Continuation and Maintenance Pharmacotherapy in Geriatric Depression: An Open-Trial Comparison of Paroxetine and Nortriptyline in Patients Older Than 70 Years

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We present preliminary data on the efficacy of paroxetine, as compared with nortriptyline, in preventing or delaying relapse and recurrence of major depression in elderly patients. Following double-blind, acute-phase pharmacotherapy, 25 patients (mean age = 72.5 years) began open-trial continuation treatment with paroxetine (mean dose = 24.5 mg/day), and 15 patients (mean age = 77.5 years) received nortriptyline (mean dose = 51.3 mg/day; mean blood level = 85.5 ng/mL). Over an 18-month period, paroxetine and nortriptyline have shown comparable efficacy in preventing or delaying relapse and recurrence, with 80% to 90% of patients remaining well. These data suggest that paroxetine holds promise for long-term maintenance treatment in patients in their 70s and older with depression; however, further controlled evaluation is necessary.

(J Clin Psychiatry 1999;60[suppl 20]:21–25)

Getting well is not enough; it is staying well that counts. This has been the guiding theme of our research and clinical practice over the past decade as we have worked with elderly depressed patients and their families to complete the first long-term maintenance studies of pharmacotherapy and psychotherapy ever conducted in recurrent depressive illness of later life.[1] These studies have tested the hypothesis that maintenance pharmacotherapy with nortriptyline and maintenance interpersonal psychotherapy (IPT-M), either singly or in combination, are superior to placebo in preventing or delaying the recurrence of major depressive episodes. Our data support this hypothesis and have also identified which patients are able to remain well on IPT-M alone, following discontinuation of antidepressant medication, and which need antidepressant medication to remain well. In the decade since we undertook to investigate long-term maintenance therapies in geriatric depression, new antidepressant medications—the selective serotonin reuptake inhibitors, or SSRIs—have become available that are better tolerated by the elderly, safer in the context of concurrent medical illnesses, and much less likely to be fatal in overdose than tricyclic antidepressants (TCAs). Because clinicians are increasingly disinclined to prescribe TCAs in the elderly and have moved to SSRIs or other drugs that are safer in overdose, testing the maintenance efficacy of such treatments has the potential of substantial generalizability. At the same time, many clinicians have expressed the concern that SSRIs may not have the staying power of TCAs (i.e., they "poop out"). To date, the long-term efficacy of these compounds in the elderly has not been assessed in a rigorous, controlled fashion.

As reflected in a recent update of the 1991 National Institutes of Health (NIH) Consensus Conference on Depression in Later Life,[2] we have made progress in understanding the variability of treatment response and illness course in geriatric depression. In this context, investigators have recognized the need for further controlled intervention studies in patients older than 70 years using modern antidepressant therapy and examining the psychosocial and neurobiological moderators of treatment success and failure (e.g., Salzman, 1994[3]; Schneider, 1996[4]). Furthermore, treatment success and failure cannot be defined solely on the basis of improvement in specific de-

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Presented at the closed roundtable "Treatment of Depression in Long-Term Care Patients," Sept. 18–19, 1998, Boston, Mass. This roundtable was supported by SmithKline Beecham Pharmaceuticals.

This research was supported in part by National Institute of Mental Health grants P30 MH52247, R37 MH43832, K05 MH00295, and T32 MH19986.

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pressive symptomatology. Getting well also means that the functional and quality-of-life decrements associated with geriatric depression are overcome.

Certainly the most compelling consequence of depression in later life is increased mortality from both suicide and medical illness. Elderly persons have the highest suicide rate of any age group, largely accounted for by older white males, with rates rising to 67.6 suicides per 100,000 in those aged 85 years and older, more than 5.5 times the overall national rate of 12 per 100,000.[5] Suicide in the elderly is more likely to be a result of depression: in patients 75 years of age and older, 60% to 75% of those who commit suicide have diagnosable depression.[6] In addition, the connection between depression and nonsuicidal mortality is now well supported in patients with myocardial infarction, in whom depression elevates mortality risk by a factor of 5,[7,8] and in nursing home patients, in whom major depression was found to increase the likelihood of mortality by 59% independent of physical health measures.[9] Hence, the selection of treatment modalities that are both safe and effective for the long-term management of geriatric depression is, literally, a matter of life and death.

