Predictors of Relapse During Fluoxetine Continuation or Maintenance Treatment of Major Depression

Patrick J. McGrath, M.D.; Jonathan W. Stewart, M.D.; Eva Petkova, Ph.D.; Frederic M. Quitkin, M.D.; Jay D. Amsterdam, M.D.; Jan Fawcett, M.D.; Frederick W. Reimherr, M.D.; Jerrold F. Rosenbaum, M.D.; and Charles M. Beasley, Jr., M.D.

Background: The goal was to examine predictors of relapse during continuation/maintenance treatment of major depression that had remitted following 12 to 14 weeks of fluoxetine therapy.

Method: The study utilizes data collected in a collaborative clinical trial including patients with DSM-III-R major depression at 5 university-affiliated outpatient psychiatry clinics. Three hundred ninety-five patients who remitted with fluoxetine therapy were randomly assigned to 1 of 4 treatments: fluoxetine for 14 weeks followed by placebo for 36 weeks, fluoxetine for 38 weeks followed by placebo for 12 weeks, fluoxetine for 50 weeks, or placebo for 50 weeks. Cox proportional hazard models were used to identify predictors of time to relapse.

Results: In addition to the previously reported longitudinal pattern of response during acute treatment, neurovegetative symptom pattern was a predictor of fluoxetine benefit compared with placebo. Greater chronicity predicted poorer survival, which was not differential by treatment. The most robust advantage of fluoxetine was seen for patients with endogenous vegetative symptoms, chronic depression, and acute treatment response characterized by onset in the third week or later and persistence of response once attained.

Conclusion: Both nonspecific pattern of response and neurovegetative symptoms characteristic of atypical depression were predictive of lack of fluoxetine efficacy in continuation/maintenance treatment. These findings have importance for both clinical management and analyses of future maintenance trials.

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Received July 21, 1999; accepted Jan. 26, 2000. From the Department of Psychiatry, Columbia University College of Physicians and Surgeons and the New York State Psychiatric Institute, New York (Drs. McGrath, Stewart, Petkova, and Quitkin); the Department of Psychiatry, University of Pennsylvania, Philadelphia (Dr. Amsterdam); the Department of Psychiatry, Rush Medical Center and Presbyterian-St. Luke's Medical Center, Chicago, Ill. (Dr. Fawcett); the Department of Psychiatry, University of Utah, Salt Lake City (Dr. Reimherr); the Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston (Dr. Rosenbaum); and Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Ind. (Dr. Beasley).

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Reprint requests to: Patrick J. McGrath, M.D., New York State Psychiatric Institute, Unit #51, 1052 Riverside Dr., New York, NY 10032-2695 (e-mail: mcgrath@pi.cpmc.columbia.edu).

Longitudinal research has demonstrated the recurrent and chronic nature of mood disorders and heightened the appreciation of the societal and individual burden of depressive illness.[1–5] Therefore, research must move beyond the consideration of acute, short-term treatment and develop guidelines for long-term treatment. The delineation of predictors of relapse during medication treatment would be of both practical and heuristic importance.

The beneficial effect of tricyclic antidepressants in preventing both relapse and recurrence of depression is well documented, but less is known about the benefit of continuation and maintenance therapy with other antidepressants.[1,6–11] Previous studies indicate that the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, sertraline, and paroxetine, like the tricyclic antidepressants, are effective in continuation therapy.[9,12–15] The prophylactic efficacy of fluoxetine in preventing recurrent episodes after a stable period of continuation has been shown.[16] Data from studies of extended therapy with SSRIs are particularly important, since a favorable side effect profile has made these medications the antidepressants of first choice in most countries, including the United States.

No predictors of survival in maintenance treatment have been clearly demonstrated. A series of studies from the New York State Psychiatric Institute[17–21] suggests that longitudinal pattern of response during acute treatment discriminates pharmacologic response from nonspecific improvement. Briefly, responses that are delayed past the second week in onset and are persistent once attained appear more likely to be pharmacologic responses; we call these *specific* longitudinal patterns. All other longitudinal patterns, called *nonspecific*, are just as likely to occur with placebo as with active drug. Since longitudinal pat-

terns of response appear to distinguish specific from nonspecific responses, we hypothesized that those with specific longitudinal patterns of response would benefit more from continuing medication. It is important to note that specific response pattern is meant to separate out a subgroup of responders in which relatively more patients are benefiting from the pharmacologic effects of the drug than from placebo effects compared with other responders. It is likely that there are other subgroups of patients who have pharmacologic effects that are either partial or are present in too small a subset to be discerned by our method in the relatively small clinical samples to which it has been applied. A previous report[22] of data from this clinical trial has shown the efficacy of fluoxetine compared with placebo in both the continuation and maintenance phases of ongoing treatment and has shown the relevance of pattern of response to prediction of relapse.

