Factors Affecting Return of Symptoms 1 Year After Treatment in a 62-Week Controlled Study of Fluoxetine in Major Depression

Frederick W. Reimherr, M.D.; Robert E. Strong, D.O.; Barrie K. Marchant, M.S.; Dawson W. Hedges, M.D.; and Paul H. Wender, M.D.

Background: In spite of impressive results in acute studies, the long-term treatment of major depression remains problematic. To explore the return of depressive symptoms and their interaction with social factors on long-term outcome, we assessed 55 patients whose depression had been treated during a 62-week, fluoxetine maintenance study, 1 year after the study's termination. ***Method:*** During the year following the study termination, patients were free to select treatment options. Assessments at the 1-year follow-up included measures of depressive symptoms (using the Hamilton Rating Scale for Depression [HAM-D]), social and marital impairment (using the Weissman Social Adjustment Scale [SAS]), personal stressors (using the Holmes Social Readjustment Rating Scale), and history of treatment during the past year. ***Results:*** At the time of the naturalistic follow-up, 53% of patients sustained their improvement in mood. Factors associated with return of depressive symptoms included personal stresses, marital maladjustment, personal decision to discontinue antidepressants, and medication failure. Psychosocial variables were associated with poor outcome in over 90% of impaired subjects. Development of subsyndromal symptoms during the 50-week double-blind phase was predictive of poorer outcome at the long-term follow-up. ***Conclusion:*** The study demonstrates that no matter how effective initial pharmacologic therapy may be, without ongoing clinical monitoring and support, particularly in dealing with issues such as marriage and handling significant life stresses, and compliance with medications, it will not be successful in the long-term treatment for a significant portion of patients with depression.

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Major depression is not merely an episodic condition, but is now recognized as a long-term, probably lifelong disorder.[1,2] Effective treatment of depression requires not only resolution of the acute symptoms of the disorder, but continued treatment to prevent relapse, and in many cases, additional treatment to prevent recurrence. The impact of social adjustment problems on the development, resolution, and prevention of depression has not been fully explored, but could be expected to have a significant effect on long-term outcome.

From the Mood Disorders Clinic, Department of Psychiatry, University of Utah Health Sciences Center, Salt Lake City.

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Correspondence to: Frederick W. Reimherr, M.D., Mood Disorders Clinic, Department of Psychiatry, University of Utah Health Sciences Center, 50 North Medical Dr., Salt Lake City, UT 83132 (e-mail: fred.reimherr@hsc.utah.edu).

Reprint requests to: Jill Gonzales, Eli Lilly and Company, DC2434, Lilly Corporate Center, Indianapolis, IN 46285.

LONG-TERM OUTCOMES

Although acute treatment of depression generally is highly effective at reducing symptoms and inducing remission, long-term naturalistic outcomes are less positive. A number of extended studies have reported 3 general patterns of continued depressive symptoms.

First, a significant number of patients suffer additional episodes of major depression. According to the Agency for Health Care Policy and Research (AHCPR), the risk for recurrence is 50% after 1 episode, 70% after 2 episodes, and 90% after 3 episodes.[3] A National Institute of Mental Health (NIMH) study of 431 patients with major depression found that after 5 years of follow-up, 60% of patients had suffered at least 1 recurrence of the illness,[4] and after 15 years of follow-up, that number had grown to 85%.[5]

A second outcome that occurs in a smaller, yet significant percentage of patients, is the continuation of symptoms at an intensity sufficient to meet the criteria for major depression. For example, in the NIMH study described above, the estimated probability of remaining ill for at least 5 years was 12%.[2] Other reports have documented high chronicity and poor recovery rates in a variety of patient settings over follow-up periods of up to 7 years.[6–10]

Finally, the most frequent outcome for major depression is the continuation of symptoms at a subsyndromal level.[7,8,11,12] In the most exact examination published,[13] patients in the NIMH study described above had subsyndromal symptoms at a rate (43%) almost 3 times more frequent than episodes of major depression (15%) over a 12-year follow-up period. Almost one quarter (23%) of these patients were never free of depressive symptoms for even 1 week.