Our current work has shown that maintenance therapy with the TCA nortriptyline (at steady-state levels of 80–120 ng/mL) and monthly IPT-M,[10] either singly or in combination, are superior to placebo in preventing recurrences of major depression in patients aged 60 to 69 years.[1] There are, however, no published data from controlled studies on the long-term efficacy of antidepressant medication and psychotherapy in patients 70 years and older. However, it is precisely such patients, who are the most rapidly increasing segment of the elderly population, whose response to antidepressant treatment may well be the most brittle and in whom depression will increasingly represent a source of excess medical service utilization and economic cost, reduced quality of life, morbidity, and mortality during the next 20 years.[11,12] A recent World Health Organization (WHO) study concluded that unipolar major depression and suicide accounted for 5.1% of the total global burden of disease in 1990 (with respect to a quality-adjusted life-year [QALY]-based metric, disability-adjusted life years), making depression the fourth most important cause of global burden.[11] The significance of illness burden attributable to depression increases with age weighting and is projected to grow by the year 2020, on the basis of demographic shifts toward a greater proportion of elderly in the general population. Therefore, finding ways of preventing the return of depression in patients aged 70 years and older and of maintaining the gains of acute and continuation treatment would represent a significant treatment advance and contribution to public health.

Another important question is whether there are ways of predicting which older patients require combined treatment or medication alone and which may be able to remain well on maintenance psychotherapy alone. Identifying such predictors of response will allow the cost-effectiveness of treatment choices to be maximized. There have been no studies of the cost-effectiveness (ratio of dollar costs of a treatment to QALYs gained by the treatment) for depression interventions in the elderly. The issue is not whether a given treatment is more cost-effective than no treatment, but whether a given treatment (e.g., combined medication and psychotherapy) is more cost-effective than another treatment option (e.g., monotherapy). This has public health policy implications as well as implications for clinicians as they decide which treatment is most appropriate for their elderly patients.[13,14]

Although SSRIs have become the first-line treatment for depression in later life because of their favorable side effect profile and safety in overdose,[15] no efficacy, effectiveness, or safety data exist on the long-term use of SSRIs in the elderly. The need for such data is great, given the strong tendency of relapse and recurrence in the elderly.[16] Our preliminary, open-trial data on the use of paroxetine for maintaining wellness over 18 months in elderly depressed patients in their 70s, presented here, support the promise of this agent, but also underscore the limitations of drug monotherapy.

Other data bearing on long-term efficacy have been reported by the Old Age Depression Interest Group in the United Kingdom,[17] who observed that elderly patients with major depression are 2.5 times less likely to suffer recurrence on dothiepin maintenance (75 mg/day for 2 years) than on placebo. In addition, although maintenance therapy with the SSRIs in late-life depression has not been evaluated, shorter term continuation efficacy in mixed-aged populations has been demonstrated in a placebo-controlled trial of paroxetine.[18]

In a recent extensive review of 20 randomized trials comparing the acute efficacy of TCAs and SSRIs, Schneider[4] concluded that TCAs and SSRIs have similar acute-phase efficacy, but that SSRIs are better tolerated, with dropout rates reduced by one half to two thirds. In general, the SSRIs are tolerated well by elderly patients[19–21] and, in our ongoing double-blind, randomized study comparing paroxetine with nortriptyline, show comparable efficacy in the acute pharmacotherapy of severely depressed, medically ill elderly patients with a range of cognitive impairment.[22] Moreover, a beneficial effect of paroxetine on cognitive function has also been demonstrated in elderly patients with depression.[23]

Thus, based on these considerations, paroxetine appears to be a good candidate for further study of continuation and maintenance therapy in the elderly.

