Nortriptyline for Treatment-Resistant Depression

Andrew A. Nierenberg, M.D.; George I. Papakostas, M.D.;
Timothy Petersen, Ph.D.; Karen E. Kelly, B.A.; Brian M. Iacoviello, B.A.;
John J. Worthington, M.D.; Joyce Tedlow, M.D.;
Jonathan E. Alpert, M.D., Ph.D.; and Maurizio Fava, M.D.

Background: Up to 30% of patients with major depression fail to respond to an antidepressant trial, with most taking a selective serotonin reuptake inhibitor (SSRI) as initial treatment. While the tricyclic antidepressants might be effective for SSRI nonresponders, they have been relegated to third- and fourth-line treatment. This study assesses the efficacy of nortriptyline for patients with treatment-resistant major depression.

Method: 92 patients with treatment-resistant DSM-III-R major depression, with resistance defined by at least 1, but no more than 5, well-documented adequate trials of antidepressants during the current episode, were treated openly with nortriptyline for 6 weeks. Patients were titrated up to full target doses of nortriptyline within 1 week, with target blood levels of 100 ng/mL. Response was defined as a 50% or greater decrease of baseline 17-item Hamilton Rating Scale for Depression score. We performed an intent-to-treat analysis with the last observation carried forward.

Results: Approximately 40% of patients were responders (N = 39) and 12% were remitters (N = 11) after 6 weeks of nortriptyline. Over a third of patients were unable to complete the trial.

Conclusion: Nortriptyline was effective for over a third of patients with treatment-resistant depression, and nortriptyline should be considered as potential treatment if patients fail to respond to other antidepressants.

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Corresponding author and reprints: Andrew A. Nierenberg, M.D., Massachusetts General Hospital, 15 Parkman St., WAC 812, Boston, MA 02114 (e-mail: anierenberg@partners.org).

Treatment-resistant depression is a difficult clinical problem with minimal comparative data to guide optimal management.[1] Up to a third of patients with major depression have their first antidepressant fail; treatment-resistant depression accounts for 10% to 30% of depressive episodes, and 15% to 30% of all psychiatric outpatients present with this problem.[2–4] Furthermore, treatment-resistant depression episodes represent 50% of the annual costs associated with the treatment of depression, and 21% of patients who seek treatment for depression fail to recover in up to 2 years, with 12% failing to recover after 5 years.[5–7] With an estimated 5% lifetime prevalence of major depression and a conservative estimate of a nonresponse rate of 15%, nearly 2 million Americans could suffer from treatment-resistant depression at some point in their lives.[8]

Most patients with treatment-resistant depression have experienced limited relief with the newer generation of antidepressants, and few are treated with tricyclic antidepressants (TCAs). Yet, TCAs have been found as effective as selective serotonin reuptake inhibitors (SSRIs) in the overall treatment of unipolar depression. Some evidence suggests that the TCAs may be more effective than SSRIs in the treatment of severe or melancholic subtypes.[9–13] Clinicians prescribe SSRIs more frequently than TCAs because of the more favorable side effect and toxicity profile of the SSRIs, but secondary amine TCAs (e.g., desipramine, nortriptyline) may be tolerated just as well as the SSRIs.[14]

Given the challenge treatment-resistant depression poses to modern clinicians, all treatment options should be considered, including TCAs, but few clinicians consider TCAs among their top choices. A survey of over 600 clinicians who attended an annual psychopharmacology review course at Massachusetts General Hospital (Boston, Mass.) found that only 10% chose to switch to a TCA in a hypothetical case of a patient who had not fully responded to an SSRI.[15] The goal of this study was to assess the efficacy of TCAs in the management of treatment-refractory depression. Our hypothesis was that the proportion of patients that would respond to an open trial of nortriptyline would be greater than the estimated 10% placebo response rate in clinical trials of treatment-resistant depression.[16]