Antidepressant Treatment

Despite this discouraging picture, there are positive reports regarding long-term antidepressant treatment in a number of long-term controlled studies. These studies have demonstrated the efficacy of a variety of medications, including imipramine,[14–18] sertraline,[19,20] citalopram,[21,22] paroxetine,[23] mirtazapine,[24] and milnacipran,[25] in the prevention of major depressive episodes. In some cases, antidepressant treatment has been shown to result in improvements in both mood and social adjustment.[25,26]

Although many studies have conclusively documented the need for continuation treatment, only one study has addressed the issue of the optimal length of treatment for relapse prevention. In this study,[17] patients were treated for 12 weeks with open-label fluoxetine and were then randomly assigned to 1 of 4 treatments: placebo for 50 weeks, fluoxetine for 14 weeks followed by placebo, fluoxetine for 38 weeks followed by placebo, or fluoxetine for 50 weeks. These transfer points represented total treatment times with fluoxetine of 12 weeks, 26 weeks, 50 weeks, or 62 weeks. Of the patients switched to placebo at 12 weeks, 48.6% relapsed during the following 12 weeks compared with 26.4% of fluoxetine patients. Of the patients switched at 26 weeks, the figures were 23.2% versus 9.0%, and after the 50 weeks, the figures were 16.2% and 10.7%. The first 2 comparisons were statistically significant in favor of fluoxetine. The conclusion from these data is that many patients should be continued on treatment for at least an additional 6 months after initial remission of symptoms to prevent relapse.

In the area of prevention of recurrence, Gilaberte and colleagues[27] recently completed a study of fluoxetine treatment that included the longest open-label period of any prophylaxis study. Following 32 weeks of open-label treatment, patients were randomly assigned to placebo or continued fluoxetine. One hundred forty of 253 patients met entry criteria for the 48-week double-blind maintenance period, with 70 randomized to fluoxetine and 70 to placebo. Over the course of the double-blind period, patients taking fluoxetine were significantly less likely to suffer a recurrence (20% vs. 40%; $p = .010$) and remained symptom-free for a significantly longer period of time (295 days vs. 192 days; $p = .002$) compared with those patients given placebo.

Unfortunately, naturalistic follow-up studies[28–30] have not replicated the positive long-term outcomes seen in the controlled studies described above. The World Health Organization (WHO) recently conducted a naturalistic study of mental disorders in general health care among patients with confirmed depressive illnesses.[28] At 3 months of follow-up, patients who were treated with antidepressants were better in terms of overall symptom profile and suicidal thoughts relative to patients who were treated with sedatives, even though the patients on antidepressant treatment displayed more symptoms initially. However, this advantage did not persist in the long term. By the end of 1 year, approximately 60% of those on either drug treatment and 50% of those with no drug treatment at all still met the criteria for depression.

Clinical and Social Factors Associated With Recovery and Relapse

The symptoms of depression have a negative impact on social adjustment as well as mood.[31–36] Social adjustment is variously defined, but generally refers to relationships with spouse, children, and other relatives; social relationships outside the home; social-leisure activities; and performance in the work place, in school, or as a homemaker. Although it has been suggested that social adjustment problems are a consequence of the mood disorder,[37] there is also evidence that ongoing social adjustment problems increase the risks for recurrence of depression.[38] The complex interaction between social adjustment and mood disorders is not well understood.

