Maintenance Treatment for Old-Age Depression Preserves Health-Related Quality of Life: A Randomized, Controlled Trial of Paroxetine and Interpersonal Psychotherapy

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OBJECTIVES: To determine whether maintenance antidepressant pharmacotherapy and interpersonal psychotherapy sustain gains in health-related quality of life (HR-QOL) achieved during short-term treatment in older patients with depression.

DESIGN: After open combined treatment with paroxetine and interpersonal psychotherapy, responders were randomly assigned to a two (paroxetine vs placebo) by two (monthly interpersonal psychotherapy vs clinical management) double-blind, placebo-controlled maintenance trial. HR-QOL outcomes were assessed over 1 year.

SETTING: University-based clinic.

PATIENTS: Of the referred sample of 363 persons aged 70 and older with major depression, 210 gave consent, and 195 started acute treatment; 116 met criteria for recovery, entered maintenance treatment, and were included in this analysis.

INTERVENTIONS: Paroxetine; monthly manual-based interpersonal psychotherapy.

MEASUREMENTS: Overall HR-QOL as measured using the Quality of Well-Being Scale (QWB) and six specific HR-QOL domains derived from the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) subscales.

RESULTS: All domains of HR-QOL except physical functioning improved with successful acute and continuation treatment. After controlling for any effects of psychotherapy, pharmacotherapy was superior to placebo in preserving overall well-being ($P = .04$, effect size (r) = 0.23), social functioning ($P = .02$, $r = 0.27$), and role limitations due to emotional problems ($P = .007$, $r = 0.30$). Interpersonal psychotherapy (controlling for the effects of pharmacotherapy) did not preserve HR-QOL better than supportive clinical management.

CONCLUSION: Maintenance antidepressant pharmacotherapy is superior to placebo in preserving improvements in overall well-being achieved with treatment response in late-life depression. No such benefit was seen with interpersonal psychotherapy. **J Am Geriatr Soc 55:1325–1332, 2007.**

Key words: depressive disorder; aged; quality of life; antidepressive agents; psychotherapy

Depression is one of the major causes of decline in the health-related quality of life (HR-QOL) of elderly persons.[1,2] Because HR-QOL matters to patients and families and is a crucial outcome of depression treatment beyond improvement in symptomatic status, clinicians need to know whether treatment improves and maintains it.

To the authors' knowledge, only two randomized, controlled trials have examined the long-term effect of treatment on various domains of HR-QOL. In the Maintenance Therapies in Late-Life Depression (MTLD)-I study, it was found that patients receiving combined nortriptyline and interpersonal therapy reported better maintenance of social functioning than patients receiving monotherapy.[3] In the Improving Mood—Promoting Access to Collaborative Treatment (IMPACT) trial, primary care patients assigned to the multicomponent intervention (care management, education, antidepressant management, brief problem-solving psychotherapy) reported better overall quality of life and physical functioning at 1[4,5] and 2 years[6] than those in usual care.

Nevertheless, it is not clear whether the improvements in overall HR-QOL seen in the IMPACT trial were are due to pharmacotherapy, psychotherapy, or better use of medical services. For example, does the most common inter-

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vention in late-life depression, long-term selective serotonin reuptake inhibitor (SSRI) treatment, improve HR-QOL? To the authors' knowledge, no randomized, controlled trial has demonstrated the superiority of SSRI over placebo in maintaining HR-QOL in older persons suffering from depression. Here, findings from the double-blind, randomized, placebo-controlled maintenance treatment phase of a study (MTLD-II) of paroxetine and interpersonal psychotherapy in patients aged 70 and older seeking treatment for major depression are presented.[7] It has recently been reported that patients who recovered from an episode of depression with paroxetine and interpersonal therapy were less likely to experience a recurrence of depression if they received 2 years of maintenance treatment with paroxetine. No such benefit was evident for monthly psychotherapy.[7] The present analysis examined the long-term effects of treatment on quality of life, hypothesizing that paroxetine would be superior to placebo and interpersonal psychotherapy would be superior to clinical management, controlling for the effects of the other treatment.