METHOD

Subjects were recruited through an outpatient clinical trial to assess the efficacy of lithium augmentation compared with placebo augmentation for those subjects who fail a prospective trial of nortriptyline at the Depression Clinical and Research Program (DCRP) at Massachusetts General Hospital. This report is on the open phase of the study. A total of 92 outpatients were entered from 1992–1999, with inclusion criteria as follows: men and women aged 18 to 70 years with major depression as diagnosed using the Structured Clinical Interview for DSM-III-R (SCID-P)[17] and a score on the 17-item Hamilton Rating Scale for Depression (HAM-D-17)[18] equal to or greater than 18. Treatment resistance was defined as at least 1, but no more than 5, failed adequate trials during the current episode. We defined treatment resistance using the Harvard Antidepressant Treatment History form (HATH),[19] which gives specific criteria for the adequate dose and adequate length of a trial for it to be considered a failure. An adequate trial is defined as having an adequate dose (which varies from medication to medication and for some medications is determined by blood levels) for a length of time of at least 6 weeks. Exclusion criteria for this trial were a history of organic mental or seizure disorder, serious or unstable medical illness, active substance abuse or dependence disorders within the past 12 months, acute suicidal risk (as assessed through clinical interview and by the HAM-D-17), pregnancy, lactation, bipolar I or II disorder, psychotic disorders, history of adverse reaction or allergy to study medications, concomitant use of psychotropic medications, and clinical or laboratory evidence of thyroid abnormalities. Participants in this study signed Institutional Review Board–approved informed consent immediately prior to the initial study visit.

After providing informed consent, eligible subjects were started on a regimen of open-label nortriptyline, 25 mg, the first day that was increased by 25 mg per day until an initial dose of 100 mg unless they had to stop the dose increase because of the lack of tolerability. Subjects continued taking their dose of nortriptyline for 6 weeks, after which time they were reassessed by a clinician for depressive symptoms. Blood levels of nortriptyline were obtained at weeks 2 and 6; dose adjustments were made after the second week if blood levels were < 100 ng/mL. Those responding to nortriptyline were followed for up to 3 years at the DCRP. Study visits occurred at initial screening, baseline, and then weekly for 6 weeks. The HAM-D-31, the Clinical Global Impressions-Severity of Illness scale (CGI-S),[20] and the CGI-Improvement scale (CGI-I)[20] were completed at each study visit and administered by experienced psychiatrists and psychologists. The primary outcome measure was the change in HAM-D-17 total score between baseline and week 6. We performed an intent-to-treat analysis (ITT), with the last observation carried forward (LOCF) (N = 92). For this analysis, the last available HAM-D-17 data point was carried forward for those patients who discontinued the study. Response was defined as greater than or equal to a 50% reduction in total HAM-D-17 score (last visit – baseline visit). Remission was defined as a HAM-D-17 score less than or equal to 7 during the last visit.

Standard errors for proportions, as well as power calculations to compare the percentage of responders with the estimated placebo response of 10%, were calculated with *Power and Precision*.[21]

RESULTS

The mean ± SD age for all patients was 41.1 ± 11.7 years, and the gender distribution was 50% female. The mean age at onset of depression was 22.4 years, the mean duration of the current episode was 96.2 months, and the mean ± SD HAM-D-17 score at baseline was 21.3 ± 3.9. The mean nortriptyline dose and blood level at week 6 were 121.2 mg and 101.0 ng/mL, respectively. There was no statistically significant difference in the mean blood nortriptyline levels between responders and nonresponders at week 6. For all patients, the mean ± SD number of failed trials at initial screening was 2.3 ± 1.5. No significant differences were found in mean number of failed trials when comparing responders and nonresponders ($p = .36$). For the entire group, 31 patients had failed 1 medication; 18, 2 medications; 15, 3 medications; 16, 4 medications; and 12, 5 medications. Table 1 presents frequencies of different antidepressants failed by patients during their current major depressive episode.