Factors associated with either recurrent or persistent symptoms include poor family functioning,[8] but not psychosocial stress[9]; additional diagnosis on Axis I, II, or III[39]; partial recovery[40,41]; double depression[42]; more chronic symptoms[43–46]; life stresses[44]; personality[47–51]; and marital problems.[52,53] In an intriguing study,[54] personality disorder was found to delay recovery, but not alter the quality of response. Andrew et al.[9] found that psychosocial stress was associated less with recovery in severely depressed women than in women who suffered from milder depression. Furthermore, it has been suggested that the impact of marriage and social variables on outcome diminishes in importance for patients with more severe depression.[55]

McGrath et al.[56] performed an extensive analysis of the data from the fluoxetine relapse prevention study described above[17] in an effort to identify predictors of relapse. The most robust advantage for fluoxetine was seen for patients with endogenous vegetative symptoms and chronic depression. Patients with reversed neurovegetative symptoms characteristic of atypical depression responded to a lesser degree to fluoxetine prophylaxis. In addition, patients with a delayed and persistent "true drug" response relapsed more often while receiving placebo than patients with an early or nonpersistent "placebo" response. Among patients with a true drug response, there was a significantly higher rate of relapse in patients receiving placebo substitution than in those

with continued fluoxetine therapy. Among patients with a placebo response, the difference was not significant. These findings suggest that fluoxetine's efficacy during continuation treatment may be limited to patients with certain clinical characteristics.

This study extends the examination of the relapse prevention study[17] to include both mood and social adjustment in patients at 3 key junctures: at baseline, after 12 weeks of open treatment with fluoxetine, and at 1 year after patients had terminated from the program. In addition to determining clinical outcome, the long-term assessment enabled us to explore whether significant, long-lasting improvements were produced by the administration of antidepressant medication, whether any moderating variables, such as marital adjustment, affected long-term outcome, and whether the variables identified by McGrath et al.[56] continued to impact long-term outcome.

METHOD

Original Study

The original study was conducted at 5 sites across the United States, has been described in detail elsewhere,[17] and is briefly reviewed here. After subjects received a comprehensive description of the study, written informed consent was obtained. Subjects were required to meet the following criteria: age 18 to 65 years old; DSM-III-R diagnosis of major depressive disorder (MDD) with duration of at least 1 month; and a 17-item Hamilton Rating Scale for Depression (HAM-D-17) score of at least 16 at admission.

The original study consisted of 3 phases: a 5- to 9-day baseline phase in which no antidepressants were administered; a 12- to 14-week acute phase in which all patients received open-label fluoxetine; and a 50-week double-blind, continuation phase. Patients who experienced a remission of at least 3 weeks' duration while on open-label treatment were allowed to enter the 50-week continuation phase. In the double-blind phase, patients were randomly assigned to 4 treatment groups: placebo for 50 weeks, fluoxetine for 14 weeks followed by placebo for 36 weeks, fluoxetine for 38 weeks followed by placebo for 12 weeks, or fluoxetine for the entire 50 weeks. When on active medication (either open-label or double-blind), patients received a fixed 20-mg dose of fluoxetine once per day and were not allowed other psychoactive medications. During this period patients were assessed for both relapse and ongoing subsyndromal symptoms of depression. This report uses a subset of the population consisting of all patients randomized into the double-blind phase at the Salt Lake City, Utah, treatment site. They remained in the double-blind period an average of 18 weeks. One year after patients left the original study, they were contacted and reevaluated for the long-term follow-up examination.

Long-Term Follow-Up Study

During the year that elapsed between the end of the double-blind period and the long-term assessment, patients were no longer in a treatment mandated by the study, but made independent decisions regarding continued treatment with medication and/or psychotherapy. As participants terminated the double-blind period, they were encouraged to seek further treatment; patients were given psychiatric referrals, offered treatment by the study psychiatrists on a private basis, and even offered financial assistance for further treatment.

At the long-term evaluation, patients were evaluated with a 21-item HAM-D. Scores from 10 through 17 (corresponding to scores of 8 to 15 on the HAM-D-17) were considered to demonstrate subsyndromal symptom levels, while higher scores were assumed to indicate a recurrence of depression (full relapse) and lower scores indicated stable remission of depression (stable recovery). In addition, the Holmes Social Readjustment Rating Scale[57] was administered, and each item was reviewed in an interview format to assess potential factors associated with treatment failure. Information regarding life stresses was reviewed by 2 of the authors, and a collective decision was made regarding the presence of stresses that might have been significant for the patient. Typical psychosocial problems considered potentially significant included major financial problems, serious medical illness, severe medical or mental illness in a child, or substantial employment problems.

