

ORIGINAL ARTICLE

Maintenance Treatment of Major Depression in Old Age

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ABSTRACT

BACKGROUND

Elderly patients with major depression, including those having a first episode, are at high risk for recurrence of depression, disability, and death.

METHODS

We tested the efficacy of maintenance paroxetine and monthly interpersonal psychotherapy in patients 70 years of age or older who had depression (55 percent of whom were having a first episode) in a 2-by-2, randomized, double-blind, placebo-controlled trial. Among patients with a response to treatment with paroxetine and psychotherapy, 116 were randomly assigned to one of four maintenance-treatment programs (either paroxetine or placebo combined with either monthly psychotherapy or clinical-management sessions) for two years or until the recurrence of major depression. Clinical-management sessions, conducted by the same nurses, social workers, and psychologists who provided psychotherapy, involved discussion of symptoms.

RESULTS

Major depression recurred within two years in 35 percent of the patients receiving paroxetine and psychotherapy, 37 percent of those receiving paroxetine and clinical-management sessions, 68 percent of those receiving placebo and psychotherapy, and 58 percent of those receiving placebo and clinical-management sessions ($P=0.02$). After adjustment for the effect of psychotherapy, the relative risk of recurrence among those receiving placebo was 2.4 times (95 percent confidence interval, 1.4 to 4.2) that among those receiving paroxetine. The number of patients needed to be treated with paroxetine to prevent one recurrence was 4 (95 percent confidence interval, 2.3 to 10.9). Patients with fewer and less severe coexisting medical conditions (such as hypertension or cardiac disease) received greater benefit from paroxetine ($P=0.03$ for the interaction between treatment with paroxetine and baseline severity of medical illness).

CONCLUSIONS

Patients 70 years of age or older with major depression who had a response to initial treatment with paroxetine and psychotherapy were less likely to have recurrent depression if they received two years of maintenance therapy with paroxetine. Monthly maintenance psychotherapy did not prevent recurrent depression. (ClinicalTrials.gov number, NCT00178100.)

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N Engl J Med 2006;354:1130-8.
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DEPRESSION HAS A STRONG TENDENCY to recur in elderly persons, with rates of recurrence of 50 to 90 percent over a period of two to three years¹; hence, the goal of treatment is not only recovery but also the prevention of recurrence.² Finding practical and affordable depression-management strategies that prevent recurrence is of great importance.³⁻⁶

There are few data from controlled studies on the efficacy of maintenance antidepressant medication or depression-specific psychotherapy in patients 70 years of age or older. We have reported that maintenance nortriptyline, monthly interpersonal psychotherapy, and the two in combination⁷ are superior to placebo plus clinical-management sessions in preventing recurrences among patients 59 years of age or older who have had multiple episodes.⁸ Selective serotonin-reuptake inhibitors (SSRIs) have now become the first-line treatment for depression in the elderly because of their favorable side-effect profiles and low risk of complications after an overdose.⁹ However, there is little information about the long-term efficacy of SSRIs or psychotherapy in the elderly, and the available data are conflicting.^{10,11} There is also no consensus about whether long-term maintenance pharmacotherapy is appropriate after a first episode of depression; most experts support the use of only 6 to 12 months of continued treatment for patients who have a first episode of depression in old age.⁹

We assessed whether long-term antidepressant treatment would affect the recurrence of depression specifically in people 70 years of age or older, the majority of whom were having a first episode of depression, since this population is at high risk for recurrence, cognitive impairment, intercurrent medical illness, and suicide.²

METHODS

The study setting was a university-based clinic for the treatment of depression in elderly patients. The study was conducted after approval from the university's institutional review board. Between March 1, 1999, and February 28, 2003, we recruited 210 patients, 195 of whom started short-term treatment (Table 1). The patients were at least 70 years of age; met the criteria of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV),¹² for current major depression (nonpsychotic and

nonbipolar), as determined according to the Structured Clinical Interview for DSM-IV Axis I Disorders, version 2.0¹³; and had a score of at least 15 on the 17-item Hamilton Rating Scale for Depression¹⁴ (scores can range from 0 to 52, with higher scores indicating more severe depression) and at least 17 on the Folstein Mini-Mental State Examination¹⁵ (scores can range from 0 to 30, with higher scores indicating better mental status). All patients provided written informed consent.