METHODS

The MTLD-II study was conducted at a university-based clinic for the treatment of major depression in old age. Between March 1, 1999, and February 28, 2003, patients aged 70 and older with current, nonpsychotic, major depression, recurrent or single episode, diagnosed using the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* Axis I Disorders[8,9] (SCID/DSM-IV) were recruited. Participants were required to have a score of 15 or higher on the 17-item Hamilton Rating Scale for Depression (HRSD-17)[10] and a score of at least 17 on the Folstein Mini-Mental State Examination (MMSE).[11] All participants provided written informed consent. The University of Pittsburgh institutional review board approved the study.

Interventions, Randomization, and Participant Flow

Figure 1 presents the participant flow; 195 participants received open acute treatment with paroxetine and weekly interpersonal psychotherapy. Sixty-four of them were self-referred from the community (through media and word of mouth), and 41 were referred from mental health settings, 32 from other studies, 30 from community and university primary care settings, 20 from the university psychiatric hospital, and eight from Veterans Affairs clinics. Response was defined as a score of 10 or less on the HRSD-17 for 3 consecutive weeks. The 151 responders then received 16 weeks of open continuation treatment with paroxetine (10–40 mg/d) and interpersonal psychotherapy every other week aimed at preventing relapse (reemergence of depressive symptoms during the same episode).[12] Of these, 116 patients did not relapse during open continuation treatment, entered the double-blind placebo-controlled maintenance phase, and constituted the group used for this analysis. Maintenance treatment was designed to prevent recurrence or emergence of new episodes of major depression.[12] As described elsewhere,[13] 69 patients required the addition of nortriptyline, bupropion, or lithium to achieve response; of these, 19 were later randomly assigned to paroxetine with a second agent and 19 to placebo without a second agent.

A project statistician generated the randomization schedule at the beginning of the trial. Randomization was stratified according to number of depressive episodes (single vs multiple), need for second agent, and cognitive impairment (scores of $\leq$130 vs $>$130 on the Dementia Rating Scale (DRS))[14]; randomization was blocked to adjust cell sizes over the study period. One hundred sixteen patients were randomly assigned to clinical management plus paroxetine (n = 35), clinical management plus placebo (n = 18), monthly interpersonal psychotherapy plus paroxetine (n = 28), or monthly interpersonal psychotherapy plus placebo (n = 35). Only the research pharmacist and the open-monitoring committee (but not the treatment team or outcome assessors) knew which patients were assigned to paroxetine or placebo. Placebo and paroxetine tablets were identical in size, weight, and appearance. Augmentation medications, when used, were similarly blinded. Paroxetine along with any augmentation pharmacotherapy was tapered over 6 weeks under double-blind conditions and discontinued in patients assigned to maintenance placebo. The same clinician (nurse, social worker, or psychologist) who had treated patients during their acute and continuation treatment continued to see them monthly. Clinical management consisted of monthly 30-minute sessions that included questions about symptoms and any possible adverse effects but no specific psychotherapy. Monthly psychotherapy sessions were 45 minutes long. All clinical management and psychotherapy sessions were videotaped for blind rating of elements specific to interpersonal psychotherapy and to clinical management to ensure fidelity with manual-based treatment-delivery procedures. Clinicians ensured adherence through educating patients and family members, pill counts, and reminders at each clinic visit. Maintenance treatment lasted 2 years or until recurrence of a major depressive episode, whichever occurred first. Because only 54 of 116 participants remained in the study in the second year, the analyses were focused on first-year data.

Outcome Measures

Self-rated measures of HR-QOL, the Quality of Well-Being Scale (QWB)[18] and the 36-item Medical Outcomes Study Short-Form-Health Survey (SF-36),[19] were administered at study entry, at randomization, at the end of the first year of long-term treatment, and at the point of recurrence or exit from the study. The QWB is a preference-weighted measure that combines mobility, physical, and social subscales to provide a single index of desirability of health conditions on the continuum between death (0.00) and optimum health (1.00). Six subscales of the SF-36 were also examined: physical functioning; social functioning; role limitations due to physical problems (role limitations—physical); role limitations due to emotional problems (role limitations—emotional); vitality, energy, or fatigue (vitality); and general health perceptions. SF-36 subscales generate scores from 0 (worst possible impairment) to 100 (no impairment). The mental health subscale from this analysis was excluded because of its collinearity with the HRSD-17, and the bodily pain subscale was excluded because of its poorer convergent validity than that of other pain measures.[20,21] Collinearity between the HRSD-17, on one