SUBJECTS AND METHOD

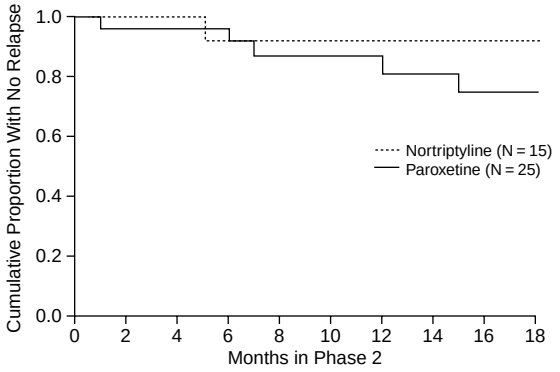
Our Mental Health Clinical Research Center for Late-Life Mood Disorders (Pittsburgh, Pa.) conducted a ran-

Table 1. Subject and Treatment Characteristics: Open-Trial Continuation Treatment (N = 40)[a]

Variable	Paroxetine N = 25	Nortriptyline N = 15
Demographic		
Age, y	72.5 (6.3)	77.5 (5.6)
Gender, N		
Male	7	1
Female	18	14
Race, N		
White	22	12
Black	3	2
Other	0	1
Axis 1, Order 1, N	9 MDD single episode	7 MDD single episode
	13 MDD recurrent episode	7 MDD recurrent episode
	3 PDD, senile onset with depression	1 PDD, senile onset with depression
Pretreatment		
17-item HAM-D score	20.5 (3.2)	23.8 (4.2)
MMSE score	26.7 (3.5)	26.1 (2.4)
DRS score	130.9 (12.4)	129.1 (9.6)
Continuation treatment		
Dose entry, mg/d	24.5 (6.9)	51.3 (19.9)
Range	20–40	20–75
Blood level, ng/mL	162.4 (110.2)	85.5 (33.1)
Range	24–470	41–161
17-item HAM-D score	5.6 (3.7)	5.3 (4.6)
Current duration, mo	11.4 (6.4)	8.1 (5.0)
1-year MMSE score	26.8 (4.1)	24.5 (4.9)
N	18	8
1-year DRS score	128.9 (16.8)	127.0 (19.2)
N	18	7

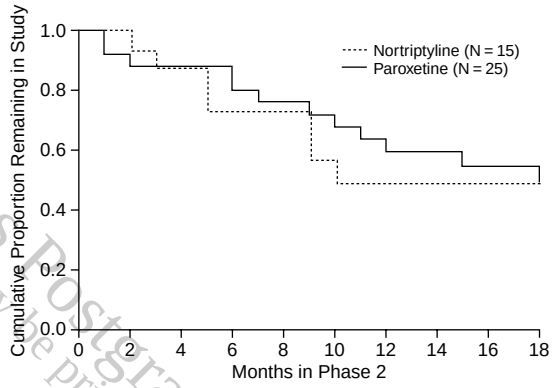
[a]All values shown are mean (SD) unless specified otherwise.
Abbreviations: DRS = Dementia Rating Scale, HAM-D = Hamilton Rating Scale for Depression, MDD = major depressive disorder, MMSE = Mini-Mental State Examination, PDD = primary degenerative dementia.

Figure 1. Survival Analysis of Patients Taking Paroxetine or Nortriptyline During Phase 2 (continuation) Treatment[a]



[a]During mean follow-up interval of 11.9 months, 5 of 25 subjects taking paroxetine experienced a relapse or recurrence of major depression compared with 1 of 15 subjects taking nortriptyline.

