 47.0 (86) | 63.5 (92) | 1.67 | 1.05 to 2.67 | .03 |

[a]All means and standard deviations reported in their original units.
[b]Log transformation used in the analyses.
[c]Square root transformation used in the analyses.
Abbreviation: CIRS-G = Cumulative Illness Rating Scale for Geriatrics.

out medication resistance and psychotic features using analyses of variance for continuous measures and $\chi^2$ tests for categorical measures.

## RESULTS

Table 1 presents the characteristics of the 328 participants who contributed to this analysis. Most participants were women who suffered from severe recurrent depression with melancholia. Psychotic features were observed in 93 (28.4%) of the participants. The median duration of current episode was 30 weeks; the course was chronic (i.e., chronic depression or dysthymia) in 22.6% of participants; 54.3% of participants were classified as medication-resistant.

After receiving a mean (SD) of 11.2 (4.7) ECT treatments, 183 participants (55.8%) were classified as remitters, 140 were treated with unilateral ECT only and received a mean (SD) of 8.3 (2.4) treatments, and 188 were treated with a mean (SD) of 13.3 (4.8) unilateral and bilateral (N = 146) or bilateral treatments only (N = 42). Remission was achieved by 97 participants (69.3%) treated with unilateral ECT only and 86 participants (45.7%) treated with unilateral and bilateral or bilateral treatments only.

The univariate logistic regression analyses identified 4 statistically significant predictors of nonremission: younger age (OR = 0.98; p = .01), longer episode duration (OR = 1.23; p = .03), chronic depression/dysthymia (OR = 2.22; p = .003), and medication resistance (OR = 1.96; p = .003). Sex, burden of comorbid physical illness (CIRS-G score), recurrence, melancholic features, and episode severity were not significant predictors (Table 2). Study site was not a significant predictor either.

On backward elimination logistic regression, only chronic depression/dysthymia (OR = 1.84, 95% CI = 1.06

**Table 3. Characteristics and Outcomes of Participants With and Without Psychotic Features and Medication Resistance**

| Characteristic | Medication-Resistant Nonpsychotic (N = 173) | Inadequate Treatment Nonpsychotic (N = 62) | Psychotic Features (N = 93) | p Value |
|---|---|---|---|---|
| Age, mean (SD), y | 51.8 (17.9) | 66.9 (14.5) | 61.5 (17.9) | < .0001 |
| Duration of episode, mean (SD), wk | 80.6 (89.6) | 33.6 (51.2) | 38.2 (61.8) | < .0001 |
| Median | 51 | 17.5 | 20 | |
| CIRS-G, mean (SD), total score | 5.5 (4.3) | 7.9 (4.6) | 7.1 (4.9) | .0015 |
| Age at onset, mean (SD), y | 34.3 (16.3) | 47.2 (19.6) | 45.4 (19.1) | < .0001 |
| Male, % (N) | 30.1 (52) | 32.3 (20) | 35.5 (33) | .66 |
| Recurrent depression, % (N) | 77.5 (134) | 79.0 (49) | 75.3 (70) | .85 |
| Melancholic features, % (N) | 74.6 (129) | 88.7 (55) | 90.3 (84) | .002 |
| Chronic depression/dysthymia, % (N) | 35.3 (61) | 8.1 (5) | 8.6 (8) | < .0001 |
| Severe depression, % (N) | 87.9 (152) | 67.7 (42) | 98.9 (92) | < .0001 |
| Met remission criteria, % (N) | 48.6 (84) | 69.4 (43) | 60.2 (56) | .01 |

Abbreviation: CIRS-G = Cumulative Illness Rating Scale for Geriatrics.

to 3.21, p = .03) and medication resistance (OR = 1.67, 95% CI = 1.05 to 2.67, p = .03) were statistically significant predictors of nonremission (Table 2).

Table 3 compares the characteristics and outcomes of participants with and without psychotic features and medication resistance. In this comparison, participants with psychotic depression were treated as a single group since only 4 of them had an ATHF score of 3 or more.[17] Among the nonpsychotic medication-resistant completers, 84 (48.6%) met remission criteria, compared to 43 (69.4%) of the inadequately treated nonpsychotic completers, and 56 (60.2%) of the psychotic completers ($\chi^2 = 9.02$, df = 2, p = .01).

## DISCUSSION

The main finding of this study is that medication resistance and chronicity are associated with relatively lower rates of remission shortly following an acute course of ECT. These results persist after backward elimination logistic regression and do not seem to be confounded by age, presence of psychosis, or episode severity.

