

Effect of Medical Comorbidity on Response to Fluoxetine Augmentation or Dose Increase in Outpatients With Treatment-Resistant Depression

ROY H. PERLIS, M.D., DAN V. IOSIFESCU, M.D.

JONATHAN ALPERT, M.D., PH.D., ANDREW A. NIERENBERG, M.D.

JERROLD F. ROSENBAUM, M.D., MAURIZIO FAVA, M.D.

This study assessed the effect of general medical comorbidity on response to next-step antidepressant treatments among subjects with major depressive disorder whose depression failed to respond to an 8-week open trial of 20 mg/day of fluoxetine. Of the 386 outpatients in the open trial, 101 who remained depressed were randomly assigned to double-blind treatment with either an increased dose of fluoxetine or lithium or desipramine augmentation for 4 weeks. The Cumulative Illness Rating Scale (CIRS) was used to assess baseline general medical comorbidity, and the Hamilton Depression Rating Scale was used to assess depressive symptoms. Logistic regression analysis showed that CIRS score was not associated with likelihood of remission or premature study discontinuation. Medical comorbidity thus does not appear to be associated with significantly poorer outcome among patients whose major depressive disorder failed initially to respond to an initial trial of 20 mg/day of fluoxetine. (Psychosomatics 2004; 45:224–229)

Major depressive episodes are common among patients with comorbid general medical illness.^{1,2} Longitudinal studies have suggested that medically ill depressed patients may be at greater risk for a chronic course of depression or for incomplete recovery.^{3–5} Similarly, in a previous study,⁶ the depressive symptoms of patients with higher levels of medical comorbidity were less likely to respond to open treatment with fluoxetine than were those of patients with little or no comorbidity, consistent with an earlier report of poorer outcome of tricyclic antidepressant treatment in medically ill patients.⁷

On the other hand, previous treatment trials have sug-

gested that patients with comorbid physical illness have a rate of symptom response to antidepressants that is comparable to that of patients without comorbid illness, at least among geriatric populations.^{8,9} Response rates also appear to be similar among patients with particular medical illnesses, such as cardiovascular disease,¹⁰ cancer,^{11,12} and human immunodeficiency virus infection.^{13–15}

Overall, initial antidepressant treatment fails for approximately one-third of patients.¹⁶ The effect of medical comorbidity on antidepressant efficacy in patients with treatment-resistant depression has not been investigated systematically. Other putative clinical and sociodemographic moderators of antidepressant response, such as depressive subtype¹⁷ or presence of social supports,¹⁸ have been inconsistently identified in studies of treatment-resistant depression. For example, greater depression severity has been associated with better¹⁹ as well as poorer^{20,21} outcome.

In the present investigation, we examined the moder-

Received Jan. 9, 2003; revision received Oct. 10, 2003; accepted Nov. 7, 2003. From the Depression Clinical and Research Program, Massachusetts General Hospital; and the Department of Psychiatry, Harvard Medical School, Boston. Address reprint requests to Dr. Perlis, Depression Clinical and Research Program, Massachusetts General Hospital, WACC 812, 15 Parkman St., Boston, MA 02114; rperlis@partners.org (e-mail). Copyright © 2004 The Academy of Psychosomatic Medicine

ating effect of general medical illnesses on treatment outcome in a controlled trial involving patients whose major depressive disorder failed to respond to an 8-week trial of 20 mg/day of fluoxetine.²² During the initial 8 weeks, response rates were lower among patients with a greater burden of comorbid medical illness.⁶ We hypothesized that the therapeutic disadvantage seen during open treatment would persist with next-step treatment as well.

METHOD

Subjects

The details of the methods for the original trial have been reported elsewhere²² and are summarized here. Eligible subjects were drug-free outpatients who met the criteria for major depressive disorder as diagnosed with the Structured Clinical Interview for DSM-III-R—Patient Edition,²³ had an initial 17-item Hamilton Depression Rating Scale²⁴ score ≥ 16 , and were between 18 and 65 years of age. All subjects signed written consent forms approved by the Massachusetts General Hospital Institutional Review Board. All subjects were recruited by the Depression Clinical and Research Program of the Massachusetts General Hospital between 1992 and 1998.