We screened 363 patients, 153 of whom were excluded and 210 of whom agreed to participate (Fig. 1). Of the 195 who began short-term treatment, 151 (77.4 percent) had a clinical response (i.e., a Hamilton score of 0 to 10 for 3 consecutive weeks) and began 16 weeks of continued treatment, which was intended to stabilize and further improve the clinical response. Of these 151 patients, 116 (76.8 percent) remained well and were randomly assigned to a two-year maintenance-treatment program.

During short-term treatment, 10 of 195 patients (5.1 percent) were withdrawn from the trial: 3 because of hyponatremia, 2 because of rash, and 1 each because of nausea, orthostasis, unsteady gait, confusion, and paresthesias. During continued treatment, 5 of 151 patients (3.3 percent) were withdrawn from the trial: 2 because of sexual dysfunction, 1 because of tremors, and 2 because of gastrointestinal symptoms. Two patients, both with preexisting cardiac disease, died after myocardial infarction (one each during short-term and continued treatment). No patient committed suicide.

The patients received open treatment with paroxetine and weekly psychotherapy; the dose of paroxetine was initially 10 mg per day and was titrated over an eight-week period to a maximum of 40 mg per day. After having a response, the patients began 16 weeks of open continued treatment consisting of paroxetine and psychotherapy, with paroxetine continued at the same dose but with the frequency of psychotherapy decreasing to once every 2 weeks. As detailed elsewhere,^{16,17} 69 patients received augmented pharmacotherapy with bupropion, nortriptyline, or lithium. If successful, augmented pharmacotherapy was continued for the remainder of a patient's participation unless he or she was randomly assigned to placebo during maintenance therapy. Thirty-eight of the 69 patients receiving augmented pharmacotherapy participated in the maintenance phase

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Patients Starting Short-Term Treatment (N=195)	Patients Starting Maintenance Treatment (N=116)†			
		Paroxetine + Psychotherapy (N=28)	Paroxetine + Clinical Management (N=35)	Placebo + Psychotherapy (N=35)	Placebo + Clinical Management (N=18)
Demographic characteristic					
Age at entry (yr)	77.1±5.6	77.6±7.0	77.0±5.9	77.4±5.0	74.8±4.4
Female sex (%)	66	68	60	71	56
White race (%)‡	91	93	91	94	94
Married (%)	41	50	40	49	39
Yr of education	12.9±2.9	13.3±3.7	12.9±2.5	12.4±2.9	13.3±2.4
Clinical characteristic					
Recurrent episode (%)	45	43	40	40	39
Age at onset of major depression (yr)	63.0±18.7	66.4±19.6	63.7±18.1	62.0±20.1	61.2±19.4
Median duration of current episode (wk)	39	57	26	36	43
Hamilton Rating Scale for Depression score§					
At baseline	20.5±3.6	20.6±4.2	19.5±2.7	20.3±3.3	19.8±2.4
At randomization		6.0±2.9	4.9±2.7	5.5±2.7	5.8±2.2
Cumulative Illness Rating Scale score¶	10.0±4.1	10.5±4.1	9.5±4.6	9.7±3.8	8.6±3.7
Folstein Mini-Mental State Examination score	27.8±2.5**	27.7±3.1	27.5±2.5	28.0±2.4	28.7±1.1
Mattis Dementia Rating Scale††					
Score	131.5±10.0**	131.3±14.0	130.7±9.6	131.7±9.1	134.4±8.1
Scaled score	8.5±3.2				
Brief Symptom Inventory Anxiety subscale score‡‡	1.16±0.86§§	1.13±1.02	1.12±0.89	1.13±0.81	0.82±0.67
Pittsburgh Sleep Quality Index score¶¶	10.5±4.1	11.9±4.5	10.0±3.8	10.1±4.1	10.5±4.5

* Plus-minus values are means ±SD.