Figure 2. Time to Termination for Any Reason[a]



[a]Reasons for terminating include relapse/recurrence, side effects, medical illness, and death.

domized, double-blind acute efficacy study (12 weeks) of nortriptyline versus paroxetine in moderately depressed (per DSM-IV criteria and predominantly inpatient) and medically burdened patients (mean age at study entry = 73 years). Patients visited the research clinic weekly for monitoring of depressive symptoms and side effects and for supportive care, but they received no formal psychotherapy. Depression in 22 (49%) of 45 patients randomly assigned to treatment with paroxetine remitted; depression in 12 (33%) of 36 patients treated with nortriptyline remitted. Following completion of the double-blind acute treatment (phase 1), patients were offered the opportunity to continue in open continuation and maintenance treatment for an additional 18 months. Twenty-five of 27 subjects whose depressions remitted during medication-clinic treatment with paroxetine (including 5 subjects crossed over to open paroxetine treatment after failing nortriptyline) elected to enter open continuation treatment (phase 2), while 15 of 16 nortriptyline responders (including 4 subjects who had initially failed paroxetine) agreed to open continuation therapy with this agent. Paroxetine and nortriptyline doses were held constant with doses used during acute-phase pharmacotherapy. Summary demographic, clinical, and treatment intensity measures are presented in Table 1. We examined rates of relapse and recurrence via survival analysis.

RESULTS

During a mean follow-up interval of 11.9 months (median = 11.5 months), 5 of 25 subjects experienced a depressive relapse during continuation and maintenance therapy with paroxetine (mean dose = 24.5 mg/day), and 1 of 15 subjects taking nortriptyline experienced a relapse (Figure 1). Figure 1 suggests that paroxetine and nortriptyline may have similar efficacy for preventing relapse during continuation and maintenance treatment. A survival plot displaying time to termination for any reason (Figure 2), which includes not only relapse and/or recurrence but also dropouts due to side effects, medical illness, and death, also suggests

Table 2. Reasons for Discontinuation

Paroxetine (25 subjects entered continuation treatment with paroxetine)
5 subjects experienced a depressive relapse
2 subjects withdrew consent
1 subject left owing to sexual dysfunction
2 subjects died
1 subject experienced onset of manic episode
1 subject experienced intolerable sedation
Nortriptyline (15 subjects entered continuation treatment with nortriptyline)
1 subject experienced a depressive relapse
2 subjects withdrew consent
1 subject was noncompliant
2 subjects had other medical problems contraindicating further use of nortriptyline
1 subject left owing to side effects

Figure 3. Mean ± SD 17-Item HAM-D Scores During Paroxetine and Nortriptyline Continuation and Maintenance Treatment

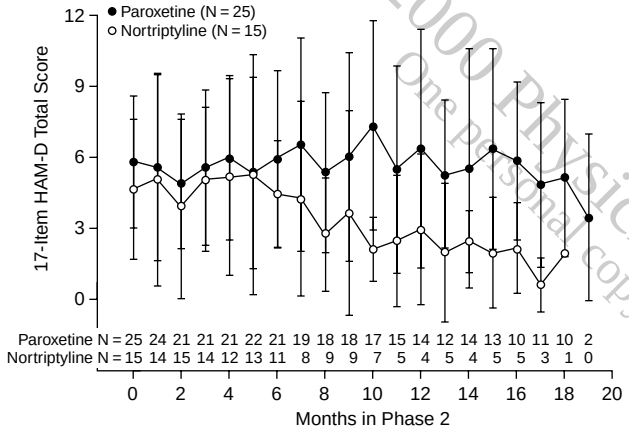
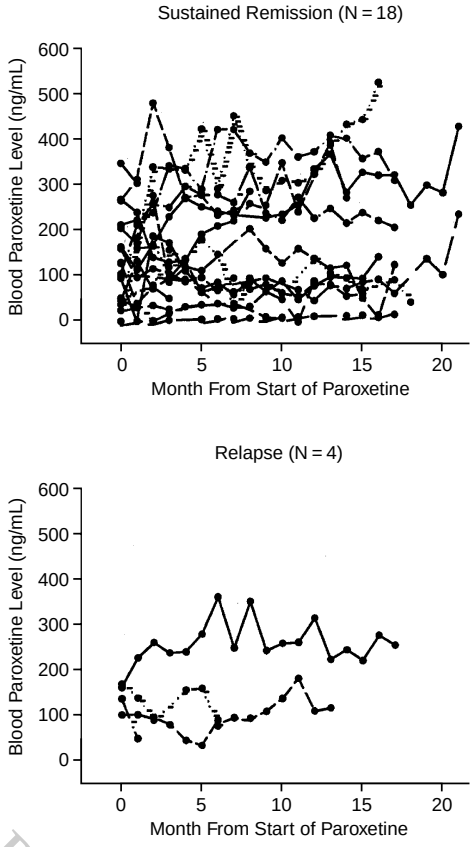