The following patient groups were excluded: pregnant women; women of childbearing potential who were not using a medically accepted means of contraception; women of childbearing potential who were taking a birth control pill; lactating women; patients with serious suicide risk; patients with serious or unstable medical illness; patients with a history of seizure disorder; patients with a DSM-III-R diagnosis of organic mental disorder, substance use disorder active within the last year, schizophrenia, delusional disorder, psychotic disorder not elsewhere classified, bipolar disorder, or antisocial personality disorder; patients with a history of multiple adverse drug reactions or allergy to the study drugs; and patients with mood-congruent or mood-incongruent psychotic features, current use of other psychotropic drugs, or clinical or laboratory evidence of hypothyroidism. We also excluded patients whose past episodes of depression had failed to respond to a trial of either higher doses of fluoxetine (60–80 mg/day), the combination of fluoxetine and desipramine, or the combination of fluoxetine and lithium; patients whose current major depressive episode had failed to respond to at least one adequate antidepressant trial, defined as 6 weeks or more of treatment with either ≥ 150 mg/day of imipramine (or its

tricyclic equivalent) or ≥ 60 mg/day of phenelzine (or its monoamine oxidase inhibitor equivalent).

At the screening visit, study physicians generated for each subject a list of all existing and past medical illnesses, detailed by organ systems, and a list of current and past medical treatments. Each subject also underwent a physical examination and screening laboratory tests. The results of these procedures and any subsequent medical assessments were incorporated in the list of medical illness. A clinician (D.V.I.) reviewed the baseline visit notes for all patients enrolled in the trial and assigned each patient a score on the Cumulative Illness Rating Scale (CIRS)^{25,26} ranging from 0–4 for each of 13 organ systems, excluding mental health. This evaluator was blind to treatment outcome and the study hypotheses and had no access to postrandomization data at the time the CIRS scores were generated.

The CIRS is a comprehensive recording of all comorbid diseases of a patient. It classifies comorbidities by 14 organ systems and provides a rating of severity on a scale from 0 to 4. If two diseases are present within the same organ system, the disease with the highest severity score is counted. A score of 0 represents “no problem;” 1, “current mild or past significant problem;” 2, “moderate disability requiring first-line treatment;” 3, “uncontrollable chronic problems or significant disability;” and 4, “end organ failure requiring immediate treatment.” For this study we never assigned a score of 4, since the presence of severe/emergent medical conditions was an exclusion criterion. For each patient, we generated a total CIRS score as well as a count of number of organ systems with scores >0 .

All patients were treated openly with 20 mg/day of fluoxetine for 8 weeks and then became eligible for a 4-week, double-blind, triple-dummy, randomized study if they continued to meet the criteria for major depressive disorder and had treatment-resistant symptoms. Resistance to treatment was defined as failure to achieve a reduction $\geq 50\%$ in score on the 17-item Hamilton depression scale and a score ≥ 10 on that scale at the time of randomization. All subjects were taking 20 mg/day of fluoxetine when they entered the double-blind portion of the study.

Over the 6 years of the study, a total of 386 outpatients (212 women and 174 men) volunteered to participate in the study and were treated openly with 20 mg/day of fluoxetine. The mean age of this group was 39.9 years (SD = 10.6). Of these 386 patients, 101 (26.2%) did not have an adequate response to the open fluoxetine treatment over the 8-week trial and agreed to be randomly assigned to treatment with a higher dose of fluoxetine, fluoxetine plus lithium, or fluoxetine plus desipramine.

Medical Comorbidity and Fluoxetine Response

Procedures

The subjects were randomly assigned to one of three treatments: 40–60 mg/day of fluoxetine, 20 mg/day of fluoxetine plus 25–50 mg/day of desipramine, or 20 mg/day of fluoxetine plus 300–600 mg/day of lithium. During the first week of the double-blind portion of the study, the patients were instructed to take one 20-mg capsule of fluoxetine and one study capsule (fluoxetine or placebo) every morning, and to take one 25-mg tablet of desipramine or placebo or one 300-mg tablet of lithium or placebo at bedtime. After 1 week, the investigators were permitted to increase the dose, if the patient's symptoms were not responding, or to maintain the same regimen. The patients whose dose was increased were instructed to take one 20-mg capsule of fluoxetine and two study capsules (fluoxetine or placebo) every morning and two 25-mg tablets of desipramine or placebo or two 300-mg tablets of lithium or placebo at bedtime. Dose escalations were based on clinical response and tolerance of side effects.

