DEPRESSION AND ANXIETY 13:38–44 (2001)

PAROXETINE VERSUS NORTRIPTYLINE IN THE CONTINUATION AND MAINTENANCE TREATMENT OF DEPRESSION IN THE ELDERLY

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Elderly depressed patients are vulnerable to recurrence of depression and benefit from long-term antidepressant therapy. Physicians increasingly use selective serotonin re-uptake inhibitors (SSRIs) as maintenance therapy, although in the absence of data showing that SSRIs are as efficacious as tricyclic antidepressants (TCAs) in the prevention of depression relapse and recurrence. Our objective was to evaluate, in an open trial, the efficacy of paroxetine versus nortriptyline for preventing recurrence of depression in the elderly. Elderly patients with major depression were randomly assigned in a double-blinded fashion to receive either paroxetine or nortriptyline for the acute treatment of depression. Patients who did not respond or tolerate their assigned medications were crossed over openly to the comparator agent. Patients whose depression remitted continued antidepressant medication (paroxetine n = 38; nortriptyline n = 21) during an open 18-month follow-up study. We examined the rates of and times to relapse and to termination of treatment for any reason. Paroxetine (PX) and nortriptyline (NT) patients had similar rates of relapse (16% vs. 10%, respectively) and time to relapse (60.3 weeks vs. 58.8 weeks, respectively) over 18 months. A lower burden of residual depressive symptoms and side effects during continuation and maintenance treatment was evident in nortriptyline-treated patients. Paroxetine and nortriptyline demonstrated similar efficacy in relapse and recurrence prevention in elderly depressed patients over an 18-month period. Depression and Anxiety 13:38–44, 2001.

Key words: *depression; geriatric; recurrence; paroxetine; nortriptyline; continuation and maintenance treatment*

INTRODUCTION

Depression is a common and serious condition in the elderly. The prevalence of depression in community-residing elderly is between 1 and 3%; prevalence rates are higher in health care settings, with approximately 10% of elderly patients in primary care settings and 15% in acute care or nursing care facilities being clinically depressed [for review, see Mulsant and Ganguli, 1999]. Not only is major depression common, but it also has serious health consequences. In a nursing home population major depressive disorder, independent of physical health, increased the likelihood of death by 59% over 1 year [Rovner et al., 1991]. In cardiac patients, depression increased by five-fold the risk of mortality 6 months following myocardial infarction [Frasure-Smith et al., 1993]. In acutely hospitalized older patients, the presence of six or more depressive symptoms was associated with two- to three-fold increased risk of diminished health and was a strong predictor of loss of function [Covinsky et al., 1997]. The Medical Outcomes Study found that depression was as debilitating as advanced coronary artery disease [Wells and Burnam, 1991]. Of par-

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Contract grant sponsor: National Institute of Mental Health; Contract grant number: P30 MH52247, R37 MH43832, R01 MH37869, R01 MH59381, K01 MH01613, K05 MH00295, and T32 MH19986.

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Received for publication 1 May 2000; Accepted 26 July 2000

ticular importance to geriatric populations, the effects of depression and medical illness on functioning appear to be additive [Wells et al., 1989].

Depression is a chronic illness with relapses and recurrences. In a large observational study of depressed patients, a cumulative recurrence rate of 85% was noted, with the majority of patients suffering a recurrence within 5 years [Mueller et al., 1999]. Most studies of recurrence risk have been conducted in mid-life patients. Available data in the elderly suggest that elderly patients have similar rates of recurrence, although the time between episodes is shorter, with most relapses occurring within 2 years [Zis et al., 1980; Georgotas et al., 1989; Reynolds et al., 1999]. These observations and others [Flint and Rifat, 2000] highlight the importance of keeping patients well following the acute treatment of a depressive episode (via continuation and maintenance therapy).