† There are no significant differences between groups.

‡ Race was self-reported by the patients.

§ Scores for the 17-item Hamilton Rating Scale for Depression range from 0 to 52, with higher scores indicating more severe depression.

¶ Scores for the Cumulative Illness Rating Scale for Geriatrics range from 0 to 52, with higher scores indicating worse health status.

|| Scores for the Folstein Mini-Mental State Examination range from 0 to 30, with higher scores indicating better mental status.

** The value is based on 193 patients.

†† Scores for the Mattis Dementia Rating Scale range from 0 to 144, with higher scores indicating better cognitive function.

‡‡ Scores for the Brief Symptom Inventory Anxiety subscale range from 0 to 3, with higher scores indicating worse condition.

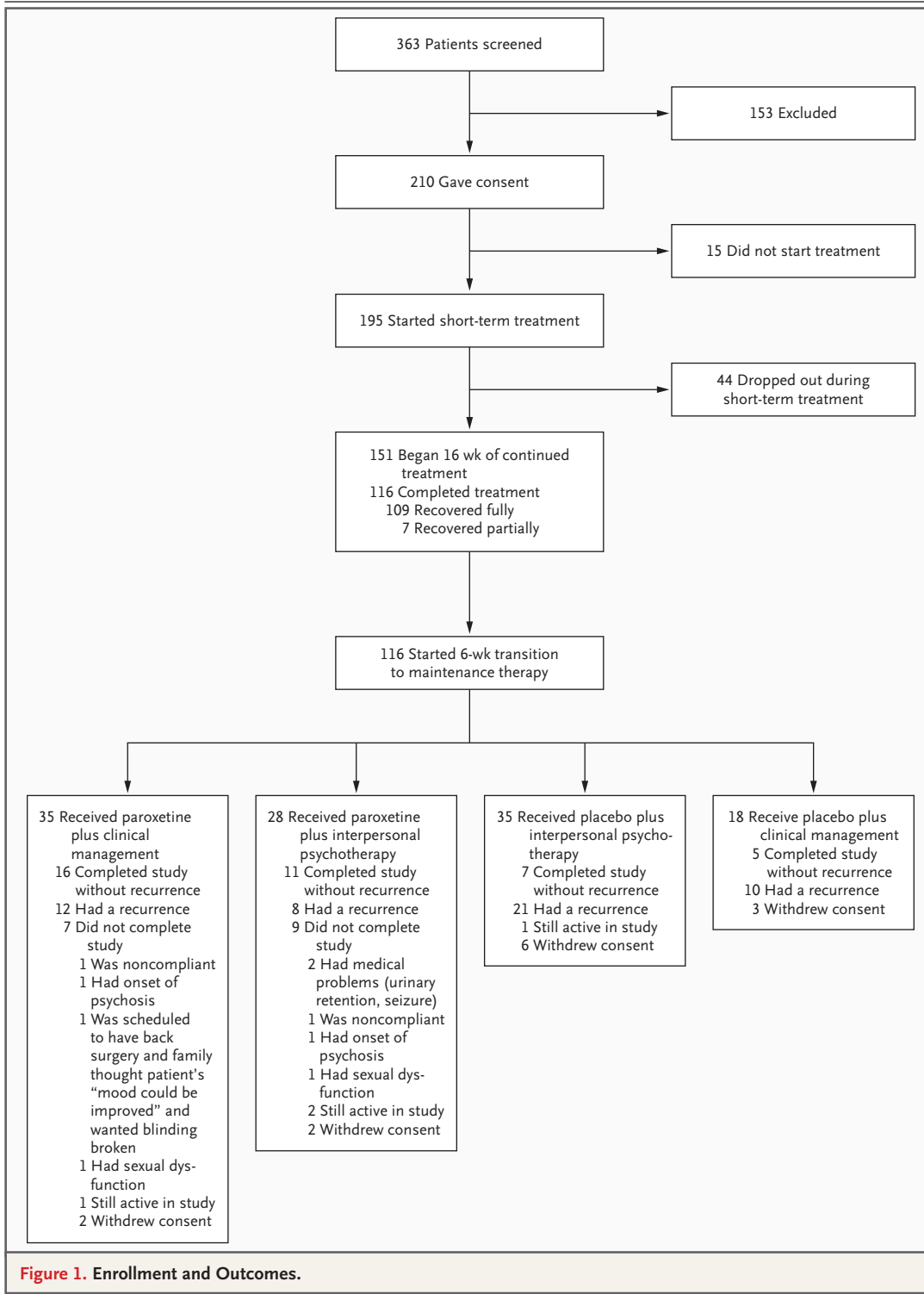
§§ The value is based on 179 patients.