Another finding of interest is that among patients with atypical depression, maintenance of acute imipramine treatment response was no better than a switch to placebo, whereas phenelzine response is well maintained.[23] This finding is in contrast to those of many studies that show good maintenance of response for patients with depression not selected for atypical features.[10,11] Reimherr and colleagues[24] found that among 61 patients with globally defined atypical depression, 57% (21 of 37) responded to fluoxetine whereas 29% (7 of 24) responded to imipramine ($\chi^2 = 5.8$, df = 1, $p < .02$). This suggests that fluoxetine might have greater efficacy than tricyclics for patients with atypical depressive symptoms and that atypical depressive symptoms might predict better survival among patients treated with fluoxetine.

The present study reports analyses from a multicenter, double-blind, randomized clinical trial comparing fluoxetine maintenance for periods of up to 50 weeks with placebo substitution. Three hundred ninety-five patients who achieved remission from major depression during 12 to 14 weeks of acute therapy with a fixed 20-mg dose of fluoxetine were randomly assigned to continue on this dose of fluoxetine or switch to placebo. We had the following a priori hypotheses:

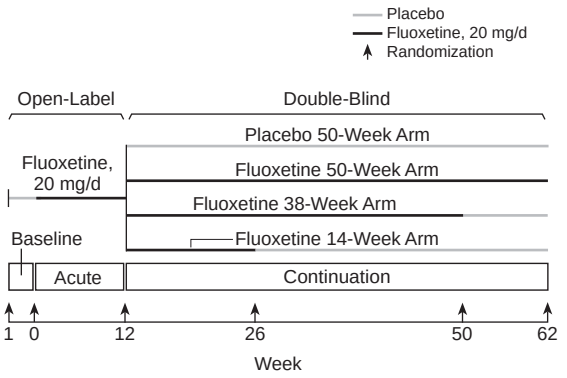
1. Patients with atypical depressive symptoms will show improved survival compared with those with more typical depression.
2. Increased chronicity of depressive illness will predict poorer survival not differential by treatment.

METHOD

Subjects

Male and female outpatients aged 18–65 years who currently met Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R)[25] criteria for major depression of at least 1 month's duration were included. These criteria are essentially identical to DSM-IV criteria.[26] Diagnoses, including that of melancholic subtype, were determined using the Structured Clinical Interview for DSM-III-R (SCID), patient version.[27] While subjects with antecedent dysthymia were included, the presence of dysthymia was not systematically recorded. A minimum score of 16 was required on a modified Hamilton Rating Scale for Depression (HAM-D-17*),[28] described below under Ratings. All subjects gave written informed consent after complete description of the study.

Figure 1. Study Design



Patients were excluded for unstable medical illnesses, pregnancy or lactation, serious suicidal impulses, history of psychosis or organic mental disorder, history of mania or antisocial personality disorder, substance abuse disorders active within the last year, or laboratory evidence of hypothyroidism. Patients were also excluded if they had received fluoxetine for 3 months in a previous episode, or if they had not responded to a previous 8-week treatment trial with fluoxetine at a daily dose of ≥ 20 mg in the current episode.

Design

The design of the study is indicated in Figure 1. Patients who met study entry criteria at both the beginning and the end of the 1-week no-therapy baseline began 12 to 14 weeks of open fluoxetine treatment at a fixed 20-mg/day dose. The required 12-week treatment could be extended to 14 weeks for 2 groups of patients who were improved after 11 weeks of treatment: those who had not yet sustained remission for 3 consecutive weeks and those who had remitted but had a subsequent more-symptomatic week due to an identifiable social stressor. Remission at the end of open-label treatment was defined as 3 consecutive weeks with both a HAM-D-17* score ≤ 7 and a failure to meet criteria for major depression. Response to acute therapy, the optimal length of continuation therapy, and long-term safety results will be the subject of separate reports. The relationship of plasma drug levels to outcome has been reported.[29]