Multiple studies have demonstrated that maintenance antidepressant medication is superior to placebo in keeping depression in remission [for review, see Montgomery and Kasper, 1998a,b]. Reynolds et al. [1999] conducted the only randomized placebo-controlled trial in the elderly comparing long-term maintenance efficacy of pharmacological and psychosocial maintenance antidepressant therapies and found a significant advantage for nortriptyline, either singly or in combination with interpersonal psychotherapy, when compared to placebo. In an open medication trial using either nortriptyline or phenelzine plus/minus other adjuvant therapy, nearly 75% of elderly patients remained well at 2 years [Flint and Rifat, 1997] and 70% at 4 years [Flint and Rifat, 2000]. Similar results have been observed in an open pilot study using venlafaxine [Amore et al., 1997]. These and other maintenance pharmacotherapy trails are promising; however past studies used tricyclic antidepressants, monoamine oxidase inhibitors, and atypical anti-depressants that are currently considered second-line treatment in the elderly.

The current recommended first-line therapy for depression in later life is a serotonin selective re-uptake inhibitor (SSRI) because in comparison to tricyclic antidepressants like nortriptyline, SSRIs are safer in overdose, better tolerated, and do not require monitoring blood levels or EKG analysis prior to initiation of therapy [for review, see Montgomery, 1998; Dunner, 1994]. Multiple clinical trials have found similar efficacy between SSRIs and TCAs in the acute treatment of geriatric depression, with SSRIs being better tolerated [for review, see Schneider, 1996]. While evidence suggests that SSRIs and TCAs are essentially equivalent in the acute phase of treatment, it is not known whether they are also comparable during continuation and maintenance treatment in preventing the recurrence of depression.

The NIH consensus panel on the diagnosis and treatment of depression in late life recommended that depressed geriatric patients be maintained on anti-depressants for at least 6 months for first episodes of depression and at least 1 year for recurrent depressive episodes [Lebowitz et al., 1997]. Given concerns about high rates of relapse and recurrence, many investigators have advocated up to 2 years of maintenance anti-depressant medication in the elderly [Old Age Depression Interest Group (OADIG), 1993; Flint & Rifat, 1997]. With the exception of our prior preliminary results that compared paroxetine to nortriptyline in maintenance therapy for depression in geriatric patients [Walters et al., 1999], we know of no studies that have compared the maintenance efficacy of SSRIs to TCAs. In our previous study, we reported 40 patients who were followed for up to 18 months. We found that paroxetine and nortriptyline were equally effective in maintaining wellness. Given the constraints on the use of nortriptyline in medically burdened patients and the reluctance of many physicians to use TCAs over SSRIs in geriatric patients, we have extended and expanded our observations to include an analysis of rates of relapse, recurrence, residual depressive symptoms during continuation/maintenance treatment, side-effect burden, and relation between relapse/recurrence and variability in level-to-dose ratios of paroxetine and nortriptyline. Greater variability in level-to-dose ratios has been linked to non-compliance with antidepressant pharmacotherapy [Miller et al., 2000]. The current study investigated the rate of recurrence in 59 patients treated openly with either nortriptyline or paroxetine during a follow-up time of up to 18 months.

SUBJECTS AND METHOD

The study reported here is based upon a larger clinical trial in which we recruited 116 elderly patients suffering from major depression to compare the efficacy of nortriptyline and paroxetine during acute treatment [phase 1: Mulsant et al., 1999] . In the primary, acute-phase trial, 55 patients were recruited from inpatient treatment facilities and 61 from the community by a combination of referrals, radio, and newspaper advertisements. Patients were treated under double-blind conditions for up to 12 weeks with either paroxetine (n = 62) or nortriptyline (n = 54), followed for a minimum of 12 weeks, and considered to have remitted if they achieved a 17-item Hamilton Depression Rating Scale (HRSD) [Hamilton, 1960] score of 10 or less for 3 weeks. When patients were not responding to the study medication, or had medical conditions or side effects that precluded use of a study medication, the blind was broken and patients were switched to the alternate study medication. A total of 38 patients remitted with paroxetine (29 who were initially started on paroxetine, and 9 patients who failed nortriptyline and were subsequently "rescued" with paroxetine), and 21 patients remitted with nortriptyline (19 who were initially started on nortriptyline and 2 patients who failed paroxetine and were "rescued" with nortriptyline). After depression remitted, patients were given the opportunity to undertake

an open 18-month continuation and maintenance trial (phase 2) using the medication to which they responded. A separate IRB-approved protocol was followed for phase 2, and informed consent to participate in phase 2 was elicited from patients separate from consent to participate in phase 1.