¶¶ Scores for the Pittsburgh Sleep Quality Index range from 0 to 21, with higher scores indicating a poorer quality of sleep.

of the study, with 19 randomly assigned to paroxetine and 19 to placebo.

Patients who made a full or a partial recovery were randomly assigned to one of four maintenance treatments: paroxetine plus monthly clinical-management sessions, placebo plus monthly clinical-management sessions, paroxetine plus monthly psychotherapy, and placebo plus monthly psychotherapy. The paroxetine, placebo, and aug-

mented-pharmacotherapy tablets were identical in size, weight, and appearance. For patients assigned to maintenance placebo, the paroxetine dose was slowly tapered (together with the dose of any augmented pharmacotherapy) over a period of six weeks under double-blind conditions until discontinuation of the medication. The patients continued to receive maintenance therapy for two years or until recurrence of major depres-



sion. At the time of data analysis, four patients were still receiving maintenance therapy and had not yet completed two years of therapy; data from these patients were treated as censored observations.

The randomization schedule was generated by a project statistician at the beginning of the trial. Randomization was stratified according to the number of episodes (single vs. multiple), use of augmented pharmacotherapy, and level of cogni-

tive impairment (a score of more than 130 vs. a score of 130 or less on the Mattis Dementia Rating Scale [scores can range from 0 to 144, with higher scores indicating better cognitive function]). Randomization was blocked to adjust cell sizes over the study period. The treatment team and outcome assessors were unaware of the patients' treatment assignments, and only the research pharmacist and the open-monitoring committee knew which patients were assigned to paroxetine and which to placebo.

The patients were seen monthly by the same clinician (a nurse, social worker, or psychologist) who had treated them during short-term and continued treatment. Patients assigned to clinical management were seen for 30-minute visits; they received no specific psychotherapy but were asked about symptoms and any possible adverse effects. The same clinicians conducted clinical-management sessions and psychotherapy. At each visit, orthostatic blood pressure and pulse were measured, body weight was recorded, and clinical ratings were performed with the use of the Hamilton Rating Scale for Depression.¹⁷ Patients assigned to monthly psychotherapy were seen for 45-minute sessions. In order to ensure fidelity to manual-based treatment-delivery procedures, all clinical-management and psychotherapy sessions were audiotaped so that elements specific to interpersonal psychotherapy and to medical management could be rated in a blinded fashion.¹⁸ The clinicians encouraged and monitored adherence by education of patients and family members, pill counts, and reminders at each clinic visit.

Recurrence of a major depressive episode, as defined by DSM-IV criteria and a Hamilton score of at least 15, was determined by administration of the Structured Clinical Interview for DSM-IV Axis I Disorders, version 2.0,¹³ and independently confirmed clinically by a geriatric psychiatrist. Assessment of possible recurrence was performed as needed at any point during maintenance treatment. Both assessors were unaware of patients' treatment assignments. GlaxoSmithKline provided paroxetine tablets for use in this research study but had no other role in study design, data accrual, or data analysis.