Remitted patients were randomly assigned to 1 of 4 treatment groups: (1) fluoxetine for 14 weeks followed by placebo for 36 weeks, (2) fluoxetine for 38 weeks followed by placebo for 12 weeks, (3) fluoxetine for 50 weeks, or (4) placebo for 50 weeks. Because of the long half-life of fluoxetine's active metabolite, medication was discontinued without any tapering. After randomization, patients were seen weekly for 2 weeks, every 2 weeks for 16 weeks, and monthly for the remaining 32 weeks. Weekly visits were scheduled if HAM-D-17* score increased to ≥ 10 and continued until HAM-D-17* score decreased to ≤ 7 for 3 consecutive weeks or patient met relapse/recurrence criteria. A patient who met criteria for major depression for 2 weeks at any time during the discontinuation phase or who sustained a HAM-D-17* score of ≥ 14 for 3 consecutive weeks was considered to have relapsed and was removed from the study.

Ratings

Eligibility and efficacy ratings used a modified HAM-D, the HAM-D-17*. The asterisk denotes that this is a subset of items from the 28-item version of the HAM-D that incorporates positive as well as reverse vegetative signs. In addition to the standard 21 items, the 28 items include the following: 3 hypersomnia items (time in bed, oversleeping, and napping), increased appetite, weight gain, psychic retardation, and motoric retardation. If the summary score of the customary 17 items including typical neurovegetative symptoms (insomnia and weight loss) was at least equal to the sum of the 17 items containing the reverse vegetative items (hypersomnia and weight gain), the patient was considered positive neurovegetative. Other patients were considered reverse neurovegetative. Whichever set of items yielded the higher score at baseline was used for all subsequent ratings.

Patients who achieved a weekly Clinical Global Impressions-Severity[30] score of "no pathology" or "minimal pathology" were considered responders for that week; others were considered nonresponders. On the basis of previous work by our group on the longitudinal pattern of response to antidepressants during acute treatment, *specific* patterns of longitudinal response were defined as those in which the first onset of response was both delayed until after the second week and was persistent; that is, the onset of improvement was not followed by an unimproved week.[17] All other longitudinal response patterns were considered *nonspecific*.

Statistical Analysis

Subjects who were randomly assigned to discontinue fluoxetine at weeks 14, 38, or 50 were included and censored after the point of switch to placebo if they had neither dropped out nor relapsed by then. Cox proportional hazard models were employed to identify predictors of time to relapse and discover any interactions between factors and the drug effects. Potential predictors and all interactions were entered as covariates in the initial model. Available variables considered as possible predictors of relapse included study site, age, sex, age at onset of any depressive illness, history of hypomania, presence of melancholic subtype, number of previous major depressive episodes, longitudinal pattern of response in acute treatment (specific or nonspecific), neurovegetative status (positive or reversed), and chronicity (≥ 2 years' duration of current episode = chronic). A priori hypotheses were first tested by models including only the variable of interest and the study site. A full exploratory model, which included all 2- and 3-way interactions, was then tested including all listed variables, and variables that were not significant were removed by backward elimination to arrive at the best-fitting mode. We report standard deviations for all means; all statistical tests are reported 2-tailed. Contingency tables were analyzed by the chi-square statistic, corrected for continuity.

Table 1. Sample Randomized to Discontinuation (N = 395)

Characteristic	Value[a]
Demographics	
Women	272 (69)
White	370 (94)
Age, y, mean ± SD	39.7 ± 10.3
Diagnoses	
Melancholia (DSM-III-R)	95 (24)
Bipolar, not otherwise specified (DSM-III-R)	33 (8)
Positive neurovegetative[b]	232 (59)
Depression subtypes and chronology	
Major depression subtypes	
Single episode	121 (31)
Recurrent	219 (55)[c]
Current episode chronic (≥ 2 y)	191 (48)
Age at onset of first depression, y, median	18
No. of previous major depressive episodes, mean ± SD	3.8 ± 7.9
Depression severity	
HAM-D-17* score pretreatment, mean ± SD	20.9 ± 3.6
HAM-D-17* score at randomization, mean ± SD	2.8 ± 2.2

[a]All values expressed as N (%) unless otherwise indicated.
[b]The sum of insomnia and appetite loss items exceeded the sum of hypersomnia and increased appetite items of extended Hamilton Rating Scale for Depression (HAM-D-17*).
[c]Single episode and recurrent cases do not sum to 100% since 55 subjects (14%) were rated as having episodes that were "too frequent or indistinct" to separate.

