

A Double-Blind Randomized Comparison of Nortriptyline and Paroxetine in the Treatment of Late-Life Depression: 6-Week Outcome

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Background: Some studies have suggested that selective serotonin reuptake inhibitors may be less efficacious than tricyclic antidepressants in the treatment of severe depression in older patients. The objective of this study was to compare the 6-week outcome of treatment with nortriptyline and paroxetine in older patients with a major depressive episode. **Method:** A double-blind randomized comparison of nortriptyline and paroxetine was conducted in 80 elderly (mean \pm SD age = 75.0 \pm 7.4 years) psychiatric inpatients and outpatients who presented with a major depressive episode. Dropout and response rates were compared in patients who began or completed treatment. Rates of response of inpatients and patients with melancholic depression were also compared. **Results:** Over 6 weeks, there were no significant differences in dropout rates due to side effects (nortriptyline, 14% vs. paroxetine, 19%) or for any reason (27% vs. 33%). Similarly, there were no significant differences between the rates of favorable response to nortriptyline or paroxetine (intent-to-treat analysis, 57% vs. 44%; completer analysis, 78% vs. 66%). Analyses restricted to inpatients or to patients with melancholic depression yielded similar results. **Conclusion:** Nortriptyline and paroxetine appear to have similar efficacy and tolerability in the acute (6-week) treatment of older depressed patients, including hospitalized patients and those with melancholic features. (*J Clin Psychiatry* 1999;60[suppl 20]:16–20)

Over the past decade, selective serotonin reuptake inhibitors (SSRIs) have replaced tricyclic antidepressants (TCAs) as first-line antidepressants, both in primary care and psychiatric practices.¹ This shift in prescribing patterns has been attributed to the ease of use of SSRIs (e.g., absence of need to monitor by administering electrocardiograms or measuring plasma levels) and their more benign side effect profile.^{2–4} Concerns have been raised

about a possible efficacy gap between SSRIs and TCAs, particularly for older patients with more severe depression. However, in a recent extensive review of 20 randomized trials comparing the acute efficacy of TCAs and SSRIs in more than 1500 older depressed outpatients, Schneider concluded that they have similar efficacy, but that SSRIs may be better tolerated, given that the dropout rates for SSRIs are one third to one half lower than the dropout rates found with TCAs.⁵ Nonetheless, he commented that this conclusion was questionable, especially in light of results from an open-label nonrandomized study comparing nortriptyline and fluoxetine that found a much lower rate of acute response to fluoxetine (10% vs. 83% for nortriptyline) in older inpatients with melancholic depression.⁶ In another review of studies that have compared TCAs and SSRIs, Nierenberg emphasized the need for additional head-to-head trials, particularly in difficult-to-study depressed inpatients.⁷

To determine whether older depressed patients tolerate and respond similarly to the TCA nortriptyline and the SSRI paroxetine, we analyzed the dropout and response rates after 6 weeks of treatment in an ongoing randomized controlled trial that compared the cognitive effects of both drugs under double-blind conditions.^{8,9}

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METHOD

This study was conducted in the 2 geriatric inpatient units and the outpatient late-life depression clinic of Western Psychiatric Institute and Clinic, Pittsburgh, Pa. All patients received a comprehensive evaluation that included a psychiatric history and mental status examination, a social and medical history, a physical examination, and laboratory tests.^{10,11} Study participants were also evaluated with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV)¹² and several rating scales, including a semistructured version of the 17-item Hamilton Rating Scale for Depression (HAM-D),¹¹ the Cumulative Illness Rating Scale adapted for Geriatrics (CIRS-G),¹³ the UKU side effect rating scale (UKU),¹⁴ and a standardized version of Folstein's Mini-Mental State Examination (MMSE).¹⁵ All information available was reviewed at a consensus conference attended by at least 3 faculty psychiatrists and the research staff.^{10,11} During this conference, Axis I diagnoses were established according to the criteria of the DSM-IV,¹⁶ and the age at onset of the primary psychiatric disorder was determined. During the study period, intraclass correlation coefficients measuring interrater reliability ranged from 0.91 to 0.94 for the HAM-D.