Plasma for the measurement of the nortriptyline and paroxetine levels was obtained at weekly visits during acute treatment, and monthly during continuation and maintenance treatment. Levels were analyzed by reverse-phase HPLC with UV detection using methods previously described [Pollock et al., 1992; Foglia et al., 1997]. The paroxetine and nortriptyline dosages were held constant from the acute phase of treatment, but with small adjustments of nortriptyline dosage allowed to maintain therapeutic blood levels (50–120 ng/ml). Depressive symptoms were assessed monthly during continuation and maintenance treatment with the 17-item HRSD. End points were designated as relapse or recurrence as defined by SCID criteria for major depressive episode. "Relapse" denoted re-emergence of depressive symptoms within 6 months of successful treatment of the index depressive episode and "recurrence" denoted emergence of another depressive episode 6 months or longer after successful treatment of the initial depressive episode. Termination of treatment for intolerable side effects, supervening medical conditions that contraindicated further use of the antidepressant medication, withdrawal of consent, and non-compliance with medication leading to investigator-initiated termination of subjects were also considered endpoints.

Data from 40 subjects, which have been previously presented in our preliminary results [Walters et al., 1999], are included in this analysis. We examined rates and times to relapse/recurrence, as well as time to termination of treatment for any reason. We also explored correlates of treatment failure. In analyzing baseline clinical and demographic measures of the two treatment groups (paroxetine versus nortriptyline), we used two-tailed tests to contrast continuous variables and a chi-square analysis categorical variables. For gender, race, and percent of patients with recurrent major depressive disorder, we used a Fisher Exact test because some cells had expected counts of less than five. Before the analysis, we examined the distributions of all variables. We used a natural log transformation to normalize the distribution of duration of current episode. Time to relapse/recurrence and time to termination for any reason were compared using a Kaplan-Meier survival analysis with log-rank statistic. A mixed-effect linear model with maximum likelihood estimation tested Hamilton and UKU scores during continuation/maintenance treatment for group, time, and group by time interactions. Review of plots of meaned raw data across time suggested that the NT group showed a lower level of depressed symptoms and side effects after 1 year while symptoms in the paroxetine group remained level. A contrast was used to test this observation. The monthly scores were averaged at 2-month intervals to maximize sample size and minimize the data points used in the contrast. In order to identify possible correlates of relapse/recurrence, baseline demographic and clinical measures were also compared for the 8 relapsing and the 51 non-relapsing patients. Owing to the small sample size, a Fisher Exact test was used for the categorical variables and a Wilcoxon Rank-Sum test for the continuous variables. Coefficients of variation of plasma concentration/dose quotients during acute and maintenance treatments were compared using a Wilcoxon signed-rank test as an index of treatment adherence.

RESULTS

Summary demographic, clinical, and treatment-intensity measures are presented in Table 1. Patients in the paroxetine and nortriptyline treatment groups were similar at both baseline and at the beginning of continuation/maintenance therapy; however, the nortriptyline group was older and had a higher mean HRSD score at baseline and a lower HRSD at the beginning of continuation treatment. During a median follow-up of 61.5 weeks (range 3–83.6), 6 of 38 (15.8%) patients treated with paroxetine experienced a relapse/recurrence at 4, 5, 25.3, 29, 52.6, and 67 weeks. During a median follow-up of 53.0 weeks (range 8.7–83.9), 2 of 21 (9.5%) patients treated with nortriptyline experienced a relapse/recurrence at 21.7 and 61 weeks (see Fig. 1). Using Kaplan-Meier survival analysis, the mean time to relapse was 60.3 weeks (standard error = 3.2) in the paroxetine group and 58.8 weeks (standard error = 3.0) in the nortriptyline group. The survival analysis detected no difference between the two treatment groups in rate or time to relapse.