Responders were slightly older than nonresponders (44.0 ± 12.4 years vs. 39.1 ± 10.8 years, $p = .049$), but this difference did not reach statistical significance with Bonferroni correction. No other substantial statistically significant differences were found in demographic characteristics between responders and nonresponders. No statistically significant differences were found for any clinical variables. Responders had an older age at onset of depression compared with nonresponders and lower rates of comorbid Axis I and Axis II disorders, but these differences did not reach statistical significance.

Figure 1 presents mean HAM-D-17 total score by study visit, comparing responders and nonresponders. We found that 39/92 (42.4% ± SE 5%; 95% confidence interval [CI] = 32% to 52%; power = 1.00 to reject null hypothesis that the population proportion = 0.10) patients responded to the 6-week trial of nortriptyline. For responders, there was a statistically significant decrease in HAM-D-17 total score at each study visit compared with baseline ($p < .0001$). Furthermore, responders were found to have a significantly greater reduction in both CGI-S and CGI-I scores than nonresponders at each visit (CGI-S: $p < .0001$, CGI-I: $p < .0001$; Table 2). The overall proportion of

Table 1. Frequency of Treatments Failed in the Current Depressive Episode by Patients With Treatment-Resistant Depression

Treatment(s)	% Received
SSRI	95.7
Bupropion	28.3
Tricyclic	28.3
Venlafaxine	28.3
Lithium augmentation	20.7
SSRI combination	20.7
MAOI	17.4
Trazodone	17.4
Nefazodone	16.3
Mirtazapine	15.2
ECT	2.2
Thyroid augmentation	0.0

Abbreviations: ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor.

Figure 1. Mean 17-Item Hamilton Rating Scale for Depression (HAM-D) Total Score by Visit

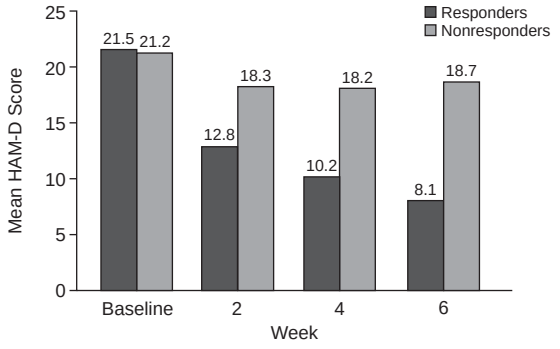

Table 2. CGI-S and CGI-I Scores in Responders and Nonresponders to Nortriptyline Treatment

	Baseline		Week 2		Week 4		Week 6		Percent Change From Baseline to Week 6	
Group	CGI-S	CGI-I	CGI-S	CGI-I	CGI-S	CGI-I	CGI-S	CGI-I	CGI-S	CGI-I
Responders (N = 39)	4.3	4.0	3.2	2.8	2.5	2.4	2.6	2.5	–39.5	–37.5
Nonresponders (N = 53)	4.5	4.0	4.2	3.7	4.0	3.6	4.3	3.9	–4.4	–2.5

Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale.

remitters was 11/92 (11.9% ± SE 3%; 95% CI = 7% to 20%). Ten of the remitters completed the trial, while 1 patient dropped out after week 4. In addition, there was no statistically significant difference between the number of nonresponders and responders who had previously failed a trial of bupropion or venlafaxine, 2 antidepressants that possess significant norepinephrine-reuptake blockade activity similar to that of nortriptyline (p = .6003). Finally, 32/92 (34.7%) discontinued the study prematurely.

DISCUSSION

For this group of patients with retrospectively assessed treatment resistance, about 40% responded to nortriptyline and about 12% remitted. The discontinuation rate of 34% was similar to rates reported for TCAs in large meta-analyses (31%–33.4%).[14,22,23] No major differences in terms of demographic and clinical characteristics were found between responders and nonresponders.