Doses were increased according to schedule until a remission of depressive symptoms occurred; however, side effects determined whether the dose was maintained at the same level or reduced. In sum, patients were taking either 40–60 mg/day of fluoxetine, 20 mg/day of fluoxetine plus 25–50 mg/day of desipramine, or 20 mg/day of fluoxetine plus 300–600 mg/day of lithium. Concomitant lorazepam was not allowed during the randomized treatment.

The patients were seen by the investigators every other week during the 8 weeks of the open treatment phase and weekly during the 4 weeks of the double-blind phase of the study. At each visit, the patients were rated with the following clinician-rated instruments: the 17-item Hamilton depression scale and the Clinical Global Impression (CGI) severity and improvement scales.

Data Analyses

An intent-to-treat approach was used in the analyses of outcome. Remission was defined a priori as a 17-item Hamilton depression scale score ≤ 7 at endpoint.²⁷ The three treatment arms were pooled for examination to maximize statistical power. Multiple logistic regression analysis was used to assess the effect of demographic and clinical features, along with the measures of medical comorbidity, on treatment outcome. Logistic regression analysis was used because it makes no assumptions about the distribution of the independent (predictor) variables and because the categorical outcome measure (remission)

was felt to be more clinically relevant than the continuous outcome measure (change in Hamilton depression scale score). For illustrative purposes, patients with and without remission were also compared by using unpaired t tests (for continuous measures) and Fisher's exact tests (for categorical measures).

RESULTS

Of the 101 patients who were randomly assigned to double-blind treatment, 88 (87.1%) completed this phase of the study. Of the 101 patients, 33 were treated with high-dose fluoxetine, 34 were treated with fluoxetine plus desipramine, and 34 were treated with fluoxetine plus lithium. As we reported elsewhere,²² there was no significant difference across the three treatment groups in the rate of non-response during the open phase of the study (51.5% [17 of 33 patients] for the high-dose-fluoxetine group, 55.9% [19 of 34 patients] for the fluoxetine-plus-desipramine group, and 47.1% [16 of 34 patients] for the fluoxetine-plus-lithium group; $\chi^2 = 0.5$, $df = 2$, $p = 0.80$). CIRS scores could not be determined for four subjects because their medical history was incomplete; these four were omitted from subsequent analyses.

Patients with remission of depression ($N = 32$ of 97 patients, 65%) and patients without remission were compared on several parameters of comorbid illness at study entry, including total CIRS score and number of organ systems affected, as well as on sociodemographic features and depression severity at randomization. Only depression severity differed significantly between groups (Table 1). Depression severity was included in the analysis because previous studies suggested that it is an independent predictor of outcome in treatment resistance.²⁸ In a logistic regression analysis that included terms for age, sex, and baseline depression severity, the CIRS score did not predict likelihood of remission (Table 2). Thirteen of the 97 subjects (13%) discontinued participation in the study before completing 4 weeks of treatment. However, the CIRS score also did not appear to predict premature discontinuation (odds ratio [adjusted for age, sex, and baseline depression severity] = 1.01, 95% CI 0.74–1.36, n.s.).

DISCUSSION

This randomized, parallel-group study examined the putative moderating effects of comorbid medical illness on treatment response in a cohort of patients whose depressive episode had failed to respond adequately to an 8-week trial

of 20 mg/day of fluoxetine. In the initial 8 weeks, rates of response were lower among patients with a greater burden of comorbid medical illness or a greater number of organ systems affected.⁶ We had expected that this effect would persist among patients who proceeded to enter a next-step treatment trial.