The large number of participants, operationalized definition of medication resistance, and prospective administration of ECT add confidence in the findings. Limitations of this study include retrospective assessment of medication resistance and the lack of control group, which would allow a comparison of ECT to alternative treatments for chronic or medication-resistant depression. In particular, our data cannot address whether the predictors of nonresponse to ECT are similar to, or different from, predictors of nonresponse to antidepressant medications. It is also difficult to compare our results with published findings because there is no consensus in the literature on this topic.[18,19] For example, recent studies disagree on whether higher medical comorbidity is associated with lower[20,21] or the same[22] rate of response to antidepressant medications. Some studies found that psychotic features are associated with a low rate of response to antidepressant monotherapy,[23] while several other studies did not.[24] Similarly, some studies have linked chronic and double depression with lower response rates,[25,26] but others found no such association.[27–29]

Additionally, the use of unilateral ECT exceeding seizure threshold by only 150% probably underestimated the absolute effectiveness of ECT.[30,51] To address this limitation, we performed a sensitivity analysis excluding the patients who had only unilateral ECT. Outcome predictors were the same on univariate logistic regression. In this smaller sample, backward elimination logistic regression identified only medication resistance as an independent predictor of nonresponse. Of note, in another published comparison of right unilateral ECT, with stimulus intensity 50%, 150%, or 500% above the seizure threshold, or bilateral ECT 150% above threshold, medication resistance was also a predictor of nonremission independent of treatment condition.[51]

Finally, when assessing predictors of treatment outcome in depression, one faces the inevitable methodological challenge of separating chronic depression from personality disorders, in particular borderline personality disorder. There is a significant overlap in diagnostic criteria for major depression and borderline personality disorder. In another analysis[31] performed on a subset (N = 139) of this sample, we found that participants with borderline personality disorder had lower remission rates, while participants with other personality disorders responded as well to ECT as those with no personality disorder. Notwithstanding these potential limitations, the results of the study deserve comment.

### Medication Resistance and ECT Outcomes

Since the decline in the use of ECT following the introduction of antidepressants, medication resistance has been the leading indication for the use of ECT. Various groups have examined the relationship between medica-

Table 4. Published Studies on the Relationship Between ECT Outcome and Medication Resistance in Major Depression

| Study | N | Group and Manner in Which ECT Outcome Is Determined | Assessment of Response or Remission After ECT | Assessment and Definition of Medication Resistance | Acute ECT Response/Remission Rate(s) |
|---|---|---|---|---|---|
| Avery and Lubrano, 1979,[45] reanalysis of the DeCarolis et al 1964 trial | 190 | Prospective assessment in patients who failed imipramine | Clinical impression | Failed imipramine 200–350 mg/d for 25 d (including 109 patients with "delusional depression") | Medication-resistant: 72% |
| Thiery, 1965[46] | 250 | Prospective crossover of imipramine, phenelzine, placebo, and ECT | Clinical impression and custom rating scale | Failed imipramine 100–200 mg/d or phenelzine 30–60 mg/d for 4 wk | Medication-resistant: 50%<br>Nonresistant[a]: 71% |
| Mandel et al, 1977[47] | 100 | Retrospective assessment in patients who failed or did not tolerate medications | Clinical impression 3 to 6 mo after ECT | Not operationalized | Medication-resistant or -intolerant: 71% |
| Paul et al, 1981[48] | 8 | Retrospective assessment in 8 patients with an adequate medication trial | Bunney-Hamburg multi-item rating scale | Failed 150 mg of imipramine equivalent for 3 wk | Medication-resistant: 100% |
| Prudic et al, 1990[49] | 53 | Prospective assessment in patients with and without adequate medication trial | HAM-D score ≤ 9 | ATHF score of 3 or more | Medication-resistant: 50%<br>Nonresistant: 86% |
| Lam et al, 1999[50] | 174 | Retrospective assessment in patients with and without adequate medication trial | CGI rating based on chart review | Custom scale based on chart review | Resistance to antidepressants not related to outcome (no rate reported) |
| Sackeim et al, 2000[51] | 80 | Prospective assessment in patients with and without adequate medication trial | HAM-D score ≤ 10 | ATHF score of 3 or more | Medication-resistant: 37%<br>Nonresistant: 65% (difference present regardless of dosage and electrode placement[b]) |
| Pluijms et al, 2002[52] | 41 | Retrospective assessment of patients with and without adequate medication trial | HAM-D score ≤ 7 or reduction in HAM-D score ≥ 50% | ATHF score of 3 or more | Medication-resistant: 28%<br>Nonresistant: 50% |
| van den Broek et al, 2004[53] | 85 | Prospective assessment in patients with and without adequate medication trial | HAM-D score ≤ 7 | ATHF score of 3 or more | Medication-resistant: 44%<br>Nonresistant: 41% |
| This study | 328 | Prospective assessment in patients with and without adequate medication trial | HAM-D score ≤ 10 and reduction in HAM-D score ≥ 60% | ATHF score of 3 or more | Medication-resistant: 49%<br>Nonresistant: 69%<br>Psychotic depression: 60% |