We also examined time to treatment termination for any reason. Treatment termination includes not only relapse or recurrence but also other causes of termination. A total of ten patients treated with paroxetine left the study: two patients died (one from stroke and one from a heart attack), one suffered intolerable sedation, one developed frontal lobe dementia, one developed psychosis, one demonstrated increased liver function tests and delirium, one complained of severe sexual dysfunction, two patients moved and were unable to arrange transportation, and one who felt depressive symptoms had remitted chose to stop medication against medical advice. A total of nine patients treated with nortriptyline left the study: one patient moved and was unable to arrange transportation, one patient was non-compliant, one patient was hospitalized with pneumonia and was switched to paroxetine by the patient's attending physician, two patients developed a rash, one patient was not taking medications properly, and three patients withdrew consent (one patient declined further treatment due to family difficulties providing transportation, one grew tired of being in the research study, and one did not think the medication was help-

TABLE 1. Demographic and clinical characteristics*

	Paroxetin (N=38)	Nortriptyline (N=21)	T-statistic/ χ^2	DF	*P*-value
Demographics					
Age	70.5 (7.0)	74.9 (5.9)	2.42	57	.02
% Male	29.0 (n=11)	9.5 (n=2)		Fisher exact = .11	
% Female	81.6 (n=31)	90.5 (n=19)		Fisher exact = .47	
% Inpatient	36.8 (n=14)	47.6 (n=10)	0.65	1	.42
Mood disorder diagnosis					
% Single MDD	50.0 (n=19)	52.4 (n=11)			
% Recurrent MDD	47.4 (n=18)	42.9 (n=9)		Fisher exact = .99	
% Other	2.6 (n=1)	4.8 (n=1)			
Duration of current episode in weeks[a]	56.3 ((78.7) median = 28 range = 3–416	62.8 (98.0) median = 26 range = 4–416	–0.37	57	.71
% Co-morbid axis 1 diagnosis	57.9 (n=22)	42.9 (n=9)	1.23	1	.27
Mean number of co-morbid Axis I	1.4 (0.6)	1.1 (0.3)			
Dx in the co-morbid population	median = 1 range = 1–3	median = 1 range = 1–2	–1.27	29	.21
Baseline Clinical Measures					
Hamilton 17-item	20.5 (3.1)	24.1 (4.3)	3.71	57	.0005
Folstein mini-mental (n=38/20)	26.8 (3.1)	25.6 (3.3)	–1.47	56	.15
Mattis dementia rating scale (n=38/19)	131.5 (11.9)	127.1 (10.6)	–1.38	55	.17
Global assessment scale	49.7 (9.8)	44.8 (9.8)	–1.85	57	.07
Cumulative illness rating scale					
Total	9.1 (4.0)	8.6 (3.4)	–0.47	57	.64
Count	5.7 (2.2)	5.2 (1.8)	–0.79	57	.43
UKU (n=37/19)	7.8 (3.6)	6.7 (3.3)	–1.16	54	.25
Number of non-psychotropic Rx	2.7 (2.5)	3.8 (2.8)			
Medications at baseline[b]	median = 2.5 range = 0–9	median = 3 range = 0–11	1.49	57	.14
Start of Continuation/Maintenance Treatment					
Hamilton 17-item	5.8 (2.4)	4.4 (2.8)	–2.02	57	.05
UKU side effects	7.8 (3.6)	6.4 (3.4)	–1.46	56	.15
Mean dose (Mg QD) (n=37/20)	24.1 (6.4) range = 10–40	52.5 (22.6) range = 20–125			
Blood level (ng/ml) (n=37/20)	115.9 (88.8) median = 87 range = 23–330	70.0 (26.2) median = 69.5 range = 21–139			

**Fifty-nine subjects started continuation/maintenance treatment with nortriptyline or paroxetine. Of these, 38 were on paroxetine and 21 on nortriptyline. Table 1 shows the baseline demographic and clinical characteristics of the two groups. Values are means and standard deviations unless noted otherwise. Table 1 also contains Hamilton 17-item, UKU side effects total scores, drug dosages, and blood levels at the start of continuation/maintenance treatment.*

[a]LN(X) transformation used in the analyses. Means and standard deviations reported in their original units.