For inclusion in the analyses, patients had to meet the following criteria: age of 60 years or older, DSM-IV major depressive episode without psychotic features or history of bipolar or schizoaffective disorder, baseline HAM-D score of 15 or above, MMSE score of 18 or above, no history of alcohol or other substance abuse or dependency during at least the past year, and no specific medical condition contraindicating treatment with either nortriptyline or paroxetine (e.g., QRS longer than 120 ms or bradycardia with heart rate below 50 beats per minute). Since a depressive disorder can cause significant cognitive impairment in older persons, it is often not possible to reliably distinguish patients with a depressive disorder and reversible cognitive impairment from patients with a primary dementia and a comorbid depression.¹⁷⁻¹⁹ Thus, depressed patients with a presumptive diagnosis of dementia were included as long as their MMSE score was 18 or above. After complete description of the study, all subjects (or their legal representatives) provided written informed consent.

Between January 1995 and October 1997, nearly 1600 inpatients and outpatients were screened for participation, 682 were clinically evaluated, 108 met the inclusion criteria and were invited to participate, 81 signed informed consent, and 80 were randomly assigned to and received at least 1 dose of study medication. These 80 patients constitute the intent-to-treat study group. Subjects were randomly assigned under double-blind conditions to treatment with either nortriptyline or paroxetine after a wash-out of all psychotropic medications except for lorazepam, which was allowed throughout the study. The randomization algorithm included stratification according to inpa-

tient versus outpatient status and cognitive status (baseline MMSE score 24 and below vs. 25 and above). Study medications were initiated, titrated, and adjusted as follows: in inpatients, initial doses were nortriptyline, 50 mg in the evening, or paroxetine, 20 mg in the morning. In outpatients, the initial doses were nortriptyline, 25 mg in the evening, and paroxetine, 10 mg in the morning. Nortriptyline doses were adjusted weekly as needed to maintain plasma drug levels between 50 and 150 ng/mL. Paroxetine doses were increased to 20 mg after 1 week in outpatients and to 30 mg after 5 weeks in all patients who still had a HAM-D score of 15 or above or who had experienced a decrease in HAM-D score of less than 50%. Patients complaining of severe anxiety and/or insomnia were prescribed lorazepam on a regular basis (e.g., twice a day or at bedtime); the lowest possible doses were used and, as much as clinically possible, doses were kept constant. Side effects were managed clinically to minimize dropouts. For instance, patients complaining of constipation were prescribed stool softeners or laxatives,²⁰ and patients complaining of severe dry mouth or urinary difficulties were prescribed bethanechol.²¹ Also, in the presence of significant side effects, titration was modified and medication doses were adjusted as needed by a nonblinded monitor.

Patients were reassessed weekly with the rating scales listed above. For the analyses presented here, dropout rates and final HAM-D scores constituted the primary outcome variables. Patients who did not receive their assigned medication for at least 4 weeks were considered dropouts. Reasons for discontinuation were classified prior to breaking the blind according to established rules and are reported descriptively. Dropout rates attributed to side effects or to any reason (i.e., total dropout rates) were compared using chi-square tests or exact probabilities as appropriate. Patients who received their assigned medication for 4 weeks or more were considered completers and included in the analysis, with data from the last observation carried forward (LOCF). Demographic and clinical variables of the patients assigned randomly to nortriptyline or to paroxetine were compared at baseline for all subjects and for completers using 2-tailed chi-square tests, exact probabilities, or t tests, as appropriate. Outcomes of the 2 treatment groups were similarly compared. In addition, categorical rates of response were calculated and compared using chi-square tests both for all included subjects (intent-to-treat analysis) and for completers. For this analysis, patients with a final (LOCF) HAM-D score of 10 or below were classified as responders.

