Antidepressant Treatment of Melancholia in Older Adults

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Objective: *This is the first prospective trial in an outpatient sample comparing the effect of nortriptyline with sertraline in the treatment of depression with and without melancholia. We hypothesized that patients with melancholia would respond better to nortriptyline than sertraline, whereas among patients without melancholia, nortriptyline and sertraline would have equal efficacy.* **Methods:** *We conducted a randomized 12-week trial comparing sertraline with nortriptyline in the treatment of patients with nonpsychotic, unipolar major depression stratified by the presence of melancholia. One hundred ten unipolar depressed patients with and without melancholia comprised our intent-to-treat sample. Seventy-two were nonmelancholic depressed and randomly assigned to treatment with sertraline (N = 40) or nortriptyline (N = 32). Thirty-eight were melancholic depressed and randomly assigned to treatment with sertraline (N = 18) or nortriptyline (N = 20).* **Results:** *The test of the interaction of medication group and melancholia status on response was not statistically significant. Among patients with melancholia, response rates were 47% to sertraline and 75% to nortriptyline, whereas among patients without melancholia, response rates were 51% to sertraline and 42% to nortriptyline. The odds of response for patients with melancholia treated with nortriptyline compared with sertraline was 3.46. The odds of response for patients without melancholia treated with sertraline compared with nortriptyline was 0.69. Similar findings were obtained in the remission and continuous outcome analyses.* **Conclusion:** *This study did not find a significant difference between sertraline and nortriptyline in the treatment of depressed older adults with melancholia.* (Am J Geriatr Psychiatry 2014; 22:46–52)

Key Words: Randomized clinical trials, antidepressants, melancholia, nortriptyline, sertraline

INTRODUCTION

Some major depressive subtypes predict differential treatment response to antidepressant medication. Specifically, patients with delusional depression respond poorly to monotherapy with a tricyclic antidepressant (TCA)[1–4] but respond to combination antidepressant–antipsychotic treatment or

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electroconvulsive therapy.[3,5,6] In patients with the atypical subtype, a series of randomized controlled trials compared a monoamine oxidase inhibitor (phenelzine) with a TCA (imipramine) and placebo[7,8] and consistently reported superior efficacy for the monoamine oxidase inhibitor compared with both placebo and the TCA. Vascular depression may be a subtype of late-life depression[9–11] that, especially in the presence of executive dysfunction, may have a lower rate of response to antidepressant medication.[12–15]

A number of studies have shown that patients with melancholic depression show a favorable response to TCAs.[16,17] Evidence suggests that selective serotonin reuptake inhibitors (SSRIs) are less effective than TCAs in the treatment of older adults with melancholic depression.[18,19] Two prospective studies by the Danish University Antidepressant Group compared an SSRI with clomipramine in the treatment of adult inpatients with melancholic depression. The first study[20] found that 60% of the clomipramine group responded (Hamilton Rating Scale for Depression [HRSD] score < 7) compared with 30% of the citalopram group. In the second study,[21] 58% of the clomipramine group responded after 6 weeks compared with 25% of the paroxetine group. Roose et al.[22] compared the efficacy of fluoxetine in elderly inpatients with unipolar major depressive disorder and cardiac disease with that of nortriptyline in an historic comparison group and found an intent-to-treat response rate of 67% among nortriptyline-treated patients with melancholia compared with 23% of fluoxetine-treated patients with melancholia. Navarro et al.[23] found similar results in a mixed sample of elderly inpatients and outpatients. However, not all studies show that TCAs are superior to SSRIs in the treatment of older adult patients with melancholic depression. For example, Mulsant et al.[24] compared 12 weeks of treatment with nortriptyline and paroxetine in 116 elderly inpatients and outpatients with depression and found no differences in the efficacy of the two drugs among patients with melancholia.