[b]Includes calcium supplements, aspirin and laxatives taken regularly. Does not include Rx medications given for short courses (less than one month), PRN medications, ibuprofen, acetaminophen, vitamins, glycerin suppositories or enemas.

ing). These data are depicted graphically in Figure 2. Using the Kaplan-Meier survival analysis, the mean time to treatment termination for any reason was 57.6 weeks (standard error = 5.0) in the paroxetine group and 46.9 weeks (standard error = 4.0) in the nortriptyline group. The survival analysis detected no difference between the two patient treatment groups in rate or time to treatment termination.

Because of the importance of side effects in determining compliance with treatment, we questioned patients monthly regarding side effects using the UKU side effects scale [Lingjaerde et al., 1987]. Level of side effects of the two treatment groups (Fig. 3) were found to covary with the temporal pattern of residual depressive symptoms as measured by the Hamilton Depression Rating Scale (HRSD) scores (Fig. 4). Using a mixed-effect linear model, no significant differences between the two groups or group by time interactions were seen in side effects or depressive symptoms. The analyses showed statistically significant time effects (UKU: F = 4.36, df = 1,57, $P = .041$; HRSD: F = 5.22, df = 1,57, $P = .026$).

Though time by treatment interaction effects were not detected, both of these figures suggest that the side effects and depression scores decreased differentially with time for the two treatment groups. Post-hoc contrast analysis showed that the side effects scores and the HRSD scores for the nortriptyline group decreased more after 1 year in contrast to these scores for the paroxetine group (UKU: F =

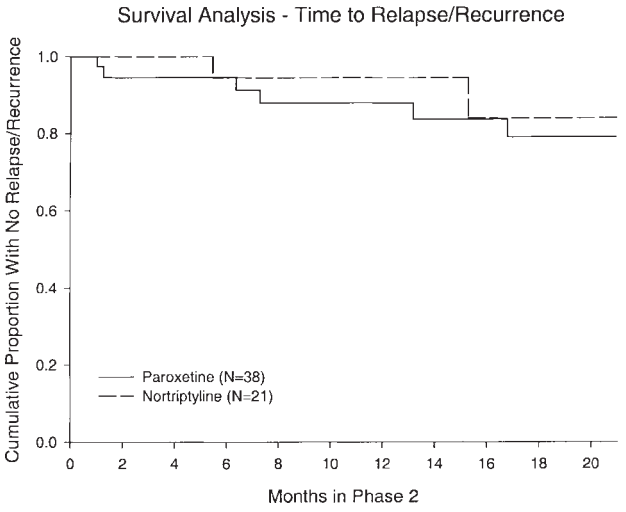

Figure 1. Kaplan-Meier survival analysis for time to relapse. All subjects who did not experience a relapse or recurrence were treated as censored observations. The curves did not significantly differ (Log rank $\chi^2 = 0.37$, df = 1, $P = 0.54$).

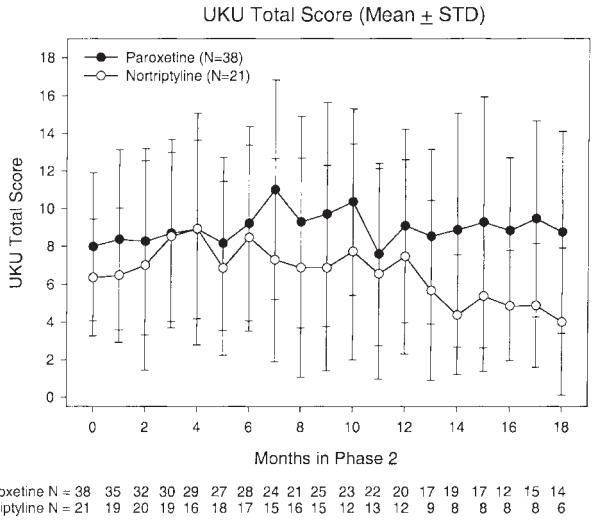

Figure 3. Mean group total UKU side effects scale score during continuation and maintenance treatment. Brackets denote standard deviations. In cases where more than one score was reported in a given month, the values were averaged individually before computing the group means. Side-effects scores decreased more after 1 year in the nortriptyline group.