RESULTS

The study group consisted of 43 inpatients (54%) and 37 outpatients (46%), 59 women (74%) and 21 men (26%), 68 (85%) of whom were white and the rest African American (N = 11) or Asian (N = 1). The mean \pm SD age was

Table 1. Demographics, Clinical Characteristics, and Treatment (intent-to-treat group)^a

Variable	Nortriptyline (N = 37)	Paroxetine (N = 43)	Statistic (t or χ^2)	df	p Value
Age, y	76.6 ± 7.9	73.5 ± 6.6	1.90	78	.06
Sex (% women)	68	79	1.36	1	.24
Race (% white)	86	84	0.12	1	.73
Inpatient (%)	54	53	0.00	1	.96
Age at onset, y (lifetime)	62.4 ± 19.4	54.0 ± 16.7	1.96	70	.06
Recurrent (%)	49	58	0.61	1	.44
Melancholic (%)	57	58	0.00	1	.95
Median duration, wk	25	27	0.61+	76	.54
HAM-D score	22.6 ± 3.7	22.3 ± 4.3	0.41	78	.67
MMSE score	27.2 ± 3.1	26.9 ± 3.1	0.37	76	.71
CIRS-G score	9.6 ± 4.0	9.7 ± 4.4	0.07	72	.94
No. of concomitant medications	7.8 ± 10.9	8.0 ± 12.7	0.09	78	.93
Use of lorazepam (%)	49	54	0.19	1	.67
Final dosage, mg/d	51.4 ± 21.4	23.0 ± 7.4	NA	NA	NA
Final plasma level, ng/mL	100.1 ± 77.9	100.3 ± 115.2	NA	NA	NA

^aAll values are mean ± SD unless indicated otherwise. Symbol: + = statistic performed on natural log transformation. Abbreviations: CIRS-G = Cumulative Illness Rating Scale-Geriatrics, HAM-D = Hamilton Rating Scale for Depression, MMSE = Mini-Mental State Examination, NA = not applicable.

Table 2. Treatment Outcomes Among Completers^a

Score	Nortriptyline (N = 27)	Paroxetine (N = 29)	t	df	p Value
Baseline HAM-D	22.4 ± 3.9	20.9 ± 3.7	1.50	54	.14
Final HAM-D	8.8 ± 3.0	9.6 ± 4.6	0.77	54	.44
HAM-D relative decrease (%)	59.5 ± 15.7	55.4 ± 17.0	0.94	54	.35
Baseline total UKU	10.3 ± 5.6	9.5 ± 5.3	0.53	50	.60
Final total UKU	6.5 ± 2.5	6.1 ± 2.5	0.56	54	.58

^aAll values are mean ± SD. Abbreviation: UKU = UKU Side Effects Scale.

Table 3. Categorical Responders (final HAM-D score of 10 or below)

Medication Group	All Patients			Inpatients			Melancholic Patients		
	N	%	p Value	N	%	p Value	N	%	p Value
Intent-to-treat analysis									
Nortriptyline	21/37	57	0.26 ^a	12/20	60	0.23 ^c	13/21	62	0.25 ^c
Paroxetine	19/43	44		9/23	39		10/23	43	
Completer analysis									
Nortriptyline	21/27	78	0.31 ^b	12/13	92	0.17 ^c	13/16	81	0.68 ^c
Paroxetine	19/29	66		9/14	64		10/14	71	

^a $\chi^2 = 1.26$, df = 1.

^b $\chi^2 = 1.03$, df = 1.

^cFisher exact test.

75.0 ± 7.4 years, and the mean age at onset of depression was 48.0 ± 23.0 years. Forty-four (55%) patients met DSM-IV criteria for the presence of melancholic features. Seventy-three subjects (91%) received a consensus diagnosis of a major depressive disorder, single (N = 39) or recurrent (N = 34). The 7 other patients received consensus diagnoses of dementia (Alzheimer's type) with a major depressive episode (N = 5), mood disorder due to a general medical condition (N = 1), or alcohol-induced mood disorder (N = 1). The median length of episode prior to enrollment in the trial was 26 weeks (range, 3 to 1300 weeks). At baseline, the 2 treatment groups were comparable for

all variables except for a trend for the patients treated with nortriptyline to be older than those treated with paroxetine (Table 1).