In fact, while the patients without remission had slightly higher CIRS scores for total disease burden and the number of systems affected, these variables were not useful predictors of treatment outcome in logistic regression models that controlled for differences in baseline depression severity. As in most existing studies of treatment-resistant depression, the small number of subjects in this study raises the possibility of type II error. However, while we cannot reject the hypothesized negative effect of comorbidity entirely, we conclude that, if a moderating effect of comorbid illness exists in this outpatient population, the

effect is modest and may not be clinically relevant. Our results are consistent with previous findings in antidepressant trials involving geriatric patients^{8,9} and in studies of patients with particular medical comorbidities such as cardiovascular disease or cancer.^{10,15}

One additional limitation of this study is the absence of a placebo-control comparator group or a comparison group that received longer-term treatment with 20 mg/day of fluoxetine. We were concerned that patients might be unwilling to accept the possibility of placebo substitution or continuation of a dose of medication that had failed to yield a response by 8 weeks.²⁹ Nonetheless, because all patients continued to take at least 20 mg/day of fluoxetine, it is possible that some of the observed benefit derived from continued fluoxetine treatment rather than any of the particular interventions. Therefore, an alternate explanation for the disparity between the poorer efficacy observed in

TABLE 1. Characteristics of Outpatients With and Without Remission of Treatment-Resistant Depression in a 4-Week, Double-Blind, Randomized Trial of Fluoxetine Dose Increase or Augmentation^a

| Characteristic | Patients With Remission (N = 32) | | Patients Without Remission (N = 65) | | p ^b |
|---|----------------------------------|------|-------------------------------------|------|----------------|
| | Mean | SD | Mean | SD | |
| Age (years) | 40.2 | 10.4 | 42.3 | 10.4 | n.s. |
| 17-item Hamilton Depression Rating Scale score after 8 weeks of open treatment with 20 mg/day of fluoxetine | 14.0 | 3.5 | 17.6 | 4.4 | 0.001 |
| Cumulative Illness Rating Scale (CIRS) score | 1.94 | 1.98 | 2.20 | 1.90 | n.s. |
| CIRS rating of number of organ systems affected | 1.63 | 1.54 | 1.83 | 1.36 | n.s. |
| Female gender | N | % | N | % | n.s. |
| | 18 | 56 | 29 | 45 | |

^aPatients who had not experienced remission of major depressive disorder after 8 weeks of open treatment with 20 mg/day of fluoxetine were randomly assigned to receive 4 weeks of treatment with 40–60 mg/day of fluoxetine, 20 mg/day of fluoxetine plus 25–50 mg/day of desipramine, or 20 mg/day of fluoxetine plus 300–600 mg/day of lithium.

^bUnpaired t tests were used for all variables except age, for which Fisher's exact test was used.

TABLE 2. Predictors of Remission Status Among Outpatients With Treatment-Resistant Depression in a 4-Week, Double-Blind, Randomized Trial of Fluoxetine Dose Increase or Augmentation^a

| Characteristic | Odds ratio ^b | 95% CI | p |
|---|-------------------------|-----------|-------|
| Age | 0.98 | 0.93–1.02 | n.s. |
| Male gender | 1.49 | 0.60–3.67 | n.s. |
| 17-item Hamilton Depression Rating Scale score after 8 weeks of open treatment with 20 mg/day of fluoxetine | 0.85 | 0.76–0.96 | 0.007 |
| Cumulative Illness Rating Scale score | 0.96 | 0.75–1.24 | n.s. |

^aPatients who had not experienced remission of major depressive disorder after 8 weeks of open treatment with 20 mg/day of fluoxetine were randomly assigned to receive 4 weeks of treatment with 40–60 mg/day of fluoxetine, 20 mg/day of fluoxetine plus 25–50 mg/day of desipramine, or 20 mg/day of fluoxetine plus 300–600 mg/day of lithium.

^bOdds ratios were adjusted for other characteristics in the model (age, sex, baseline severity).

Medical Comorbidity and Fluoxetine Response

open treatment phase and equivalent efficacy in next-step treatment might be that patients with greater medical comorbidity respond more slowly, but at equivalent rates, compared to patients with less medical comorbidity.

While medical comorbidity was assessed prospectively, CIRS scores were generated retrospectively by a single rater who was blind to treatment outcome. This instrument has shown good psychometric properties³⁰ and has been used in other studies as a measure of cumulative illness burden,³¹ including other studies of depression.^{32,33} Still, additional measures of comorbidity could be more useful in establishing not only cumulative burden, but the relevance of particular organ systems and treatments.