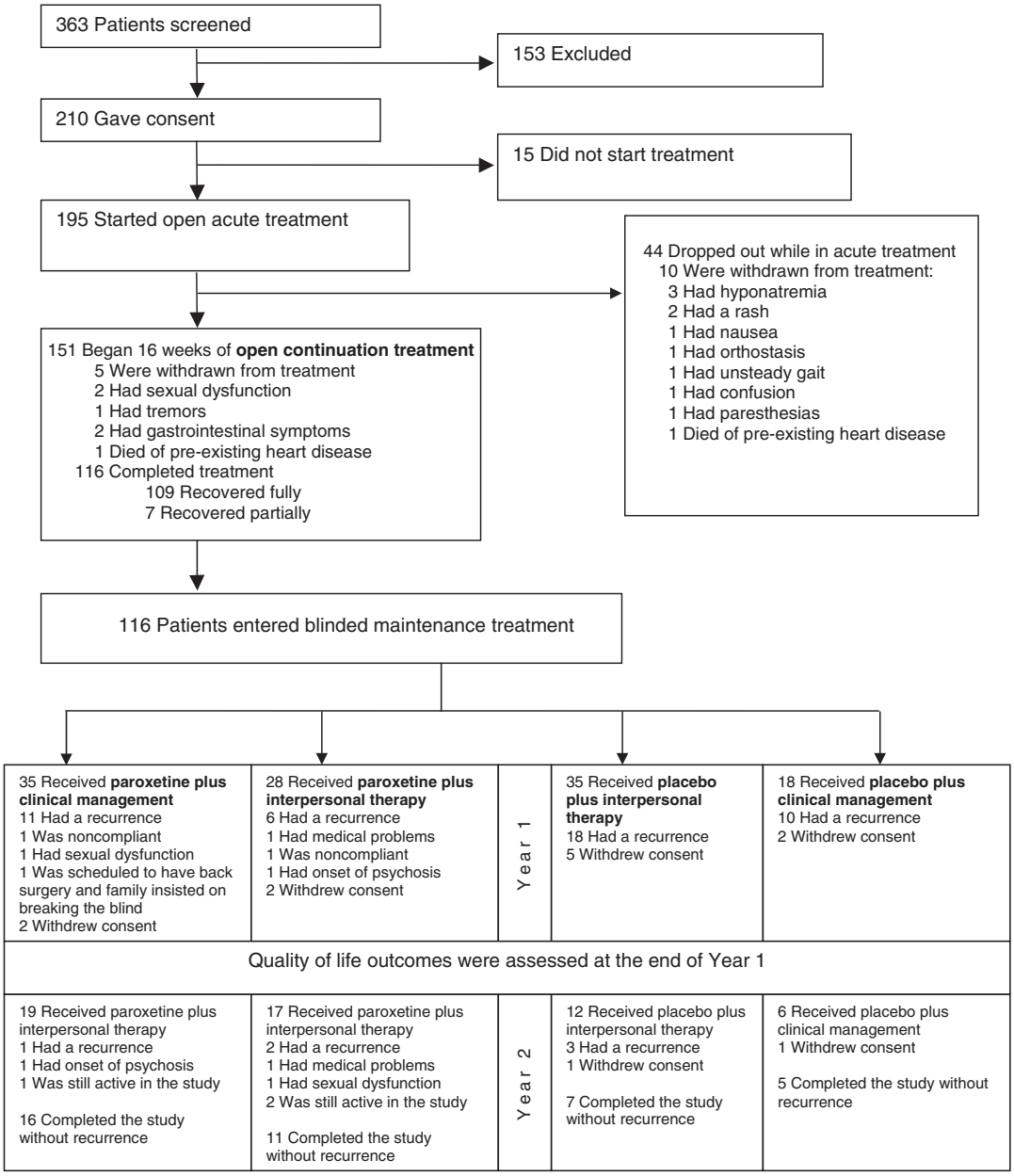

Figure 1. Recruitment and outcomes. *Reprinted with modifications from Reynolds[7].