RESULTS

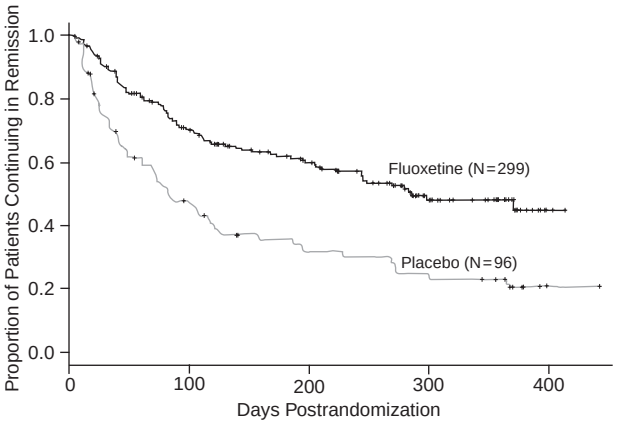
Demographic and diagnostic variables describing the 395 patients who were randomized in the continuation phase are presented in Table 1. The group was almost entirely white and predominantly female with a high degree of chronicity. Slightly more than half were categorized as having positive neurovegetative status. The patients had very low residual depression scale scores at the end of acute therapy. The only significant difference between the groups at randomization on any of the variables examined

was that the proportion of women in the 50-week placebo arm was slightly greater than in the other 3 treatment groups (data not shown).

A survival curve for all randomly assigned patients is presented in Figure 2. Data for patients randomly assigned to switch to placebo after either 14 or 38 weeks of maintenance treatment on active fluoxetine are censored after the point of switch. Analysis of data on patients switched to placebo at these points has been published previously.[31] The hazard ratio, that is, the ratio of risk of relapse for placebo-treated patients divided by the risk of relapse for fluoxetine-treated patients, is 2.22 (95% confidence interval [CI] = 1.62 to 3.05, log-rank test = 32.6, df = 1, $p < 5 \times 10^{-7}$). No interaction was found between study site and treatment effect on survival. The median times of survival were 284 days (95% CI = 224 to > 400) for fluoxetine and 84 days (95% CI = 62 to 127) for placebo. The median lower bound for fluoxetine is almost twice the upper bound for placebo, demonstrating the clear advantage for fluoxetine.

Of all 395 randomized patients, 126 (32%) dropped out without meeting relapse criteria, of whom 80 (64% of dropouts) were receiving fluoxetine at the point of dropping out. All dropouts are included in the survival analyses with censoring applied after the point of dropping out. Significantly more dropouts with fluoxetine were due to side effects (16 [20%] of 80) compared with placebo (2 [4%] of 46; $\chi^2 = 4.6$, df = 1, $p < .05$). Significantly more dropouts with placebo were due to lack of efficacy (17 [37%] of 46) compared with fluoxetine (11 [14%] of 80; $\chi^2 = 8.7$, df = 1, $p < .005$). There was no difference between treatments in the proportion of dropouts for other reasons (27 [59%] of 46 taking placebo; 53 [66%] of 80 taking fluoxetine; $\chi^2 = 0.4$, df = 1, NS).

Figure 2. Survival by Treatment (N = 395)[a]



[a]Log-rank test = 25.8, df = 1, $p < .0001$.