Although the findings from inpatients and mixed samples are suggestive, the hypothesis that TCAs are superior to SSRIs in the treatment of older adult outpatients with melancholia has yet to be tested in a prospective study. Results of a 6-week clinical trial comparing nortriptyline with fluoxetine in the treatment of adult outpatients with melancholia provide some support for this hypothesis, but this study was a reanalysis of existing data.[18] In this study, we report results from the first prospective, randomized, controlled trial comparing the efficacy of an SSRI (sertraline) to a TCA (nortriptyline) in older adult outpatients. We expected medication condition to interact with diagnostic subtype (melancholic versus nonmelancholic) in determining antidepressant response. In particular, we hypothesized that in patients with melancholia, the efficacy of nortriptyline would be superior to that of sertraline, whereas among patients without melancholia, nortriptyline and sertraline would have equal efficacy.

METHODS

This study was a double-blind, randomized, 12-week clinical trial comparing nortriptyline with sertraline in depressed patients aged 45 years and older stratified by the presence of the melancholia subtype. Patients were recruited between August 1997 and July 2004 by radio and newspaper advertisements and/or through referral from other physicians. At the initial visit, a comprehensive psychiatric evaluation, including a Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV); 24-item HRSD; a Mini-Mental Status Examination (MMSE); Newcastle I scale for the assessment of melancholia; and a medical history, were performed. If the patient met inclusion criteria and signed an informed consent, a physical examination, electrocardiogram, complete blood count, chemistries, electrolytes, and thyroid panel were performed.

Inclusion criteria were as follows: (1) age 45 years and older; (2) major depressive disorder, single or recurrent, nonpsychotic, by DSM-IV criteria; (3) HRSD at least 16 at the initial visit and at the end of 1 week of placebo; and (4) willing and able to give informed consent. Exclusion criteria were as follows: (1) current or history of obsessive-compulsive disorder, psychotic disorder, or substance dependence (other than nicotine) within the past year by DSM-IV criteria; (2) judged to be a current suicide risk or serious suicide attempt within the past year; (3) status post–myocardial infarction, coronary artery bypass, or angioplasty with a positive history of angina or a positive stress test; (4) QRS interval greater than 0.12 seconds or Qtc interval at least 46 msec; (5) treatment with Coumadin, heparin, or Type 1 antiarrhythmic medications; (6) diagnosis of narrow-angle glaucoma;

(7) MMSE score no more than 24; (8) stroke, epilepsy, or Parkinson disease; (9) acute, severe, or unstable medical condition; (10) positive urine toxicology screen for drugs of abuse, including amphetamine, barbiturates, cocaine, marijuana, methadone, methaqualone, opioids, and phenylcyclohexyl piperidine; and (11) treatment in the current episode of depression with either nortriptyline with a plasma level between 50 and 150 ng/mL, desipramine or imipramine with a plasma level of 250 ng/mL or greater for at least 4 weeks, or paroxetine 40 mg, fluoxetine 40 mg, or sertraline 200 mg for at least 4 weeks.

Patients who met inclusion and exclusion criteria and signed an informed consent were given 1 week of single-blind placebo. If patients still met inclusion and exclusion criteria at the end of the placebo week and did not reduce their HRSD score by 25% or more, they were randomized. The assessments performed at the end of the placebo week and every visit thereafter included the HRSD, the Montgomery-Åsberg Depression Rating Scale, the Beck Depression Inventory, and the Clinical Global Impression of severity and improvement. The Hamilton Anxiety Rating Scale was performed at baseline and at the end of weeks 2, 4, and 8 of treatment; the Medical Outcomes Study 36-Item Short-Form Health Survey and the 30-item MMSE were performed at baseline and at the end of week 12 or upon early termination. Stratification of the sample was based on diagnosis of melancholia by DSM-IV criteria (questions resolved by case conference). Randomization was done using permuted blocks of 10.

Participants randomized to sertraline received 50 mg for 1 week and then 100 mg for the next 4 weeks. If the patient did not meet criteria for remission (HRSD < 10) by week 5, the dose was increased to 150 mg. If the patient did not show evidence of response by week 9, the dose was increased to 200 mg. The nortriptyline dose was calculated at 1 mg/kg; one-third of that dose was given days 1 through 3, two-thirds on days 3 through 6, and the full dose of medication was given on day 7. A plasma level was drawn 7 days later, and the dose of nortriptyline was adjusted so the plasma level was within 80−120 ng/mL. To preserve the blind, blood was drawn for all patients regardless of medication group.