The Weissman Social Adjustment Scale (SAS)[58] was administered at baseline, at the end of 12 weeks of open treatment, and again 12 months after the patient relapsed or otherwise terminated the double-blind phase. The SAS is an interviewer-administered scale developed to assess social adjustment in patients with depression; it provides both a global score and scores in the specific areas of work, social-leisure activities, extended family, marriage, and parental functioning. Scores in the moderate or severe range on the global scale were considered clinically significant in terms of overall social adjustment. Similarly, scores in the moderate or severe range were considered clinically significant when addressing specific areas like marital functioning.

The diagnosis of a personality disorder (according to DSM-IV criteria) was based upon a review of the case, combining information from the treating psychiatrist, clinic staff, and the research assistant conducting the interviews. These evaluations were done in case conferences, and if consensus was not reached, an additional evaluation was done.

If patients were believed to be unstable, changing medication, or experiencing significant life changes at the time of the long-term assessment, an additional evaluation was conducted once the patient's condition had stabilized. In 39 of the 59 cases, a second long-term evaluation was performed to confirm the patient's long-term status. Al-

though the 2 evaluations were consistent in most cases, the changes that were observed did not alter overall outcomes. Consequently, only information from the second evaluation was used in the data analysis.

To test overall study effects, analysis of variance (ANOVA), was performed using the SPSS, Version 6.1.4 (Chicago, Ill.), statistical package with the HAM-D scores as the dependent variable. Group and treatment differences were assessed using the McNemar test for comparisons of categorical variables when the samples were related or the Pearson chi-square when the samples were independent. A paired t test was used to compare continuous variables at the baseline and open phase.

RESULTS

One hundred sixteen patients from our site signed consent forms for entry into the original study. Fifty-nine showed marked improvement after 12 weeks on fluoxetine treatment and, based on a rigid set of criteria, were allowed to enter the double-blind phase of the study. Baseline demographic and clinical characteristics of those patients who were excluded from (N = 57) and those who were eligible for (N = 59) the double-blind phase are found in Table 1. In addition, scores at the end of the 12-week open phase for those patients (N = 57) who continued into the double-blind phase are also included. (Data on social adjustment at the 13-week period were not acquired for 2 patients.)

The data reported in Table 1 show that before entering treatment, the patient population was highly symptomatic with multiple indicators of chronic depressive illness. There were no baseline differences on the depressive symptoms or SAS between the patients who entered the double-blind phase and those who were excluded. At baseline, over 90% of all patients were seen as moderately or severely impaired on the overall SAS score. Patients admitted into the double-blind portion of the study showed a major improvement in both the overall score (McNemar test $p < .001$) and each of the subscales of the SAS. This difference was significant at the $p < .001$ level for social leisure, at the $p < .005$ level for extended family and economic functioning, and at the $p < .05$ level for marital, parental, and work subscales. The change in HAM-D scores was even more dramatic with an average improvement of 85%.

Of the 59 eligible patients (2 did not enter the double-blind phase and 2 more were lost to long-term follow-up) for the double-blind phase, 32 patients continued on medication, usually fluoxetine (N = 22). The dose of fluoxetine (or any other medication) was not limited during this naturalistic follow-up period. Three patients were treated with both medication and psychotherapy, and 23 declined all treatment. The patients on medication had been on medications continuously since the end of the original study.