Predictors of Relapse

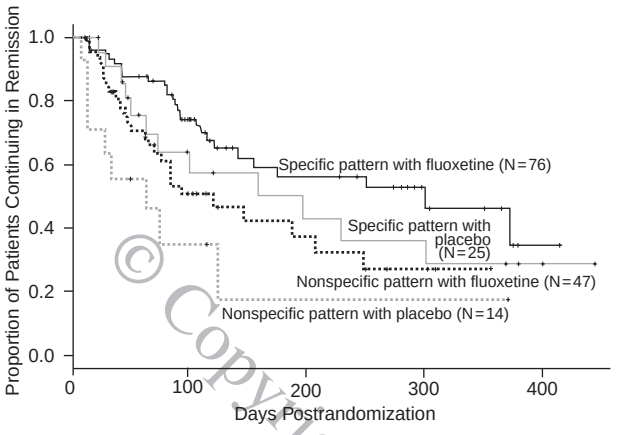
Longitudinal pattern. As we have previously reported[21] from this data set, response pattern interacted significantly with treatment. Subjects with a nonspecific longitudinal pattern (either early onset or nonpersistent) showed a hazard ratio for relapse between placebo and active treatment of 1.28 (95% CI = 0.74 to 2.22), which did not differ significantly from unity, whereas those with a specific longitudinal pattern showed a significantly greater hazard for relapse with placebo compared with fluoxetine (hazard ratio = 3.08, 95% CI = 2.07 to 4.57). This supports the hypothesis that onset of response after the second week of acute treatment that persists once attained is indicative of pharmacologic response to drug, since it is only among those with a specific longitudinal pattern that drug-placebo differences are seen in continuation.

Age at onset and chronicity. We hypothesized a priori that since age at onset is a measure of chronicity, patients with early age at onset would have generally poorer survival, not different between active and placebo medication. Early-onset subjects (≤ 20 years) did have a slightly but significantly higher risk of relapse (hazard ratio = 1.41 [95% CI = 1.03 to 1.9]) compared with those with later age at onset. The effect of age at onset on survival was not differential by treatment. A similar survival analysis that used chronicity, defined as a duration of the current major depression of ≥ 2 years, instead of age at onset, produced similar results.

Neurovegetative symptom pattern. The effect of neurovegetative symptom pattern on relapse interacted significantly with both pattern and treatment. Within the patient group with reversed neurovegetative symptoms, the pattern of acute response was not predictive of differential survival, although survival was generally poorer for patients with nonspecific longitudinal patterns (Figure 3). It was with patients with positive or typical neurovegetative symptoms that the largest effect of longitudinal pattern was seen. Here, patients with specific longitudinal patterns showed the most robust drug-placebo differences seen of any subgroup studied (Figure 4). These data suggest that fluoxetine, like imipramine, is a generally poor maintenance treatment for patients with atypical depressive symptoms. There was no association between neurovegetative symptom pattern and pattern of response ($\chi^2 = 0.8$, df = 1, NS).

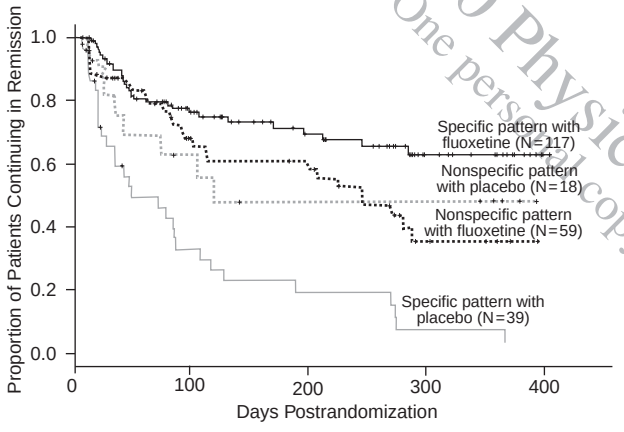
Melancholic subtype. Survival was also examined for 95 patients diagnosed as having a melancholic subtype of major depression by DSM-III-R criteria, using only melancholia and study site as covariates (Figure 5). The presence of melancholia did not affect survival with placebo, but like positive neurovegetative status, it did significantly improve survival with active fluoxetine ($p < .05$). Melancholia correlated only poorly with neurovegetative status. Of 95 patients with melancholia, 62 (65%) were rated positive neurovegetative, whereas of 300 nonmelancholics, 171 (57%) were positive neuroveg-

Figure 3. Survival by Treatment and Pattern of Response Within Reversed Neurovegetative Group (N = 162)[a]



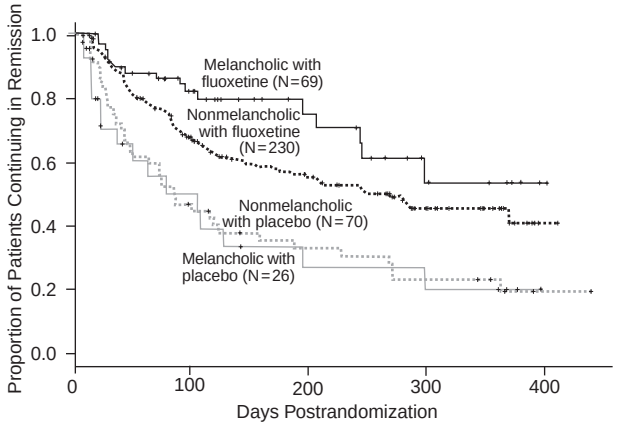
[a]Log-rank test = 14.7, df = 3, p = .002.