After random assignment, patients returned weekly. At each visit the patient met with the treating physician to review progress and side effects and with raters and research assistants for structured ratings and blood pressure measurements. Patients also completed necessary self-report measures. The study was approved by the institutional review board at the New York State Psychiatric Institute.

Statistical Analyses

The intent-to-treat group for the efficacy analyses was defined as the patients who completed the placebo lead-in, started randomized treatment, and had at least one subsequent assessment of clinical status. Descriptive statistics were calculated to characterize the sample in each of the four treatment cells (subjects with melancholia randomized to sertraline or nortriptyline, subjects without melancholia randomized to sertraline or nortriptyline). Independent sample t tests and χ^2 tests of independence were used to examine baseline differences between treatment groups on demographic variables and dropout status stratified by the presence of melancholia.

To test the primary hypothesis (differential treatment response as a function of treatment condition and depressive subtype), we conducted two sets of analyses. First, we conducted logistic regression analyses using SAS PROC LOGISTIC (SAS Institute Inc., Cary, NC) on both response (50% reduction in HRSD from baseline) and remission (HRSD < 10 at week 12). Second, we conducted a mixed effects model using SAS PROC MIXED (SAS Institute Inc., Cary, NC) to test for differences in change (serial HRSD scores) over time (12 weeks) by treatment group (dummy coded as sertraline $= 1$ and nortriptyline $= 0$). We started by establishing a baseline (unconditional) model for the total sample that included an intercept and the linear and quadratic effects of time as both fixed and random effects. Although the quadratic effect of time was statistically significant, it was not included in the final baseline (unconditional) model because it was small and unimportant. Therefore, the final baseline (unconditional) model included only the intercept and the linear effect of time as both fixed and random effects. We coded the intercept such that it reflected the average HRSD score at week 12 for the reference group (nortriptyline condition).[25] The unstandardized regression coefficient corresponds to the difference between the groups at endpoint. All statistical tests were evaluated at the 5% level.

Both sets of analyses used PROC MI and MIANALYZE in SAS (SAS Institute Inc., Cary, NC) to perform multiple imputation, a simulation

technique that replaces each missing datum with a set of $m > 1$ plausible values.[26] In our case, we chose $m = 5$, which generates five imputed data sets and is sufficient to obtain excellent results in most applications.[27] The m complete data sets are analyzed using standard statistical analyses. The results from the analyses from the m complete data sets are combined using Rubin's rules[26,27] to generate valid statistical inferences that reflect uncertainty due to missing values and, therefore, improve both the accuracy and often the statistical power of results.

RESULTS

One hundred nineteen participants were screened and signed consent to participate in the study (Fig. 1). One hundred seventeen participants met inclusion and exclusion criteria and entered a 1-week single-blind placebo lead-in (2 patients were excluded before randomization because of medical reasons). One hundred ten patients continued to meet inclusion and exclusion criteria at the end of the 1-week placebo lead-in and comprised our intent-to-treat sample. Of these 110 patients, 72 were non-melancholic depressed and were randomly assigned to treatment with sertraline (N = 40) or nortriptyline (n = 32). The remaining 38 were melancholic depressed and were randomly assigned to treatment with sertraline (N = 18) or nortriptyline (N = 20).

FIGURE 1. Flowchart of a randomized 12-week medication trial comparing sertraline with nortriptyline in the treatment of patients aged 45 years and older with unipolar depression stratified by the presence of the melancholia subtype.