A strength of this investigation is its prospective establishment of treatment resistance, which required enrollment of 386 subjects into open treatment. Moreover, despite the exclusion of patients with current substance use disorders, psychosis, and active suicide risk, the relatively broad inclusion criteria should improve the generalizability of our results. For example, while previous investigations of general medical comorbidity as a moderator of antidepressant effect have focused on geriatric populations,^{8,9} this study included patients with a broader age distribution.

At the same time, because subjects were recruited from an outpatient clinic and were specifically excluded if they were felt to have unstable medical illness, relatively few patients with severe medical illness were enrolled. The mean severity of comorbid medical illness was therefore quite low—for example, the mean CIRS severity score was 2.1. Thus, we cannot rule out a differential treatment effect among patients with very severe medical comorbidity. Studies of patients with treatment-resistant depression who also have severe comorbid medical illness will be necessary to address this question. Overall, however, our findings suggest that among patients whose depressive episode failed to respond to initial treatment with selective serotonin reuptake inhibitors, comorbid medical illness of mild to moderate severity does not appear to moderate the response to next-step interventions.

This study was supported by NIMH grant MH48483-05 (Dr. Fava), a Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression (Dr. Perlis), and a Clinical Investigator Fellowship from Harvard/MIT Division of Health Sciences and Technology (Dr. Iosifescu).

References

1. Crum RM, Cooper-Patrick L, Ford DE: Depressive symptoms among general medical patients: prevalence and one-year outcome. *Psychosom Med* 1994; 56:109–117
2. Patten SB: Long-term medical conditions and major depression in the Canadian population. *Can J Psychiatry* 1999; 44:151–157
3. Akiskal HS: Factors associated with incomplete recovery in primary depressive illness. *J Clin Psychiatry* 1982; 43:266–271
4. Swindle RW Jr, Cronkite RC, Moos RH: Risk factors for sustained nonremission of depressive symptoms: a 4-year follow-up. *J Nerv Ment Dis* 1998; 186:462–469
5. Keitner GI, Ryan CE, Miller IW, Kohn R, Epstein NB: 12-month outcome of patients with major depression and comorbid psychiatric or medical illness (compound depression). *Am J Psychiatry* 1991; 148:345–350
6. Iosifescu DV, Smith MM, Bitran S, Alpert JE, Nierenberg AA, Worthington JJ III, Fava M: Does medical illness impact the severity of depression and its treatment?, in 2001 Annual Meeting Syllabus and Proceedings Summary. Washington, DC, American Psychiatric Association, 2001, no 26
7. Popkin MK, Callies AL, Mackenzie TB: The outcome of antidepressant use in the medically ill. *Arch Gen Psychiatry* 1985; 42:1160–1163
8. Evans M, Hammond M, Wilson K, Lye M, Copeland J: Treatment of depression in the elderly: effect of physical illness on response. *Int J Geriatr Psychiatry* 1997; 12:1189–1194
9. Small GW, Birkett M, Meyers BS, Koran LM, Bystritsky A, Nemeroff CB: Impact of physical illness on quality of life and antidepressant response in geriatric major depression. *J Am Geriatr Soc* 1996; 44:1220–1225
10. Glassman AH, O'Connor CM, Califf RM, Swedberg K, Schwartz P, Bigger JT Jr, Krishnan KR, van Zyl LT, Swenson JR, Finkel MS, Landau C, Shapiro PA, Pepine CJ, Mardekian J, Harrison WM, Barton D, McIvor M, Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) Group: Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA* 2002; 288:701–709
11. Costa D, Mogos I, Toma T: Efficacy and safety of mianserin in the treatment of depression of women with cancer. *Acta Psychiatr Scand Suppl* 1985; 320:85–92
12. Holland JC, Romano SJ, Heiligenstein JH, Tepner RG, Wilson MG: A controlled trial of fluoxetine and desipramine in depressed women with advanced cancer. *Psychooncology* 1998; 7:291–300
13. Wagner GJ, Rabkin JG, Rabkin R: A comparative analysis of standard and alternative antidepressants in the treatment of human immunodeficiency virus patients. *Compr Psychiatry* 1996; 37:402–408
14. Ferrando SJ, Rabkin JG, de Moore GM, Rabkin R: Antidepressant treatment of depression in HIV-seropositive women. *J Clin Psychiatry* 1999; 60:741–746
15. Rabkin JG, Wagner GJ, Rabkin R: Fluoxetine treatment for depression in patients with HIV and AIDS: a randomized, placebo-controlled trial. *Am J Psychiatry* 1999; 156:101–107
16. Fava M, Davidson KG: Definition and epidemiology of treatment-resistant depression. *Psychiatr Clin North Am* 1996; 19:179–200
17. Fava M, Uebelacker LA, Alpert JE, Nierenberg AA, Pava JA, Rosenbaum JF: Major depressive subtypes and treatment response. *Biol Psychiatry* 1997; 42:568–576
18. George LK, Blazer DG, Hughes DC, Fowler N: Social support and the outcome of major depression. *Br J Psychiatry* 1989; 154:478–485