hand, and the QWB and other SF-36 subscales, on the other hand, did not represent a problem in the sample; Pearson correlation coefficients at baseline ranged from −0.17 (QWB and HRSD-17) to −0.39 (SF-36 role limitations—physical and HRSD-17). In the presence of significant cognitive impairment (DRS <120), HR-QOL was assessed with the help of an informant, when available. Interrater reliability for the HRSD-17 among our assessors was excellent. (Intraclass correlation coefficients ranged from 0.87 to 0.96.) The HRSD-17 has been shown to possess consistent discriminant validity in diagnosing major depression, with sensitivity of 0.70 to 0.88 and specificity of 0.99[15,16] at the cutoff score of 15 used in the current study.

Recurrence of a major depressive episode was defined according to SCID/DSM-IV[8,9] criteria and a HRSD-17 score of greater than 15 on a structured interview with a clinician. An interview with a geriatric psychiatrist was required to provide independent confirmation of the diagnosis. Both were blind to treatment assignment.

Statistical Analyses

For the analyses reported here, data from the 116 participants who were randomly assigned to maintenance treatment were considered (Figure 1). During acute and continuation treatment (baseline to randomization), there were 114 observations; one observation was missing because of cognitive impairment (no informant available) and one because of the clinical status of the patient. At the last observation during the first year of maintenance treatment,

13 data points were missing because of missing items, eight because of early recurrence (patients did not complete self-report forms), five because of participants withdrawing consent (a total of 32), five because of cognitive impairment (no informant available), and one because of physical condition of the patient. Of 32 missing data points, eight were in pharmacotherapy/clinical management, five in placebo/clinical management, 10 in monthly interpersonal psychotherapy/pharmacotherapy, and nine in monthly interpersonal psychotherapy/placebo group. The missing data pattern was further explored to ensure that it did not violate the ignorable missingness assumption of the statistical model.[17] The proportion of missing values at the last observation was not higher in patients with recurrence of depression (19%) than in the whole sample (28%). Missing items were not related to other reasons such as recurrence or cognitive impairment. Thus, it was concluded that the nature of missingness was compatible with model assumptions.[17,22]

SAS version 8 (SAS Institute, Inc., Cary, NC) was used. To assess change during the course of successful acute and continuation treatment, QWB and SF-36 subscale scores were examined at baseline and at randomization with a paired *t*-test. The time between these two assessments averaged 29.7 ± 11.2 weeks. The hypothesis that patients assigned to pharmacotherapy would better maintain their QWB and SF-36 subscale scores, whereas scores of those receiving placebo would worsen over time was then tested. Scores were obtained at two time points: randomization and the end of year 1, termination, or recurrence, whichever came first. Planned-contrast analysis[23] within a repeated-measures mixed-effects model was used. A planned-contrast approach was chosen to study group comparisons, rather than the standard main and interaction effects automatically generated in the analysis, because it provided an appropriately focused test of the specific hypothesis. The use of planned contrasts is well-grounded in statistical theory.[23] Thus, within the mixed-effects two (paroxetine vs not) by two (IPT vs not) by two (time; entry into maintenance, termination of maintenance) model, the following contrast weights were applied to each study group: 1 and 1 for the pharmacotherapy plus interpersonal psychotherapy and pharmacotherapy plus clinical management groups at maintenance entry and termination, respectively and 1 and -3 for placebo plus interpersonal psychotherapy and placebo plus clinical management groups at maintenance entry and termination, respectively. The *F* test associated with this contrast, which tests the extent to which the data supports the hypothesis, which is embodied in the contrast weights, was then computed. The effect size, *r*, associated with the *F* test was also calculated.