STATISTICAL ANALYSIS

We estimated that the enrollment of 33 patients per active-treatment group and 20 patients in the placebo group (total, 119) would provide the study

with a statistical power of at least 80 percent ($\alpha=0.05$) to detect a difference in recurrence rates of 60 percent between combined therapy and placebo and of 30 percent between each monotherapy and placebo. We assigned fewer patients to the placebo group because we hypothesized that the recurrence rate would be higher among patients receiving placebo and we wanted to maximize the number of observations in the active-treatment groups to test for pairwise differences in recurrence rates.

Our study hypothesis was that the four groups would differ from one another, and that the specific pattern of group differences would demonstrate the superiority of combined treatment (paroxetine plus interpersonal therapy) over each of the other three treatments and of either monotherapy over placebo plus clinical management. First, we used Kaplan–Meier survival analysis with log-rank chi-square statistics to test for overall differences in recurrence rates among the four maintenance treatments. We examined the survival curves stratified according to the number of episodes of major depression, level of cognitive impairment, and use of augmented pharmacotherapy. Second, to perform hypothesized pairwise contrasts, we used Cox proportional-hazards models with three dummy variables representing the four treatment groups. The Cox models tested for the effects of clinically relevant covariates on recurrence: the number and severity of concomitant medical illnesses (the “chronic medical burden”), as defined by scores for the Cumulative Illness Rating Scale for Geriatrics (CIRS-G)¹⁹ (range, 0 to 52, with higher scores indicating worse health status); anxiety, as defined by scores for the Brief Symptom Inventory Anxiety subscale²⁰ (range, 0 to 3, with higher scores indicating worse condition); cognitive impairment, as defined by scores for the Mattis Dementia Rating Scale²¹; and subjective sleep quality, as defined by scores for the Pittsburgh Sleep Quality Index²² (range, 0 to 21, with higher scores indicating a poorer quality of sleep). We also used Cox models to test for moderation of maintenance-treatment effects on recurrence, as evidenced by interaction of treatment with each clinical covariate.

RESULTS

The four maintenance groups had similar demographic and clinical characteristics (Table 1). The

time from randomization to recurrence of depression (Fig. 2) differed among the four groups ($P=0.02$). The actuarial recurrence rates (after adjustment for censoring) were 35 percent among patients receiving paroxetine plus psychotherapy, 37 percent among those receiving paroxetine plus clinical-management sessions, 68 percent among those receiving placebo plus psychotherapy, and 58 percent among those receiving placebo plus clinical-management sessions. The Cochran–Mantel–Haenszel statistic for recurrence across the four groups stratified according to the receipt of augmented pharmacotherapy was also significant ($P=0.03$). The recurrence rates were higher among those who had received augmented pharmacotherapy (74 percent) than among those who had not (29 percent, $P<0.001$).

A sensitivity analysis treating the four patients who had not yet completed two years of treatment at the time of the data analysis as having either completed the study without recurrence or as having had a recurrence of depression at the time of censoring yielded similar results to those shown in Figure 2 ($P=0.02$ and $P=0.04$, respectively).

Testing of hypothesized pairwise contrasts indicated that paroxetine plus psychotherapy was superior to placebo plus psychotherapy ($P=0.03$) and to placebo plus clinical management ($P=0.05$) in preventing recurrence. Similarly, paroxetine plus clinical management (without psychotherapy) was significantly more effective than placebo plus psychotherapy ($P=0.03$) and marginally more effective than placebo plus clinical management ($P=0.06$).

When recurrence outcomes among patients treated with paroxetine were compared with those among patients receiving placebo, after adjustment for psychotherapy status, the number of patients who needed to be treated with paroxetine to prevent one recurrence was 4 (95 percent confidence interval, 2.3 to 10.9). The relative risk of recurrence among patients receiving placebo was 2.4, as compared with those receiving paroxetine (95 percent confidence interval, 1.4 to 4.2).