Figure 4. Survival by Treatment and Pattern of Response Within Positive Neurovegetative Group (N = 233)[a]



[a]Log-rank test = 38.8, df = 3, p = 1.9×10^{-8}.

Figure 5. Survival by Treatment and Melancholic Subtype (N = 395)[a]



[a]Log-rank test = 29.3, df = 3, p = 1.9×10^{-6}.

etative (Spearman ρ = .07, NS). Nonmelancholic subjects showed drug-placebo differences ($p < .0005$), whereas reversed neurovegetative subjects showed only a trend for a difference in survival between fluoxetine and placebo ($p = .093$). When the full model including both variables was examined, melancholia no longer had a significant effect on survival once neurovegetative status was accounted for.

Other variables. Age, gender, and history of hypomania were not predictive of differential survival between drug and placebo. These analyses employed an a priori definition of relapse. To explore the possibility that patients dropping out owing to lack of efficacy might have biased the results, we repeated the analyses considering dropouts due to lack of efficacy to be relapsers; this did not affect the results obtained beyond slightly increasing the survival differences between fluoxetine and placebo.

DISCUSSION

The overall comparison between treatments, presented in Figure 2, illustrates the highly significant difference in survival between active fluoxetine and placebo that we had previously shown with these data.[22] This graphic display makes clear the relatively high relapse rate for this group of patients on treatment with active fluoxetine, most likely due to a combination of factors including the lack of a period of stabilization before discontinuation, the high level of chronicity of the subjects, and the close monitoring during follow-up. Most of the difference in survival appears during the first 4 months, after which the curves become essentially parallel. Consistent with much previous work, this finding suggests that the highest risk of relapse is during the continuation phase of the first 6 months after acute response.

In contrast to our hypothesis that fluoxetine might be more effective for patients with atypical depressive symptoms, we found no significant effect of active fluoxetine in maintaining remission for such patients. Since negative neurovegetative status was not associated with diminished fluoxetine response in the acute treatment phase of this trial, it may be that reversed neurovegetative features may not predict acute response but rather loss of effect in maintenance. Also, the lack of relationship between neurovegetative symptoms and pattern of response suggests that patients with atypical depressive patterns are no more likely to have nonspecific patterns of response. This is not surprising given the consistently modest placebo response rates in studies of atypical depression,[32] assuming nonspecific patterns are closely related to placebo response. While there have been no maintenance studies of fluoxetine in atypical depression to our knowledge, the literature on the effect of fluoxetine in the acute treatment of patients with atypical depression, which overlaps largely with the reversed vegetative symptom patients

studied here, shows mixed results.[24,33–36] A study from the New York State Psychiatric Institute[23] showed that patients with atypical depression who responded to phenelzine maintained their response over 6 months with only a 23% relapse rate on treatment with active medication, but showed a high relapse rate of 87% when switched to placebo. No difference was found in relapse rates in that study for responders to acute imipramine treatment whether maintained with imipramine (41%) or switched to placebo (47%).[23,32] These data are consistent with the results presented here. While the data are insufficient to draw a clear conclusion, fluoxetine may not be as effective as monoamine oxidase inhibitors in the treatment of atypical depression, which is consistent with its lack of protective effect for patients with reversed neurovegetative symptoms in this study.

It is of interest that the presence of positive neurovegetative symptoms appeared to be a better predictor of successful maintenance with medication than was melancholia, once both were taken into account. One study[37] has suggested that the construct of melancholia relates more closely to psychomotor symptoms than to neurovegetative symptoms, consistent with our finding of poor correlation between these constructs. These may be separate dimensions of depression, and, if so, our study suggests that the neurovegetative component relates most strongly to maintenance of antidepressant response. Further, other recent work suggests that unlike atypical depression, which appears to breed true,[38] melancholia does not exhibit higher concordance in monozygotic than dizygotic twins.[39] This result would suggest that melancholia may not be a genetically distinct subtype but rather a quantitatively more severe form of depressive illness. This would be also be consistent with our findings since a semi-quantitative severity measure appeared to account for most of the variance in outcome attributable to melancholia.