Using the same approach, effects of interpersonal psychotherapy were next tested separately for. Reflecting the hypothesis, contrast weights in this comparison were (1, 1) for the pharmacotherapy plus interpersonal psychotherapy and placebo plus interpersonal psychotherapy groups, respectively and $(1, -3)$ for the pharmacotherapy plus clinical management and placebo plus clinical management groups, respectively.

Finally, whether recurrence of depression during the first year would be a significant predictor of lower HR-QOL at final assessment and whether prevention of recurrence might account for the effects of treatment on HR-QOL was explored. The effect of recurrence as an intervening variable (i.e., as a potential mediator) was assessed.[24] Thus the relationship between drug assignment (independent variable) and HR-QOL was compared at the final assessment (dependent variable) before and after adjustment for recurrence using the difference in coefficients test[24] within the repeated-measures mixed-effects model. To achieve adequate statistical power for this comparison, outcomes with significant treatment effects of at least moderate size were identified.

RESULTS

Pretreatment demographic and clinical characteristics, as well as HR-QOL at randomization, did not differ between the four maintenance treatment groups (Table 1). The 116 participants receiving maintenance therapy did not differ significantly from 79 participants who did not respond to short-term treatment with respect to demographic characteristics, burden of physical illness, or the proportion of patients with recurrent depression. The difference in the pretreatment severity of depression approached statistical significance ($P = .05$) but was clinically negligible, with mean HRSD-17 scores of 20.1 and 21.2.

In responders (Figure 2), overall HR-QOL improved with open treatment. Improvements were observed in social functioning, role limitations—physical, role limitations—emotional, vitality, and general health perceptions but not in the physical functioning domain. Hence, the physical functioning subscale was not included in further analyses of long-term treatment efficacy. Ten of 195 patients who began paroxetine had side effects leading to treatment discontinuation. Two patients with preexisting cardiac disease died from myocardial infarction. In total, 116 of 195 patients recovered and entered maintenance treatment (Figure 1).

As shown in Figure 3, maintenance pharmacotherapy (adjusting for psychotherapy) was more efficacious than placebo in maintaining overall HR-QOL ($F[1,111] = 4.36$, effect size (r) $= 0.23$, $P = .04$), social functioning ($F[1,111] = 6.04$, $r = 0.27$, $P = .02$), and emotional role functioning ($F[1,111] = 7.59$, $r = 0.30$, $P = .007$). No significant effect of pharmacotherapy on physical role functioning ($F[1,111] = 0.12$, $P = .73$), vitality ($F[1,111] = 2.32$, $P = .13$), or general health perceptions ($F[1,111] = 0.15$, $P = .70$) was observed. Maintenance psychotherapy produced no differences from supportive clinical management in overall HR-QOL or any SF domain ($F < 2.43$, $P \geq .12$), controlling for the effects of pharmacotherapy.

It was verified that physical functioning did not worsen in the pharmacotherapy group (e.g., from adverse effects). Mean SF-36 physical functioning subscale scores at randomization and last observation were 59.6 and 60.4 in the pharmacotherapy group and 56.0 and 60.4 in the placebo group, showing essentially no change. By 12 months, of 63 patients, one in the pharmacotherapy group discontinued treatment because of sexual dysfunction, one because of psychosis, one because of supervening medical problems, and two because of nonadherence. Forty-five of 116 patients suffered a recurrence of their depression in the first year (Figure 1). There were no suicides during acute, continuation, or maintenance treatment.