[a]Nonresistance defined as placebo failure with unspecified prior treatment history.
[b]Right unilateral, with electrical dosages 50%, 150%, or 500% above the seizure threshold, or bilateral, with an electrical dosage 150% above the threshold.
Abbreviations: ATHF = Antidepressant Treatment History Form, CGI = Clinical Global Impressions scale, ECT = electroconvulsive therapy, HAM-D = Hamilton Rating Scale for Depression.

tion resistance and outcomes of ECT.[32] The most significant studies are summarized in Table 4.

Of the 4 contemporary prospective trials, 3 U.S. studies including this one[49,51] found medication resistance to be associated with nonremission; 1 recent study from the Netherlands[53] using a similar definition of medication resistance and outcome measures did not find medication resistance to be a predictor of poorer outcome. The diverging findings may be due to differences in the antidepressant medications that patients had failed prior to ECT in the different studies. On the basis of a preliminary analysis of the first 100 nonpsychotic participants included in the current analysis, we have reported that resistance to tricyclics or bupropion was predictive of a lower remission rate with ECT but resistance to selective serotonin reuptake inhibitors was not.[12]

## Chronicity of Depression and Response to ECT

In agreement with earlier studies[49,54–57] (Table 5), we found that chronicity of depression (i.e., depression with a duration longer than 2 years) independently predicted a lower remission rate.

Chronicity as a binary variable displaced continuous episode duration in backward elimination logistic regression. Even though chronicity and episode duration are significantly correlated ($r = 0.46$, $p < .0001$, $N = 328$), the size of the correlation is such that colinearity between these 2 variables is not problematic and, looking at the backward stepwise model, it appears that chronicity is indeed a better predictor of outcome than episode duration. Other studies have indeed suggested that there is a duration threshold after which poorer outcomes occur.[54–57]

This finding raises the question of whether patients who develop treatment-resistant chronic depression have an illness that is treatment-resistant from the onset or whether changes associated with treatment resistance accumulate gradually over the long course of the illness. Indeed, chronic depression has been associated with volume loss in the frontal cortex and hippocampus[33–35] and an underlying reduction in the number and size of neuronal and glial cells.[36–38]

**Table 5. Published Studies on the Relationship Between ECT Outcome and Chronicity/Duration of Major Depression**

| Study | Design | N | Assessment of Response | Relevant Findings |
|---|---|---|---|---|
| Kukopulos et al, 1977[54] | Retrospective chart review | 136 | Clinical impression | Participants with mean episode duration of 3 to 4 mo more likely to respond than those with mean duration of 7 to 8 mo |
| Dunn and Quinlan, 1978[55] | Retrospective chart review | 24 | Clinical impression | Nonresponders more likely to have episode duration longer than 1 y |
| Magni et al, 1988[56] | Retrospective chart review | 30 | Clinical impression | Nonresponders more likely to have episode duration longer than 6 mo |
| Kindler et al, 1991[57] | Retrospective chart review | 52 | HAM-D | Nonresponders had longer episode duration than responders; 0% response among 9 patients with episode duration longer than 18 mo |
| Prudic et al, 1990[49] | Prospective ECT trial in patients with and without adequate pretreatment | 53 | HAM-D | Duration of episode not a predictor of response |
| This study | Prospective ECT trial in patients with and without adequate pretreatment | 328 | HAM-D | Patients with chronic depression or dysthymia less likely to remit than patients without them; duration of episode not an independent predictor of remission |

Abbreviations: ECT = electroconvulsive therapy, HAM-D = Hamilton Rating Scale for Depression.

One potential clinical implication of the association between depression chronicity and poor ECT outcome may be when an ECT trial should be considered. Many patients suffer from depression for many months before they seek treatment.[39–41] In addition, current guidelines typically recommend the use of ECT as fourth- or fifth-line treatment for major depression.[42,43] Thus, most patients are treated with ECT after they have been depressed for extended periods of time. This is unfortunate given higher response rates with ECT than with pharmacotherapy[44] and the finding that chronic depression is associated with a lower remission rate. These findings suggest that the practice of reserving ECT as a "treatment of last resort" may decrease the chance of recovery in some patients who could potentially have responded if they had been treated with ECT earlier.

*Drug names:* bupropion (Wellbutrin and others), chlorpromazine (Thorazine, Sonazine, and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), lorazepam (Ativan and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), venlafaxine (Effexor).

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