In the subgroup of 69 patients enrolled during their first episode of depression, the recurrence rate among those receiving paroxetine (with or without psychotherapy) was 27 percent, as compared with 56 percent among those receiving placebo (with or without psychotherapy) ($P=0.003$). The recurrence rate among the 47 patients enrolled during a second or later episode of depression was

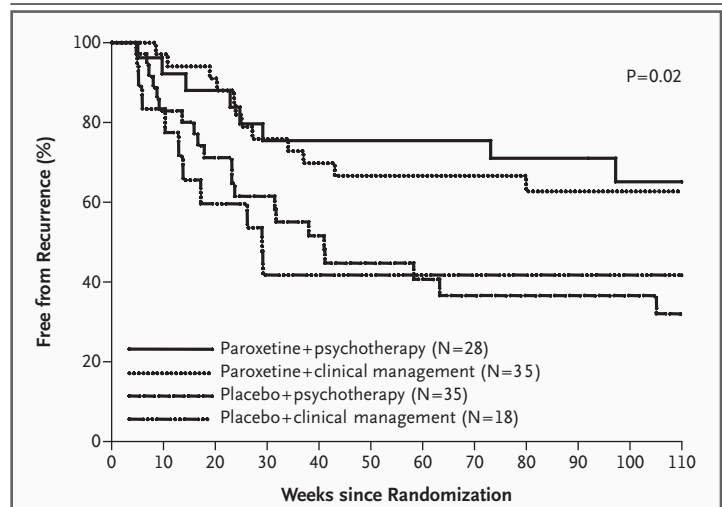


Figure 2. Time from Randomization to Recurrence.

The relative risk of recurrence among patients receiving placebo was 2.4 times that among patients receiving paroxetine ($P=0.02$; chi-square statistic=9.77 with 2 df). No effect of maintenance psychotherapy on recurrence was detected. Kaplan–Meier survival analysis with log-rank chi-square statistics was used to test for overall differences in recurrence rates among the groups. P values were based on the log-rank chi-square test.

38 percent among those receiving paroxetine (with or without psychotherapy), as compared with 62 percent among those receiving placebo (with or without psychotherapy); the difference between the rates was not significant ($P=0.22$).

In Cox models, more severe anxiety ($P=0.04$), more numerous and more severe concomitant medical illnesses ($P=0.02$), and poorer sleep quality ($P=0.001$) all predicted a shorter period without depression. A significant interaction between the medical burden (as measured by the CIRS-G score) and drug assignment ($P=0.03$) indicated a moderating effect of the number and severity of coexisting medical illnesses on the long-term outcome. The hazard ratio for the interaction between drug assignment and CIRS-G score was 1.17 (95 percent confidence interval, 1.02 to 1.35), a value consistent with the presence of a small effect. (No moderation effect was found for cognition, anxiety, or sleep.) To illustrate the interaction of the number and severity of concomitant medical illnesses with pharmacotherapy, we dichotomized the CIRS-G scores at a mean value of 10 (Fig. 3); the results showed that patients with fewer and less severe concomitant medical illnesses fared better during paroxetine maintenance therapy than those with more