Table 1. Demographic and Clinical Characteristics of Patients From 1 Site (Salt Lake City) of Original Study[17]

Characteristic	Baseline Not Eligible[a] (N = 43)	Eligible[a] (N = 59)	End of Open-Phase Entered[a] (N = 57)
Demographics			
Age, mean ± SD, y	36.8 ± 11.0	39.0 ± 11.0	
Female, N (%)	26 (61)	44 (75)	
HAM-D-17, mean ± SD	25.8 ± 3.6	24.5 ± 4.2	3.2 ± 2.5[b]
Melancholia, N (%)	12 (28)	21 (36)[c]	
Indicators of chronic depression, N (%)			
Index episode > 2 years	26 (60)	35 (59)	
Chronic depression	26 (60)	39 (66)	
2 or more previous episodes	17 (40)	28 (47)	
History of partial recovery	19 (44)	31 (53)	
Childhood onset	22 (51)	24 (41)	
< 24 months between episodes	32 (74)	42 (71)	
3 or more chronic indicators	34 (79)	48 (81)	
Moderate or severe impairment on SAS, N (%)			
Economic inadequacy	16 (37)	25 (42)	5 (9)[f]
Work	24 (55)	35 (59)	3 (6)[g]
Social leisure	35 (82)	49 (83)	16 (28)[h]
Extended family	16 (37)	35 (60)	10 (18)[f]
Marital[d]	13 (45)	20 (51)	6 (21)[g]
Parental[e]	4 (17)	13 (38)	2 (6)[g]
Overall functioning	37 (87)	57 (97)	11 (19)[h]

[a]Patients not eligible for, eligible for, and entered into the 50-week double-blind treatment phase. Of 57 "not eligible" patients, complete baseline data were available for 43 patients.
[b]$p < .001$, paired t test ($t = 32.33$, $df = 56$), baseline vs. end of open phase.
[c]Based on 58 patients.
[d]Based on group sizes of 29, 39, and 28 patients, respectively.
[e]Based on group sizes of 24, 34, and 32 patients, respectively.
[f]McNemar test is significant at $p < .005$, baseline vs. end of open phase.
[g]McNemar test is significant at $p < .05$, baseline vs. end of open phase.
[h]McNemar test is significant at $p < .001$, baseline vs. end of open phase.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, SAS = Weissman Social Adjustment Scale.

At the long-term evaluation, 29 patients (53%) were considered to have a stable recovery (HAM-D-21 score < 10), 12 patients (22%) were considered to have a full relapse (HAM-D-21 score ≥ 18), and 14 patients (25%) were considered to have subsyndromal symptoms (HAM-D-21 scores 10 to 17). Results for patients in these 3 categories are presented in Table 2 and Table 3. An ANOVA that included 6 measures ("true drug" or "placebo" response; subsyndromal symptoms during the double-blind period; medication status at long-term; having at least 3 indicators of chronicity; marital functioning [single, at least moderate problems, or no worse than mild problems]; and the SAS overall measure at the long-term evaluation) resulted in a significant relationship with HAM-D scores at the long-term evaluation ($F = 10.53$, $df = 8,44$; $p < .001$). The significance of each of these variables will be discussed in turn.

Table 2. Demographic and Clinical Characteristics Identified During Original Study[17] for the 3 Outcome Groups at 1 Study Site (Salt Lake City)*

Characteristic	Full Relapse[a] (N = 12)	Subsyndromal[b] (N = 14)	Stable Recovery[c] (N = 29)
Demographics			
Female, N (%)	10 (83)	7 (50)	23 (79)
Melancholia, N (%)	0 (0)[d]	4 (29)	2 (7)
Normal neurovegetative status, N (%)[e]	8 (67)	8 (57)	18 (62)
Indicators of chronic depression, N (%)			
Index episode > 2 years	8 (67)	11 (79)	14 (48)
Chronic depression	8 (67)	12 (86)	16 (55)
2 or more previous episodes	5 (42)	5 (36)	15 (52)
History of partial recovery	7 (57)	9 (67)	24 (84)
Childhood onset	4 (33)	6 (43)	11 (38)
< 24 months between episodes[f]	2 (29)	3 (50)	12 (63)
3 or more chronic indicators	4 (33)	7 (50)	19 (66)
Response pattern during early treatment period, N (%)			
"True drug" responders	7 (58)	11 (78)	20 (69)
Early responders	4 (33)	2 (14)	7 (24)
Inconsistent responders	4 (33)	4 (29)	8 (28)
Left prior to residual categorization	6 (50)	3 (21)	9 (31)
Presence of subsyndromal symptoms during double-blind treatment, N (%)			
Stable low HAM-D scores	0 (0)	3 (18)	12 (40)
High episodic HAM-D scores[g]	4 (33)	5 (36)	13 (45)
High average HAM-D scores[h]	8 (66)	6 (45)	4 (15)