19. Bschor T, Canata B, Muller-Oerlinghausen B, Bauer M: Predictors of response to lithium augmentation in tricyclic antidepressant-resistant depression. *J Affect Disord* 2001; 64:261–265
20. Price LH, Charney DS, Heninger GR: Variability of response to lithium augmentation in refractory depression. *Am J Psychiatry* 1986; 143:1387–1392
21. Joffe RT, Levitt AJ, Bagby RM, MacDonald C, Singer W: Predictors of response to lithium and triiodothyronine augmentation of antidepressants in tricyclic non-responders. *Br J Psychiatry* 1993; 163:574–578
22. Fava M, Alpert J, Nierenberg A, Lagomasino I, Sonawalla S, Tedlow J, Worthington J, Baer L, Rosenbaum JF: Double-blind study of high-dose fluoxetine versus lithium or desipramine augmentation of fluoxetine in partial responders and nonresponders to fluoxetine. *J Clin Psychopharmacol* 2002; 22:379–387
23. Spitzer RL, Williams JBW, Gibbon M, First MB: Structured Clinical Interview for DSM-III-R—Patient Version (SCID-P). New York, New York State Psychiatric Institute, Biometrics Research, 1989
24. Hamilton M: A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; 23:56–62
25. Linn BS, Linn MW, Gurel L: Cumulative Illness Rating Scale. *J Am Geriatr Soc* 1968; 16:62–626
26. Miller MD, Paradis CF, Houck PR, Mazumdar S, Stack JA, Rifai AH, Mulsant B, Reynolds CF 3rd: Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. *Psychiatry Res* 1992; 41:237–248
27. Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weissman MM: Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse, and recurrence. *Arch Gen Psychiatry* 1991; 48:851–855
28. Tedlow J, Fava M, Uebelacker L, Nierenberg AA, Alpert JE, Rosenbaum J: Outcome definitions and predictors in depression. *Psychother Psychosom* 1998; 67:266–270
29. Nierenberg AA, Farabaugh AH, Alpert JE, Gordon J, Worthington JJ, Rosenbaum JF, Fava M: Timing of onset of antidepressant response with fluoxetine treatment. *Am J Psychiatry* 2000; 157:1423–1428
30. Extermann M: Measuring comorbidity in older cancer patients. *Eur J Cancer* 2000; 36:453–471
31. Patrick L, Knoefel F, Gaskowski P, Rexroth D: Medical comorbidity and rehabilitation efficiency in geriatric inpatients. *J Am Geriatr Soc* 2001; 49:1471–1477
32. Alexopoulos GS, Meyers BS, Young RC, Kalayam B, Kakuma T, Gabrielle M, Sirey JA, Hull J: Executive dysfunction and long-term outcomes of geriatric depression. *Arch Gen Psychiatry* 2000; 57:285–290
33. Burrows AB, Satlin A, Salzman C, Nobel K, Lipsitz LA: Depression in a long-term care facility: clinical features and discordance between nursing assessment and patient interviews. *J Am Geriatr Soc* 1995; 43:1118–1122