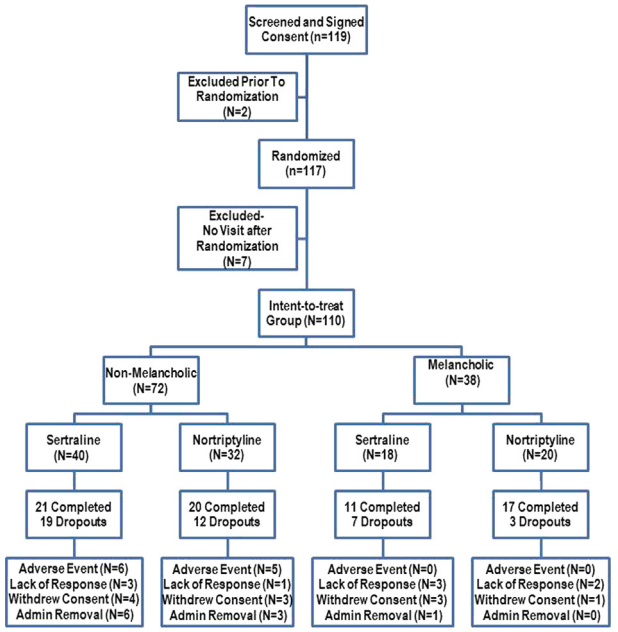


Table 1 provides descriptive statistics for sertraline and nortriptyline groups stratified by the presence of melancholia. There were no statistically significant associations or differences between patients with melancholia randomized to sertraline or nortriptyline or between patients without melancholia randomized to sertraline or nortriptyline with regard to age, gender, race, education, marital status, Cumulative Illness Rating Scale—Geriatrics, or baseline HRSD.

Dropout Rates

In the total sample, 10 patients with melancholia (26%) and 31 patients without melancholia (43%) dropped out before week 12, χ^2 (1) = 2.98, p = 0.08. In the melancholic group, seven sertraline-treated (31%) and three nortriptyline-treated (15%) patients dropped out before week 12, χ^2 (1) = 2.79, p = 0.10. In the nonmelancholic group, 19 sertraline-treated (48%) and 12 nortriptyline-treated (28%) patients dropped out before week 12, χ^2 (1) = 0.73, p = 0.39.

Hypothesis Testing

Responder analyses. The test of the interaction of medication group and melancholia status on response was not statistically significant at the 5% level (Table 2). As can be seen in Table 2, among patients with melancholia, response rates were 47% to sertraline and 75% to nortriptyline, whereas among patients without melancholia, response rates were 51% to sertraline and 42% to nortriptyline. The odds of response for patients with melancholia treated with nortriptyline compared with sertraline was 3.46 (95% confidence interval [CI]: 0.73—16.44; Cohen's d = 0.69), whereas the odds of response for patients without melancholia treated with sertraline compared with nortriptyline was 0.69.

Remitter analyses. The test for the interaction of medication group and melancholia status was not statistically significant at the 5% level (Table 2). As can be seen from Table 2, among patients with melancholia, remission rates were 41% to sertraline and 66% to nortriptyline, whereas among patients

TABLE 1. Descriptive Statistics for Sertraline and Nortriptyline Groups Stratified by the Presence of Melancholia

	Melancholics (N = 38)			Nonmelancholics (N = 72)		
	Nortriptyline (N = 20)	Sertraline (N = 18)	Test (Within Melancholics)	Nortriptyline (N = 32)	Sertraline (N = 40)	Test (Within Nonmelancholics)
Gender (% women)	50	61	χ^2 (1) = 0.47, p = 0.49	63	58	χ^2 (1) = 0.19, p = 0.67
Age, yr	60.75 (8.19)	66.39 (10.69)	t(36) = 1.84, p = 0.074	64.81 (8.25)	65.50 (8.76)	t(70) = 0.34, p = 0.74
Race (%)			χ^2 (4) = 5.13, p = 0.27			χ^2 (4) = 4.051, p = 0.40
White	75	77		75	82.05	
Black	5	5		12.50	5.13	
Hispanic	5	16		9.38	10.26	
Asian	10	0		0	2.56	
Other	5	0		3.13	0	
Education	16.29 (2.23)	14.71 (3.44)	t(32) = 1.60, p = 0.12	15.21 (3.44)	15.50 (2.57)	t(62) = 0.38, p = 0.70
Marital status (%)			χ^2 (4) = 1.42, p = 0.84			χ^2 (4) = 6.032, p = 0.20
Never married	5	5.88		21.88	32.50	
Separated	10	5.88		9.38	0	
Widowed	20	35.29		9.38	12.50	
Married	30	29.41		28.13	30	
Divorced	35	23.53		31.25	25	
CIRS-G	2.75 (2.049)	2.94 (1.95)	t(36) = 0.30, p = 0.77	3.00 (2.40)	3.93 (2.41)	t(70) = 1.62, p = 0.11
HRSD-24 baseline	27.10 (4.41)	27.28 (6.65)	t(36) = 0.10, p = 0.92	23.25 (6.73)	22.78 (3.55)	t(70)= 0.38, p = 0.70