*Abbreviation: HAM-D = Hamilton Rating Scale for Depression.
[a]21-item Hamilton Rating Scale for Depression (HAM-D-21) score of ≥ 18 at long-term assessment.
[b]HAM-D-21 score of 10 to 17 at long-term assessment.
[c]HAM-D-21 score of < 10 at long-term assessment.
[d]Based on group size of 11 patients.
[e]Patients who endorse limited appetite, weight loss, and loss of sleep more often than excessive appetite, weight gain, and excessive sleep.
[f]Based on group sizes 7, 6, and 19 patients, respectively.
[g]Occasional HAM-D-21 scores of ≥ 10, but averaging < 8 (weeks of relapse excluded).
[h]Average HAM-D-21 scores of ≥ 8 (weeks of relapse excluded).

Table 3. Clinical Characteristics Identified at the Long-Term Follow-Up for the 3 Outcome Groups at 1 Study Site (Salt Lake City)*

Characteristic	Full Relapse[a] (N = 12)	Subsyndromal[b] (N = 14)	Stable Recovery[c] (N = 29)
Medication status, N (%)			
On medication	6 (50)	9 (64)	17 (59)
Off medication	6 (50)	5 (36)	12 (41)
Moderate or severe impairment on SAS, N (%)			
Economic inadequacy	4 (33)	2 (14)	2 (7)
Work	12 (100)	4 (29)	4 (14)
Social leisure	10 (83)	5 (36)	3 (10)
Extended family	10 (83)	5 (36)	4 (14)
Marital[d]	7 (70)	2 (33)	1 (6)
Parental[e]	6 (67)	2 (40)	2 (13)
Overall functioning	12 (100)	10 (71)	3 (10)
Presence of contributing factors to long-term functioning, N (%)			
Medication failure	4 (33)	2 (14)	0 (0)
Marriage	7 (58)	2 (14)	1 (3)
Personality disorder	4 (33)	2 (14)	1 (3)
Personal problems	3 (25)	8 (57)	8 (28)
Poor psychiatric care	1 (8)	0 (0)	0 (0)
Decision to stop treatment	3 (25)	2 (14)	2 (7)
Substance abuse	1 (8)	0 (0)	0 (0)
Wrong diagnosis	0 (0)	1 (7)	0 (0)
Health problems	0 (0)	0 (0)	1 (3)

*Abbreviation: SAS = Weissman Social Adjustment Scale.
[a]21-item Hamilton Rating Scale for Depression (HAM-D-21) score of ≥ 18 at long-term assessment.
[b]HAM-D-21 score of 10 to 17 at long-term assessment.
[c]HAM-D-21 score of < 10 at long-term assessment.
[d]Based on group sizes of 10, 6, and 18, respectively.
[e]Based on group sizes of 9, 5, and 16, respectively.