Both medications were similarly well tolerated, with 5 (14%) patients assigned to nortriptyline and 8 (19%) patients assigned to paroxetine discontinuing their medication due to various side effects attributed to treatment prior to breaking the blind. Side effects for nortriptyline included atrial fibrillation (N = 2), cardiac conduction delays (N = 1), seizure (N = 1), and dizziness (N = 1); for paroxetine, they included nausea/diarrhea (N = 2), urinary retention (N = 2), sexual dysfunction (N = 1), syndrome of inappropriate antidiuretic hormone secretion (SIADH) (N = 1), orthostasis (N = 1), and parkinsonism (N = 1). In addition, 5 other patients discontinued nortriptyline due to an unrelated medical problem (N = 1), withdrawal of consent (N = 3), or inability to arrange transportation (N = 1). Similarly, 6 patients discontinued paroxetine due to noncompliance with research procedures (N = 2), withdrawal of consent (N = 3), or inability to arrange transportation (N = 1). There were no significant differences between the 2 medication groups in the rates of discontinuation due to side effects (5/37 for nortriptyline vs. 8/43 for paroxetine; $\chi^2 = 0.38$, df = 1, p = .54) or due to any reason (10/37 vs. 14/43, respectively; $\chi^2 = 0.29$, df = 1, p = .59). When outcome among completers treated with nortriptyline or paroxetine was compared, there was no difference in final UKU (side effects) total scores (Table 2) or on any UKU subscale scores except for the final autonomic side effects subscores, which were higher for nortriptyline than for paroxetine (3.7 ± 1.2 vs. 2.7 ± 2.0; t = 2.30, df = 54, p = .03).

There were no statistical differences between the 2 medication groups in either the relative decrease in HAM-D or the final HAM-D score (see Table 2). Similarly, a categorical analysis of response (Table 3) showed a slightly higher rate of response to nortriptyline than to paroxetine, but the difference did not reach statistical significance (intent-to-treat analysis: 57% vs. 44%, respectively; $\chi^2 = 1.26$, df = 1, p = .26; completer analysis: 78% vs. 66%, respectively; $\chi^2 = 1.03$, df = 1, p = .31). Similar results were obtained when outcomes were compared in

the 43 subjects who had been enrolled on inpatient units or the 44 subjects who met criteria for a major depressive episode with melancholic features (see Table 3). In these subgroups of older, more physically frail, and more severely depressed patients, the differences between the rates of response to nortriptyline and paroxetine were larger than in the entire group (in particular in the intent-to-treat analysis). However, these differences failed to reach statistical significance ($p > .15$).

To further explore whether there was an interaction between medication assignment, inpatient status, depression severity, or melancholic features in predicting response, we also performed a logistic regression with response as the dependent factor. This analysis failed to reveal a significant association between response and age, depression severity, melancholic features, inpatient status, or drug assignment, or any significant interaction between drug assignment and either inpatient status or melancholic features.

DISCUSSION

The major finding of this study was that, over 6 weeks of treatment, the tolerability of and response to a therapeutic plasma level of nortriptyline or a standard dose of paroxetine were similar in a group of older patients with a major depressive episode, irrespective of inpatient versus outpatient status or the presence or absence of melancholia. This lack of statistically significant difference between the rates of response to nortriptyline and paroxetine is probably not due to a lack of power (i.e., a type II error) since the differences observed between the 2 medication groups were small and did not appear to be clinically significant. Furthermore, these differences would not have reached statistical significance unless 4 to 5 times more patients would have been studied.

In striking contrast with the results of this report, 2 multicenter, double-blind studies from the Danish University Antidepressant Group have reported that, in younger inpatients with endogenous depression, the rate of response after 5 to 6 weeks of treatment was twice as high with clomipramine as with SSRIs.^{22,23} However, these Danish studies involved younger patients, used a more stringent definition of response (a HAM-D score of 7 or below), and compared SSRIs with clomipramine, an atypical TCA that inhibits the reuptake of both norepinephrine and serotonin and thus may be more efficacious than nortriptyline, a norepinephrine reuptake inhibitor.^{24,25}