Notes: CIRS-G: Cumulative Illness Rating Scale—Geriatrics; HRSD: Hamilton Rating Scale for Depression.

without melancholia, remission rates were 46% to sertraline and 37% to nortriptyline. The odds of remission for patients with melancholia treated with nortriptyline compared with sertraline was 2.80 (95% CI: 0.70−11.13; Cohen's d = 0.58), whereas the odds of remission for patients without melancholia treated with sertraline compared with nortriptyline was 0.69.

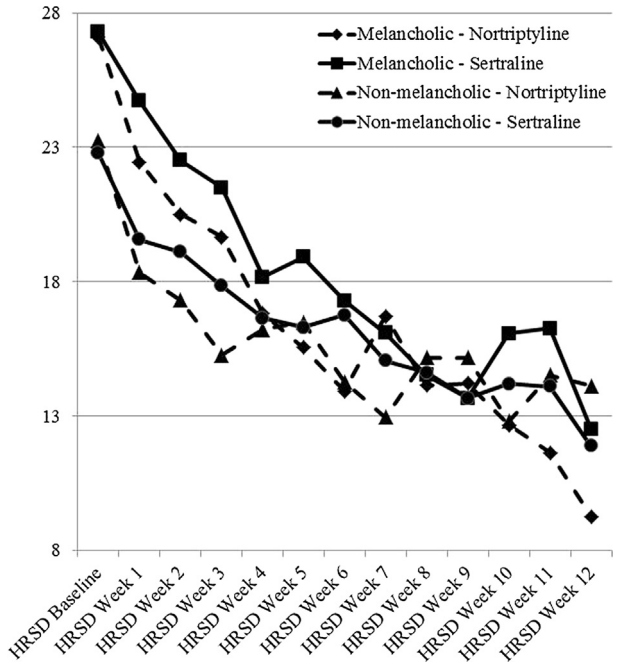
Continuous outcome analyses. Change in HRSD scores over time is graphically depicted in Figure 2, and the results of the continuous outcome analyses

TABLE 2. Parameter Estimates from Logistic and Mixed Effects Regression Models Comparing Serial Change in HRSD Scores, Response, and Remission Rates Among Patients Randomized to Treatment with Nortriptyline or Sertraline

	Estimate	Standard Error	Wald (df)	p	95% CI[a]	Odds Ratio[b]
			Logistic regression: response			
Intercept	1.11	0.56				
Sertraline	−1.24	0.79	−1.58 (99.6)	0.12	−2.80, 0.32	3.46
Melancholia	−1.43	0.68	−2.09 (179.1)	0.04	−2.79, −0.08	
Sertraline × melancholia	1.61	0.94	1.72 (136.3)	0.09	−0.24, 3.46	
			Logistic regression: remission			
Intercept	0.67	0.52				
Sertraline	−1.03	0.71	−1.46 (555.5)	0.15	−2.41, 0.36	2.80
Melancholia	−1.21	0.63	−1.92 (510.4)	0.06	−2.44, 0.03	
Sertraline × melancholia	1.41	0.84	1.67 (4,558.7)	0.10	−0.25, 3.06	
			Mixed effects			
Intercept	9.96	1.70				
Time	−1.00	0.17	−5.94 (416.2)	0.001	−1.33, −0.67	
Sertraline	2.89	2.46	1.18 (961.2)	0.24	−1.93, 7.72	
Melancholia	2.29	2.25	1.01 (201.3)	0.31	−2.16, 6.73	
Time × sertraline	0.19	0.25	0.76 (294.1)	0.45	−0.30, 0.67	
Time × melancholia	0.57	0.23	2.49 (106.6)	0.01	0.12, 1.02	
Sertraline × melancholia	−2.81	3.12	−0.90 (353.5)	0.37	−8.94, 3.32	
Time × sertraline × melancholia	−0.31	0.33	−0.93 (60.2)	0.35	−0.98, 0.36	

Notes: HRSD: Hamilton Rating Scale for Depression.
[a]The 95% confidence interval (CI) is for the given point estimate.
[b]The odds ratio refers to the exponentiation of the given point estimate.