Table 1. Demographic and Clinical Characteristics of the Patients

Characteristic	Paroxetine+Psychotherapy (n = 28)	Paroxetine+Clinical Management (n = 35)	Placebo+Psychotherapy (n = 35)	Placebo+Clinical Management (n = 18)
Demographic				
Age at entry, mean ± SD	77.6 ± 7.0	77.0 ± 5.9	77.4 ± 5.0	74.8 ± 4.4
Female, %	68	60	71	56
Caucasian, %	93	91	94	94
Married, %	50	40	49	39
Education, years, mean ± SD	13.3 ± 3.7	12.9 ± 2.5	12.4 ± 2.9	13.3 ± 2.4
Clinical				
Recurrent episode, %	43	40	40	39
Age at lifetime onset, mean ± SD	66.4 ± 19.6	63.7 ± 18.1	62.0 ± 20.1	61.2 ± 19.4
Median duration of current episode, weeks	57	26	36	43
Hamilton Rating Scale for Depression score (17-item), mean ± SD				
At baseline	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
Mini-Mental State Examination score, mean ± SD	27.7 ± 3.1	27.5 ± 2.5	28.0 ± 2.4	28.7 ± 1.1
Cumulative Illness Rating Scale score, mean ± SD	10.5 ± 4.1	9.5 ± 4.6	9.7 ± 3.8	8.6 ± 3.7
Health-related quality of life at randomization, mean ± SD				
Quality of well-being scale	0.54 ± 0.14	0.57 ± 0.13	0.53 ± 0.13	0.54 ± 0.11
Medical Outcomes Study 36-item Short-Form Survey				
Physical functioning	57.3 ± 29.5	61.5 ± 28.3	53.1 ± 27.8	61.4 ± 21.7
Social functioning	77.2 ± 19.3	75.7 ± 19.7	77.9 ± 22.6	75.7 ± 29.2
Role limitations—physical	40.2 ± 38.7	46.3 ± 39.0	44.9 ± 39.8	43.1 ± 46.0
Role limitations—emotional	45.2 ± 70.8	57.8 ± 39.6	68.6 ± 35.7	61.1 ± 40.0
Vitality	45.7 ± 21.5	56.3 ± 16.3	51.0 ± 23.7	53.3 ± 22.0
General	62.6 ± 19.5	68.2 ± 20.4	63.2 ± 20.2	65.7 ± 15.9

SD = standard deviation.

Participants who suffered a recurrence of depression during the first year reported lower HR-QOL as measured using the QWB and the role limitations—physical, role limitations—emotional, vitality, and general health perception subscales of the SF-36 ($t > 2.56$, $df = 79$, $P < .01$) than those who were depression free. Because pharmacotherapy had a moderate effect ($r = 0.30$) on emotional role functioning, the role of depressive recurrence as an intervening variable (i.e., as a potential mediator of this effect) was explored. Recurrence was a significant correlate of lower HR-QOL scores as measured using this subscale and a statistically significant intervening variable (difference in the mixed-effects model parameters: 13.25 [2.04], $t = 6.50$, $P < .001$). Thus, lower recurrence rates in the pharmacotherapy groups appeared to account for better HR-QOL outcomes.

COMMENT

This study is the first placebo-controlled maintenance trial to demonstrate that SSRI treatment preserves HR-QOL in older patients after an episode of major depression. It slowed decline in overall quality of life, as well as decline in the domains of social and emotional role functioning. It appears that lower recurrence rates in patients receiving pharmacotherapy may have been responsible for these benefits. The safety and tolerability of long-term antidepressant treatment enhanced its clinical utility in this group of older (mean age 77), medically ill, depressed people.

Meanwhile, interpersonal psychotherapy was no more effective than supportive clinical management. This is likely because of its failure to prevent recurrence of depression in the current study.[7] By contrast, interpersonal psychotherapy had previously been found to be efficacious in preventing recurrence in "young old" patients (mean age 67) who were less medically ill.[25] Physical illness, cognitive impairment, and especially disability[26] place high demands on older people's ability to cope.[27] To develop a psychological treatment with long-term efficacy in older adults, future research will need to test modified psychotherapies, taking into account factors such as cognitive impairment[28] and addressing developmental changes of late life, including increasing dependency on caregivers.

Rather than objectively measure physical, mental, or social role performance, this study assessed patients' perceptions of their quality of life. This is a unique dimension of health, which cannot be reduced to performance. Although depressive symptoms affect HR-QOL, the low correlations between HR-QOL measures and depression ratings (HRSD-17) in this study indicate that these measures are not simply a proxy for depressive symptom severity.