Figure 4. Paroxetine Blood Levels in Patients With Sustained Remission Versus Those With Relapse/Recurrence



similar efficacy for the 2 agents. Table 2 lists all reasons for termination. Figure 3 shows the mean ± SD Hamilton Rating Scale for Depression (HAM-D) scores during continuation and maintenance of paroxetine and nortriptyline treatment. These also appear to be similar.

Examination of blood paroxetine levels in patients who relapsed disclosed no difference in levels or in variability over time compared with levels in patients who remained well. This observation suggests that relapse was not due to treatment noncompliance (Figure 4).

Previously, it had been found with TCAs that the longitudinal stability in quotients of plasma drug levels divided by dose is more applicable to monitoring adherence with pharmacotherapy than plasma levels alone, because dosage changes may limit the usefulness of steady-state plasma levels.[24,25] Our preliminary data suggest paroxetine steady-state levels have comparable stability, permitting this same approach. Subjects are determined to be nonadherent if the percentage coefficient of variation in their plasma level/dose values exceeds their prior mean quotient by > 2 standard deviations, in the absence of an interacting medication. In the paroxetine pilot study, the mean ± SD percentage coefficient of variation was 19.2 ± 6.7 (N = 19), which is comparable to that of nortriptyline-treated patients (mean ± SD = 17.6 ± 9.7; N = 16). Subsequently, during maintenance treatment, 4 paroxetine-treated subjects were identified as being at least partially nonadherent. Thus, we believe this method complements pill counts and clinician interview in the assessment of pharmacotherapy treatment adherence.

DISCUSSION

Our preliminary data suggest that paroxetine has efficacy in preventing or delaying relapse and recurrence of major depression in patients aged 70 years and older with no or mild cognitive impairment and mild-to-moderate levels of chronic medical illness. Paroxetine appears to have efficacy comparable to that of nortriptyline and may be better tolerated than nortriptyline in the context of continuation and maintenance treatment. In this study, the continuation/maintenance dose of paroxetine was the

same as that prescribed during the acute phase of therapy. Thus, paroxetine holds promise for longer term maintenance treatment in severely depressed patients in their 70s as long as paroxetine dosage is maintained at the same dose used during acute-phase pharmacotherapy of the index episode. However, maintenance monotherapy fails in some patients.

The current data are consistent with observations from a placebo-controlled study of paroxetine in midlife patients, in which paroxetine was found to be better than placebo in relapse prevention and prophylaxis of major depression.[18] However, the current study was an open trial and thus preliminary. Further, controlled evaluation of the long-term efficacy of paroxetine in patients aged 70 years and older is warranted by these data. In addition, we have recently reported that long-term response to maintenance pharmacotherapy with nortriptyline in those older than 70 years leaves much room for improvement and that combined treatment with medication and interpersonal psychotherapy may be the optimal clinical strategy for relapse prevention.[1,26] Hence, we believe that controlled evaluation of paroxetine combined with IPT-M is also needed in these patients.

Drug names: nortriptyline (Pamelor and others), paroxetine (Paxil).

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