Few studies focus on switching strategies for patients with treatment-resistant major depression, and even fewer specifically focus on the use of tricyclic agents. Furthermore, studies use a wide variety of definitions of treatment resistance, making it difficult to generalize conclusions from one study to the next. To make generalizability even more complicated, available studies differ in their design, ranging from retrospective, to open, to direct comparisons and crossover models. A crossover study by McGrath et al.[24] found that 26% of patients that failed phenelzine responded to imipramine. As for SSRI nonresponders, Kocsis et al.[25] report that 47% of patients who failed to respond to sertraline subsequently responded to a trial of imipramine, but these patients were not reported to have nonresponse to other antidepressants before the trial of sertraline.

Other studies have shown the usefulness of switching from one class to another, including from TCAs to MAOIs,[16,24,20–28] from SSRIs or TCAs to SSRIs,[29–32] and from several different classes of antidepressants to venlafaxine,[33,34] bupropion,[35–38] or mirtazapine.[39]

A study comparing electroconvulsive therapy (ECT) versus paroxetine in patients who had failed at least 2 adequate trials of antidepressants reports a response rate of 28% for the paroxetine-treated group,[40] while Poirier and Boyer[33] report a 32.7% response rate for paroxetine in patients who had failed at least 2 antidepressants. A study by Nierenberg et al.[41] uses strict criteria for defining treatment-resistant depression, selecting patients who have failed 3 antidepressant trials and an attempt at augmentation, allowing for ECT to be counted as 1 of the trials. The response rate for an open trial of venlafaxine in this group was 33%. One can probably attribute much of the difference in response rates reported for venlafaxine and nortriptyline to the more narrow criteria for treatment-resistant depression in the venlafaxine study.

Limitations

One weakness of this study was the absence of placebo. Without the use of placebo, it can be difficult to separate true response from placebo response or sponta-

neous remission. Given the chronic and resistant nature of this sample, it is reasonable to assume that the placebo response rate would be much lower, perhaps as low as 10% according to some authors.[16] In this context, a response rate of 40% is clinically important. Nevertheless, placebo-controlled trials would be necessary to further explore the potential of tricyclic and other antidepressants in patients who suffer from treatment-refractory depression. In the absence of commercial support, such studies are unlikely.

Another limitation of the study concerns the duration of treatment, which was only 6 weeks. This is probably likely to account for the somewhat lower-than-expected rate of remission compared with the rate of response. Rates of remission tend to increase with the duration of the trial, as a significant proportion of patients may require more than 6 weeks to become remitters after an initial response. Our assessment of treatment resistance was retrospective, which is prone to recall bias. However, to minimize the degree of recall bias in our retrospective assessment of treatment resistance, we systematically defined treatment resistance using the HATH,[19] a method that uses specific criteria for adequate doses and length of an antidepressant trial. Retrospective treatment history to define treatment-resistant depression has been widely used in other studies.[42]

Strengths

The strengths of this study are that 62/92 patients (67.4%) failed a minimum of 2 adequate antidepressant trials before treatment with nortriptyline; this was not a study of nortriptyline for patients who failed just 1 antidepressant. Since the open trial of nortriptyline was designed to generate nonresponders for the second phase of the study (the placebo-controlled trial of lithium augmentation), if any bias were present, it would be toward the direction of minimizing response to nortriptyline to generate more subjects. Thus, the finding that over 40% responded was greater than anticipated and should be interpreted as a reasonable estimate of the value of nortriptyline for treatment-resistant depression. This study had a power of 100% to reject the null hypothesis that the estimated placebo response rate was 10%.

CONCLUSION

Over 40% of patients with treatment-resistant depression responded to nortriptyline. At the very least, nortriptyline should be considered as a treatment option after another antidepressant fails. More definitive evidence about the role of nortriptyline for patients who are not helped by multiple treatments will be forthcoming from the National Institute of Mental Health (NIMH) Sequential Treatment Alternatives to Relieve Depression study (STAR*D: http://www.edc.gsph.pitt.edu/stard).

Drug names: bupropion (Wellbutrin and others), desipramine (Norpramin and others), imipramine (Tofranil and others), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

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