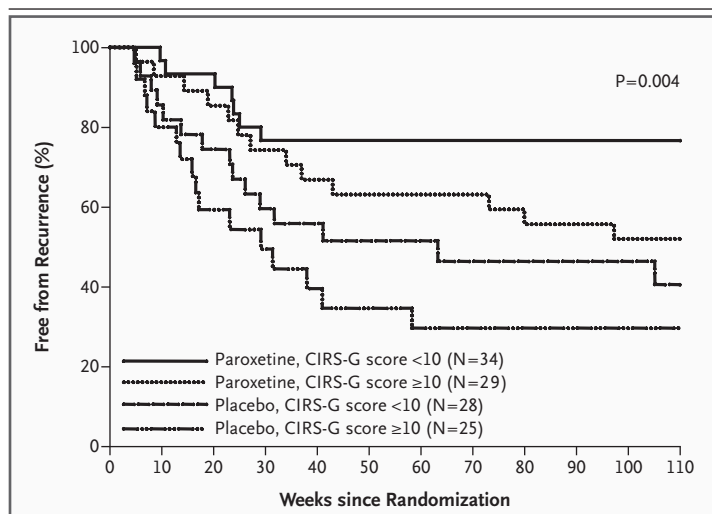


Figure 3. Effect of the Number and Severity of Concomitant Medical Illnesses on the Efficacy of Maintenance Therapy with Paroxetine.

Patients with a greater number of and more severe concomitant medical illnesses, as indicated by scores of 10 or more on the Cumulative Illness Rating Scale for Geriatrics (CIRS-G), had higher rates of recurrent depression and did not fare as well during treatment with paroxetine as those with fewer and less severe concomitant medical illnesses. Although both paroxetine use and the score on the CIRS-G affected risk (main or direct effect, $P=0.004$), paroxetine was more effective in preventing recurrence in patients with fewer and less severe concomitant medical illnesses (interaction effect, $P=0.03$). Kaplan–Meier survival analysis with log-rank chi-square statistics was used to test for overall differences in recurrence rates among the groups. P values were based on the log-rank chi-square test.

numerous and more severe concomitant medical illnesses.

DISCUSSION

Our data provide support for the use of maintenance SSRI pharmacotherapy, but not interpersonal psychotherapy, to prevent recurrent depression in people 70 years of age or older, including those with a first episode of depression. To date, there has been no consensus about the appropriateness of long-term maintenance treatment for a first episode of depression in elderly patients, with most experts calling for only 6 to 12 months of continued treatment.⁹

We identified 10 published double-blind, placebo-controlled, maintenance trials of SSRIs and other nontricyclic antidepressants in adult patients,^{23–32} but only 2 studies among patients 65 years of age or older.^{10,11} All 10 studies in adults had positive findings, but the results of studies in elderly patients were mixed. Klysner et al.¹⁰ demonstrated the maintenance efficacy of citalopram,

whereas Wilson et al.¹¹ failed to find a difference between sertraline and placebo. In the study by Klysner et al., 85 percent of 121 participants (mean age, 74 to 75 years) were having their first episode of major depression. Among the 60 patients randomly assigned to citalopram, 19 (32 percent) had a recurrence during the 48-week maintenance-treatment period, as compared with 41 of the 61 patients receiving placebo (67 percent). Our data from patients receiving paroxetine replicate these findings and extend them to patients receiving two years of maintenance treatment, thereby adding substantially to the body of knowledge regarding long-term treatment strategies in elderly depressed people, especially those with a single episode of major depression. To place our observation within a broader medical context, the number of patients needed to be treated with paroxetine for two years to prevent a recurrence of depression is 4; in comparison, four large trials³³ of statins, which are widely used for the prevention of a second myocardial infarction, found that the number of patients needed to be treated with statins for five years to prevent another myocardial infarction was 21.

Our results are also noteworthy because few data from controlled studies provide support for the short-term efficacy of SSRIs in late-life depression. Only two published randomized, controlled trials of any SSRI in older adults, both of which used fluoxetine, are included in the Cochrane Database of Systematic Reviews (most recent update, February 25, 2005).³⁴ For short-term treatment, the pooled results give a number needed to treat of 8.5. In a large, eight-week, placebo-controlled trial of sertraline in the elderly, the adjusted mean difference between groups in scores on the Hamilton Rating Scale for Depression was only 1.5 points at the end of the study.³⁵ The only other published study of short-term SSRI treatment, a multisite, placebo-controlled trial of citalopram,³⁶ failed to demonstrate short-term efficacy in patients 75 years of age or older. In contrast to studies of short-term efficacy, our study supports the efficacy of maintenance therapy with SSRIs in preventing a recurrence of depression among people with first episodes in later life who have apparently benefited from initial SSRI treatment and interpersonal psychotherapy.