What our data do not allow us to address is the relationship between neurovegetative status and the concept of atypical depression, as defined in DSM-IV.[26] If this categorical distinction were predictive of maintenance outcome, it might be more clinically useful than a dimensional measure of neurovegetative symptoms. We are currently conducting a replication of this study that includes data on atypical subtype diagnosis to address this question.

These analyses could be applied to make useful clinical predictions about maintenance treatment. For example, patients with an early onset of depression, typical vegetative symptoms, and a specific longitudinal pattern could be advised strongly that, for them, the advantage of fluoxetine continuation over placebo is large (60%, 95% CI = 42% to 79%) and continuation/maintenance warrants great efforts to control side effects. Other patients without any of these 3 features have little or no discernible advantage from continued fluoxetine treatment, at least at a fixed daily dose of 20 mg. Some data suggest that increased dosage is often useful in this situation.[40] If such a patient wished to discontinue fluoxetine, for example because of side effects, these data might assist in advising the patient that discontinuation would not be likely to cause a real loss of benefit and that they might be as well served by trying another medication.

One of the previous findings of note from this study was the relatively high relapse rates for patients maintained on fluoxetine treatment. Our finding of numerically lower survival rates compared with the Montgomery et al. study[16] may be due to our inclusion of patients with reversed neurovegetative symptoms resulting from using a modified HAM-D as an entry criterion. Since the Montgomery et al. study selected patients who had a cutoff score on the HAM-D version that does not include reversed vegetative items, patients with positive neurovegetative patterns were more likely to be enrolled. Other possible explanations include our use of a fixed lower dose, other sample differences, and some combination of these factors. The higher relapse rates with placebo in the present study suggest that the samples were different in the 2 studies and may account for some of the difference in relapse rates on active fluoxetine treatment.

Comparing rates of relapse across studies is inherently unreliable because of differences in sample inclusion, exclusion, and relapse criteria. Even granting that the differences could be meaningful, there are several other explanations. First, it is possible that patients were not adherent to the medication regimen. This is not likely given the significant drug-placebo differences seen, care taken in the study to ensure compliance, and the good tolerability of fluoxetine. Secondly, it is possible that some true tachyphylaxis to the effect of fluoxetine occurred in these patients. The dose of fluoxetine used here is the minimal effective dose according to the current prescribing information. In comparison, the Montgomery et al. study[16] reported a relapse rate of 26% over 1 year with a fixed 40-mg daily dose of fluoxetine, compared with 57% with placebo. In the largest and most thorough naturalistic study,[40] intensity of medication treatment appears to be inversely correlated with relapse rates. Some clinical observations suggest a tendency for loss of effect from fluoxetine and other SSRIs. Loss of efficacy of fluoxetine in maintenance treatment at a 20-mg daily dose appears to respond to dose increase in about two thirds of patients.[41] Further, the suggestion has been made that this loss of efficacy may result from a relative dopamine deficiency induced by fluoxetine treatment and that it may be responsive to treatment with postsynaptic dopamine agonists.[42] Thirdly, the high relapse rates seen with both fluoxetine and placebo may be a reflection of the patient population, which had a high level of chronicity and presumably a much higher likelihood of relapse. As noted above, the inclusion of reversed neurovegetative symptom cases also contributed to poorer

survival. In addition, out of a conservative stance regarding safety, patients in the continuation phase of this study were examined much more frequently than has been done in other maintenance studies. This frequent monitoring may have had the effect of artifactually raising the relapse rate since some of these periods of worsening may have remitted if the patient had been simply followed without alteration of treatment.

We believe that these findings, if replicated in a prospective study, may have considerable clinical utility in allowing clinicians to make more accurate prognoses for their patients during long-term treatment with SSRIs. If confirmed, our findings would be important in future research both to stratify groups randomly assigned to discontinuation and to analyze the survival data for their effect.

Study Limitations

The study enrolled patients at tertiary care, university-affiliated research clinics. Most were white, had limited comorbidity, and were chronically depressed. They may not adequately represent patients seen in other clinical settings. The fixed dosage used may also be unrepresentative of usual clinical practice.

Drug names: fluoxetine (Prozac), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft).

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