FIGURE 2. Change in HRSD scores over the 12-week trial for patients with and without melancholia by treatment condition.



are reported in Table 2. HRSD scores decreased significantly over time, but this change did not depend on the interaction of medication group and melancholia status. At endpoint, nortriptyline-treated patients with melancholia had an HRSD score of 9.96, whereas sertraline-treated patients with melancholia had an HRSD score of 12.85. This difference was not statistically significant and corresponded to a small to medium effect size (Cohen's d = 0.37). Among patients without melancholia, there was a 0.09 point difference in endpoint HRSD scores between the treatment groups; nortriptyline-treated patients had an endpoint HRSD score of 12.25, whereas sertraline-treated patients had an endpoint score of 12.34.

DISCUSSION

This is the first prospective trial in an outpatient older adult sample comparing the effect of TCAs (nortriptyline) to SSRIs (sertraline) in the treatment of major depression with and without melancholia. We hypothesized that patients with melancholic depression would respond better to nortriptyline compared with sertraline, whereas among patients without melancholia, nortriptyline and sertraline would have equal efficacy. Contrary to our hypothesis, the test of the interaction between medication group and melancholia status on response was not statistically significant.

We did not observe a significant interaction despite previous research suggesting that melancholia may be associated with a superior response to TCAs relative to SSRIs. There are several possible reasons why this study produced a negative finding. The first possibility is that our results reflect accurate estimates of the population, and patients with melancholia do not preferentially respond to TCAs.

A second possible explanation for the negative finding is that this study was underpowered. Supporting this possibility are the large odds ratios associated with the dichotomous outcome analyses. If the dichotomous outcome analyses had been statistically significant, it might have reflected an artifact from dichotomizing a continuous variable. Indeed, the dichotomous outcome analyses revealed medium to large effect sizes between nortriptyline- and sertraline-treated patients with melancholia, whereas the continuous outcome analysis revealed a small to medium effect size (see Fig. 2). One reason for this discrepancy is that the endpoint mean of the nortriptyline group fell slightly below the HRSD cut point of 10 (HRSD week 12 = 9.27) used to define remission, whereas the endpoint mean of the sertraline group fell slightly above the HRSD cut point of 10 (HRSD week 12 = 12.52). This highlights the importance of conducting analyses using both continuous and dichotomous outcomes because relying exclusively on dichotomous outcomes or dichotomizing continuous outcomes can produce misleading results.[28] Indeed, it is well known that dichotomizing continuous outcome data can produce misleading results by magnifying a small mean difference in clinical data.[29]

A third possibility is that depression severity, and not melancholia status, is associated with differences in treatment response to SSRIs and TCAs. Indeed, patients with melancholia (HRSD = 27.18) were significantly more depressed at baseline than patients without melancholia (HRSD = 22.99). However, looking at remission rates to sertraline and nortriptyline among patients with melancholia above and below the median HRSD score (HRSD = 26) reveals that the difference in remission rates between treatment

conditions is in fact larger among less severely depressed patients with melancholia than more severely depressed patients. Among patients with melancholia that have a baseline HRSD less than 26, remission rates were 44% to sertraline (4 of 9) and 78% to nortriptyline (7 of 9), whereas among patients with a baseline HRSD at least 26, remission rates were 22% to sertraline (2 of 9) and 45% to nortriptyline (5 of 11).

The findings from this study should be interpreted in the context of several limitations. First, the size of the melancholia subsample was small. Nevertheless, the rate of melancholia in our study is not significantly different from that of similar studies.[19] Second, the sample was primarily white, and the results may therefore not be generalizable to other ethnic groups. Third, data were missing, as is typically the case in clinical trials, and we accommodated for missing data using multiple imputation; this is a superior method compared with traditional approaches using mean substitution or complete case analysis.

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