15.98, df = 1,57, $P = .0002$; HRSD: F = 24.66, df = 1,57, $P < .0001$).

In exploratory analyses of correlates of relapse and recurrence, we compared several variables in the eight patients who relapsed and the 51 who did not. We found no significant differences between the relapsing and non-relapsing patients in age, sex, proportion with single vs. recurrent depression, duration of current episode, age at first episode, number of Axis I co-morbidities, recruitment site, pre-treatment Hamilton scores, Folstein Mini-Mental State Examination [Folstein et al., 1975], Mattis Dementia Rating Scale, Cumulative Illness Rating Scale [Linn et al., 1968], Global Assessment Scale, time to remission, or drug levels over time. We did find that patients

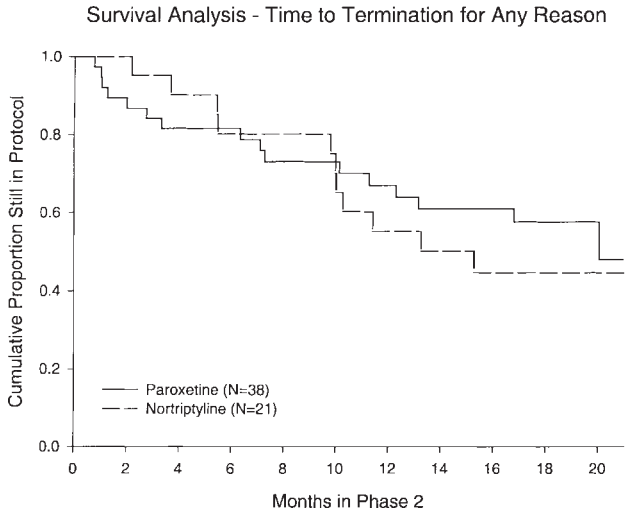

Figure 2. Kaplan-Meier survival analysis for time to treatment termination for any reason. All subjects who finished the protocol by study design, or were still active in the protocol (i.e., had not relapsed/recurred or dropped out for other reasons) were treated as censored observations. All reasons for termination are described in results. The curves did not differ significantly (Log rank $\chi^2 = 0.25$, df = 1, $P = 0.62$).

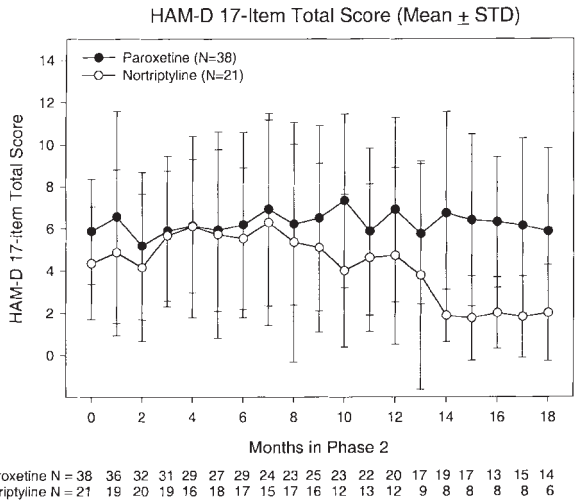

Figure 4. The mean group Hamilton 17-item scores during continuation and maintenance treatment for the two treatment groups. In cases where more than one HRSD was reported in a given month, the values were averaged individually before computing the group means. Depression scores decreased more after 1 year in the nortriptyline group.

who relapsed had a higher mean Hamilton depression score at the start of continuation treatment: 7.5 (S.D. 3.0) vs. 4.9 (Wilcoxon Rank sum z = 2.41, $P<.02$) (S.D. 2.4). For the eight subjects who relapsed, we detected no difference in the coefficient of variation in the plasma concentration/dose quotients during acute treatment and continuation/maintenance treatment.