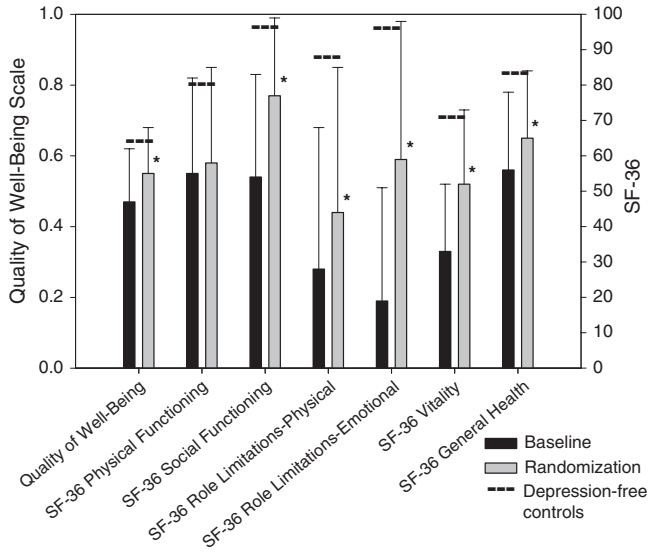

Figure 2. Improvement in health-related quality of life during short-term open treatment, N = 114. SF-36 = Medical Outcomes Study 36-item Short Form Survey. *Control data, presented here as a reference point, were derived from 24 community-dwelling depression-free older adults. Mean age ± standard deviation 76.0 ± 6.6; mean education 13.9 ± 2.2 years; ethnicity 88% (21/24) Caucasian; Cumulative Illness Rating Scale adopted for Geriatrics: 8.2 ± 3.1. Thus, although health-related quality of life HR-QOL improved in patients, it did not achieve levels reported by nondepressed controls.
*$P \leq .001$ for the difference between baseline and randomization, paired *t*-test.

Can these findings be generalized to older depressed patients in the community? With respect to demographic characteristics and degree of cognitive impairment, the patients in the current study were similar to the participants of two large trials of depression management in primary care,[29,30] including a high level of education, although the patients in the current study were predominantly (93%) Caucasian, limiting the generalizability of the findings with respect to minorities. They also suffered from more-severe depressive symptoms, reflecting the fact that the study included only patients with major depression. A more-important caveat is that, as we learn from these trials, depression care managers, use of treatment guidelines, and collaboration between generalists and psychiatrists are needed to help older patients continue taking their antidepressants and to monitor treatment response. Furthermore, the findings apply only to patients who tolerate and respond to short-term antidepressant treatment (116/195 patients in this study). Alternatively, this study included patients with severe physical illness and cognitive impairment, who are often excluded from randomized, controlled trials. The proportion of women in the sample (65%) was also representative of the higher prevalence of depression in women. This arguably enhances the clinical relevance of the findings for general medical practice.

The lack of short-term improvement in the SF-36 physical functioning domain or a benefit of maintenance pharmacotherapy for role limitations—physical and general health perception domains replicate a previous study in which protocol-based treatment with nortriptyline or interpersonal therapy was no better for improving physical well-being in nongeriatric depressed patients than usual care.[31] In contrast, the IMPACT trial of collaborative depression treatment in primary care[4] found modest differences in the physical component scores on the SF-12 (a shortened version of the SF-36) between the intervention group and treatment as usual. Overall, these results suggest that current approaches to depression treatment have at most a modest long-term effect on perceived physical well-being of older patients. Considering that hypertension, heart disease, osteoarthritis, diabetes mellitus, and chronic lung disease were prevalent in depressed patients in the current study, these findings emphasize the need for strategies to coordinate and integrate the management of these conditions with depression treatment.

Overall, the effects of pharmacotherapy on HR-QOL observed in this study range from modest (0.23) for overall quality of life and social functioning (0.27) to moderate for emotional role functioning (0.30)—the domain most directly affected by depression. These effects compare favorably with small or nonsignificant effects of secondary prevention programs in coronary heart disease,[32] angiotensin-converting enzyme inhibitors,[33] and calcium channel blockers[34] in congestive heart failure and with the effects of various antihypertensive agents.[35]

In summary, long-term antidepressant pharmacotherapy conveys a modest[36] benefit for overall quality of life of elderly patients seeking treatment for depression. No such benefit was evident for monthly interpersonal psychotherapy.