Contrary to our hypothesis, the current data failed to provide support for the efficacy of maintenance psychotherapy, despite the fact that we

had sufficient power to detect a clinically significant effect. The failure to demonstrate the efficacy of psychotherapy in the prevention of recurrence among patients 70 years of age or older could reflect differences between the patients in the current study and those in our earlier study,⁸ since the psychotherapists who treated the patients were largely the same in both studies. The patients in the current study were, on average, 10 years older than those in the previous study (77 vs. 67 years) and had more cognitive impairment and coexisting medical illnesses. The results stand in contrast to those of previous studies that have demonstrated moderate prophylactic effects of psychotherapy in nongeriatric adults³⁷ and in the “young” elderly (mainly 60 to 75 years of age).⁸ The patients in both previous studies had recurrent major depression, whereas the majority of patients in the current study had late-onset first episodes of depression. Late-onset depression occurs in a heterogeneous group of patients, some of whom may be in the preclinical stages of Alzheimer’s disease or vascular dementia.³⁸ Their ability to learn and to modify their behavior (executive function) may be compromised; hence, psychotherapy for such patients may need to involve caregivers more extensively. More research is needed to address this issue as well as the use of other types of psychotherapy — such as problem-solving therapy — for such patients.³⁹ Moreover, all patients in the maintenance phase of our study had received psychotherapy during short-term treatment. The recurrence rates might have been higher among patients receiving maintenance SSRI therapy who were not initially treated with psychotherapy.

Given that the number and severity of concomitant medical illnesses (especially hypertension, coronary artery disease, diabetes, hyperlipidemia, osteoarthritis, and chronic lung disease) also affected the risk of recurrence and exerted a

slight moderating effect on the response to long-term antidepressant treatment, it is clinically appropriate to link and integrate long-term disease-management strategies for both depression and other coexisting medical illnesses in elderly persons. Since most older people are treated for depression in the general medical sector, integrating and appropriately reimbursing long-term disease management for both depression and other coexisting medical disorders are important. Recent studies have demonstrated the effectiveness of strategies for short-term and continued treatment of depression in elderly patients in primary care settings.^{3,4,6} Our data indicate that such strategies should be extended to encompass long-term maintenance treatment to prevent recurrence.

In summary, we evaluated both pharmacologic and psychotherapeutic strategies for preventing recurrence of major depression in patients 70 years of age or older and demonstrated that two years of maintenance treatment with paroxetine is effective. This observation can inform long-term disease-management strategies for the treatment of elderly patients with depression in general medical settings.

Supported by grants (P30 MH52247, P30 MH071944, R37 MH43832, and R01 MH37869, to Dr. Reynolds; K24 MH65416, to Dr. Pollock; P30 MH30915, to Dr. Kupfer; K01 MH01684, to Dr. Butters; and K01 MH01613, to Dr. Mulsant) from the National Institute of Mental Health and a grant (P60 MD000207) from the National Center for Minority Health and Health Disparities. GlaxoSmithKline provided the paroxetine tablets.

Dr. Pollock reports having served as a member of the Paxil-Controlled-Release National Psychiatry Advisory Board and having received support from GlaxoSmithKline for laboratory research not connected with the research described in this article. Dr. Mulsant reports having received honoraria from GlaxoSmithKline. No other conflict of interest relevant to this article was reported.

We are indebted to the staff of the Clinical Trials Management Unit in the Advanced Center for Intervention and Services Research for Late-Life Mood Disorders for their help in recruiting, assessing, and treating patients in this study, and to Katherine Slomka, Karen Callas, and Sally Lagattuta for administrative assistance.

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