DISCUSSION

Depression is a recurrent illness. Approximately half to three quarters of patients with a single episode of depression will have a second episode [NIMH/NIH Consensus Development Panel, 1985]. In patients with two previous depressive episodes, 70 to 90% of patients will have additional episodes [Depression Guideline Panel, 1993]. Data on recurrence risk were obtained predominantly in mid-life or mixed aged samples. By comparison there is limited information on recurrence risk in the elderly. Previous reports suggest the elderly also have high rates of recurrence, but the time between episodes is shorter [Zis et al., 1980; Georgotas et al., 1989; Reynolds et al., 1999]. Thus, the elderly appear to be highly vulnerable to depression recurrence and need long-term treatment with antidepressants.

Over the last decade the prescription patterns of physicians treating depression have changed considerably. Increasingly, physicians use SSRIs as first-line therapy for depression. SSRIs are safe in overdose, do not require extensive laboratory testing, and are well tolerated by the elderly. Evidence suggests that SSRIs are comparable to TCAs in the acute treatment of geriatric depression [for review, see Schneider, 1996]. However, there is clinical lore that SSRIs are not as efficacious over the long run, with some clinicians expressing concern that SSRIs "poop out." We present evidence here that is contrary to that notion, with the observation of similar efficacy between paroxetine and nortriptyline in the 18-month treatment of depression in late-life, and with comparable rates and time to relapse/recurrence. We also report similar rates of dropout between patients treated with the two drugs. However, when we analyzed residual symptoms of depression and side-effects, we found that the nortriptyline group improved more than the paroxetine group (see Figs. 3, 4), and that improvement in the two domains co-varied, as we have noted before [Marraccini et al., 1999]. These findings offer support for the use of paroxetine in the long-term treatment of geriatric depression but raise the possibility that nortriptyline may do a better job in reducing residual symptoms. These findings are also relevant to current discussions of the cost of antidepressants. On the one hand, cost differential would favor nortriptyline over paroxetine if the relapse rate and dropout rate are equivalent; on the other, the greater safety of paroxetine, especially in very old patients, represents a compelling argument for its use with this population.

It should be noted that the two treatment groups differed in age and severity of depression. The nortriptyline group was older and had a higher mean pretreatment HRSD. Both of these variables would predict that the nortriptyline group would fare worse than the paroxetine group, but this prediction was not borne out by our findings. It should also be noted that our rate of relapse (10–15% over 18 months) is lower than what has been reported by similar studies. Flint and Rifat [1997] reported a recurrence rate of 26% over 2 years in a group of 84 elderly patients treated predominantly with nortriptyline and 30% over 4 years [Flint and Rifat, 2000]. The Old Age Depression Interest Group [1993] reported recurrence rates of approximately 30% over 2 years in a double-blind placebo controlled study of 69 geriatric depression patients treated with dothiepin. Reynolds et al. [1999] reported a recurrence risk of approximately 55% in patients over 70 years old treated with nortriptyline alone. The difference in recurrence risk observed could reflect our small sample size, open study design, site, and intensity of treatment.

We sought to identify preliminary predictors of patient relapse. Any clinical features that could point to patients requiring closer follow-up would be helpful. It has been reported that higher levels of acute and chronic stressors, poorer social supports, younger age at first depressive episode, higher anxiety, older age, and poorer sleep are associated with a worse prognosis [Dew et al., 1997]. Unfortunately, because of our small sample size, we were limited in our ability to find such associations and were unable to identify any baseline characteristics that predicted treatment failure. We did find a higher mean HRSD at the start of continuation treatment in the patients who relapsed. While this could be a chance finding, other studies have also reported that higher residual symptoms of depression [Alexopoulos et al., 1996] or anxiety [Flint and Rifat, 2000] are associated with subsequent relapse.

In summary, we compared the long-term treatment efficacy of paroxetine to nortriptyline in the prevention of depression recurrence in the elderly. We found equal efficacy between the two drugs with similar rates of and time to relapse. While these results are encouraging, they need to be replicated in a controlled trial with a larger sample size before the long-term efficacy of paroxetine in the treatment and prevention of depression recurrence in the elderly can be considered to be demonstrated.

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