Roose et al.⁶ compared the response to nortriptyline ($N = 42$) and fluoxetine ($N = 22$) in older inpatients (mean age = 71 years) with cardiac disease who were hospitalized at the New York State Psychiatric Institute (NYSPI) for treatment of severe depression. As in the Danish studies, the response rate to the TCA (in this study, nortriptyline) was more than twice as high as the response rate to fluoxetine—82% vs. 28%—in the completers (i.e., pa-

tients who had received nortriptyline for 4 or more weeks or fluoxetine for 6 to 7 weeks). Thus, while the response rate in these older inpatients treated with nortriptyline was similar to the response rate of our older patients treated with nortriptyline (82% vs. 78%), the response rate to fluoxetine was markedly lower than our patients' response rate to paroxetine (28% vs. 66%).

In both studies, age of subjects, size of study groups, duration of treatment, and medication doses were comparable. Thus, the marked difference in results may be due to (1) other differences in study design, (2) differences between the subjects treated at the NYSPI and in our study, or (3) differences between the efficacy of fluoxetine and paroxetine in the treatment of late-life depression. While our study was a randomized clinical trial, patients at NYSPI were not assigned randomly to nortriptyline or fluoxetine. Thus, as pointed out by Roose et al.,⁶ it is possible that the poor response to fluoxetine was due to unidentified differences between the patients they treated with nortriptyline and the patients they treated with fluoxetine. Response criteria at the NYSPI (HAM-D score less than 8) were also more stringent than response criteria in our study (HAM-D score less than 10). However, changing response criteria in our study reduced response rate similarly in both medication groups, and therefore, it did not create a significant difference between the groups (data not shown). In the NYSPI study, all subjects were inpatients, a higher proportion of them (70%) were suffering from melancholic depression, and, based on the mean HAM-D score of 27 (number of items unspecified), their depression may have been more severe. Nevertheless, we found similar rates of response to nortriptyline and paroxetine when we restricted our comparison to inpatients or to patients with melancholic features, even though we used the more stringent DSM-IV criteria for melancholia as opposed to the DSM-III and DSM-III-R criteria that were used in the NYSPI study.⁷

Finally, while the TCA used in both studies was nortriptyline (with doses adjusted based on plasma drug levels), 2 SSRIs with very different pharmacokinetic profiles were used: fluoxetine at the NYSPI and paroxetine in our study. While randomized controlled trials have found various SSRIs to have a similar efficacy in younger patients, there is some evidence that this may not be the case in older patients. Results of 2 randomized controlled trials in older depressed patients have suggested a slower and possibly lower response to fluoxetine than to either paroxetine²⁶ or sertraline.²⁷ In a large placebo-controlled study of fluoxetine in older depressed outpatients, the response to fluoxetine was significantly higher than the response rate to placebo (44% vs. 32%), but it was lower than what is typically expected in outpatients with mild-to-moderate depression.²⁸ Two other studies in older depressed inpatients have reported similar rates of response between clomipramine and paroxetine²⁹ and between amitriptyline

and paroxetine.³⁰ Similarly, in a 12-week randomized controlled trial, no differences were found between the response rates of 40 older outpatients with melancholic depression treated with either nortriptyline or sertraline.³¹ Thus, these results and our data are consistent. Taken together, they suggest that the very low rate of response to fluoxetine reported by Roose et al.⁶ in older inpatients with severe depression may not be generalizable to other SSRIs.

In conclusion, results from this study suggest that, in older patients with severe depression, the short-term (6-week) efficacy of a standard dose of paroxetine is comparable to the efficacy of a therapeutic plasma level of nortriptyline. Additional studies are required to confirm this result, to determine the relative effectiveness of various SSRIs and other newer antidepressants, and to compare the long-term efficacy of TCAs and SSRIs in preventing depressive relapses and recurrences in late life.

Drug names: amitriptyline (Elavil and others), bethanechol (Urecholine), clomipramine (Anafranil and others), fluoxetine (Prozac), lorazepam (Ativan and others), nortriptyline (Pamelor and others), paroxetine (Paxil), sertraline (Zoloft).

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