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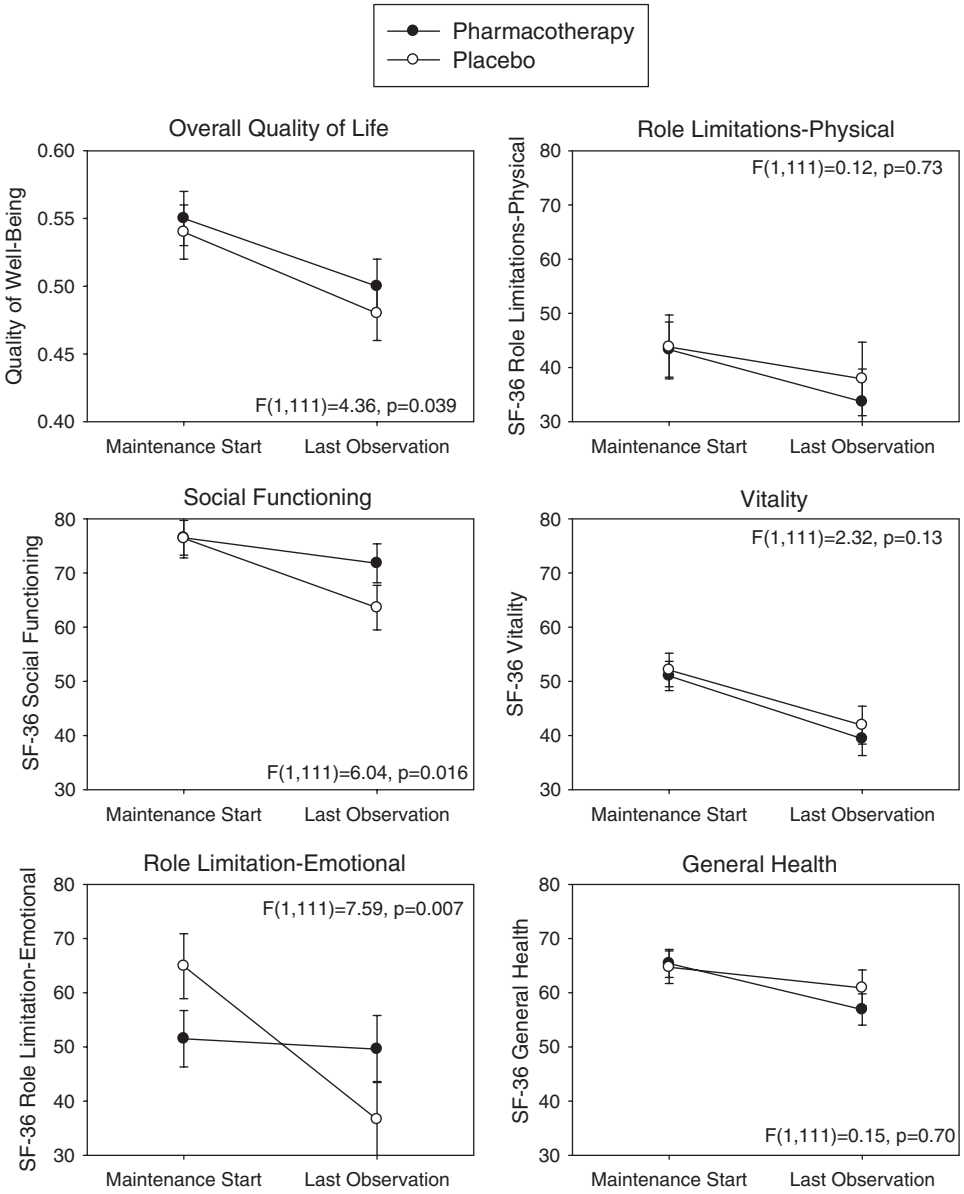

Figure 3. Health-related quality of life during 1 year of maintenance treatment. Contrast hypothesis: no decline in the pharmacotherapy groups versus linear decline in the placebo groups. Time between start of maintenance and the last observation averaged 29.7 ± 11.2 weeks. Missing data: 2/116 at start of maintenance and 32/116 at the last observation.

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