In their analysis of the original study, McGrath et al.[56] found that endogenous neurovegetative response patterns and a delayed and persistent ("true drug") response were predictive of fluoxetine benefit compared to placebo and that chronicity was associated with poorer survival. We found no relationship between neurovegetative status and outcome as measured by HAM-D scores ($F = 0.24$, $df = 3,51$; $p = .62$). The 2 response patterns "true drug" versus "placebo" were not directly related to outcome as measured by HAM-D scores ($F = 2.00$, $df = 3,50$; $p = .12$). While there was an interaction between the 2 response patterns and medication status at the long-term, the selection bias regarding medication status made its interpretation difficult. Given the relative difference in past publications, this sample size was too small to conclude that a difference does not exist for the medication response pattern described by McGrath et al.[56] Similarly, no simple relationship was found between chronicity and long-term outcome. An ANOVA of the 6 measures of chronicity (onset of current episode ≥ 24 months ago, current episode considered chronic, 2 or more previous episodes of depression, history of only partial recovery between episodes of depression, onset of depression in childhood, < 24 months between the current and previous episode) resulted in no significant relationship with HAM-D scores ($F = 0.64$, $df = 6,48$; $p = .57$) at the long term. Finally, we specifically examined whether there were more responders on medications and nonresponders off medications for each of these 3 variables (neurovegetative status, true drug vs. placebo response, and chronicity). There was no obvious pattern. The lack of significance suggests that other variables had gained prominence in this naturalistic period.

Despite the fact that all patients who were randomized had completely remitted, many of them experienced a subsyndromal level of symptoms during the double-blind period as shown in Table 2. A number of patients (N = 18) were not assessed for subsyndromal depressive symptoms during the double-blind phase because they left treatment too early to be categorized. None of the patients in the full relapse group who were assessed displayed a stable remission of symptoms during the double-blind part of the study. These patients were all considered to have subsyndromal

symptoms based on either occasional HAM-D scores ≥ 10 (high episodic HAM-D scores) or average HAM-D scores ≥ 8 (high average HAM-D scores). In contrast, of patients who were doing well at the long-term evaluation, 40% displayed a stable remission of symptoms during the double-blind part of the study. Patients who demonstrated subsyndromal HAM-D scores at the long-term evaluation fell halfway between these 2 groups. These differences did not achieve significance as main effects in the general ANOVA previously reported; however, when their relationship to HAM-D scores at the long-term outcome was assessed separately from other variables, the ANOVA approached significance ($F = 2.76$, $df = 3,51$; $p = .051$).

The use of medications at the long-term evaluation appeared unrelated to outcome as measured by HAM-D scores. This was true based on a general ANOVA in which medication use was just one of several measures and in a simple ANOVA assessing only medication status. As indicated in Table 3, a substantial number of the patients doing well had decided not to continue using medication, whereas a number of patients experiencing full or subsyndromal relapse symptoms remained on medications. Given this selection bias, it is not surprising that no interaction was found between medication status and HAM-D scores ($F = 0.06$, $df = 1,53$; $p = .99$).

Although baseline and 12-week SAS scores were unrelated to HAM-D scores at the long-term evaluation, the SAS scores at the long term were related. ANOVA for the SAS at that period was significant ($F = 11.94$, $df = 9,45$; $p < .001$), with significant main effects for marital stability ($p = .05$), work ($p < .001$), and overall functioning ($p < .001$).

In conference, each case was reviewed to verify all major problem areas that might have been related to the return of depressive symptoms. The coincident factors identified are presented at the end of Table 3. All patients with full relapse, but only 34% of patients with stable recovery, were found to have experienced at least 1 of the conditions in the list. Based on these factors, direct medication failure per se was seen as a factor for deterioration in only 6 patients, while psychosocial problems such as personal stresses, marital problems, and personality disorder were substantially more common. Nearly 90% (N = 23) of the symptomatic patients had at least 1 psychosocial factor present, including a decision not to use medication, personality disorder, poor marital adjustment, or significant personal stresses (such as severe illness in family members and problems with children, work, health, or finances). In general, the percentage of patients experiencing a problem was directly related to outcome, with full relapsers experiencing the most problems and those in full recovery the least. Marital problems appeared to show this pattern most clearly, with full relapsers experiencing the most problems (58%) and those in full recovery the least (3%). In contrast, the existence of significant personal problems was highest for the patients experiencing subsyndromal symptoms (57%), while the patients in full recovery and full relapse were similar, at 28% and 25%, respectively. Why this factor should relate to outcome in this unusual manner is unclear.

Since marital problems were associated with an unfavorable outcome in one third (9 of 26) of those who were not doing well, and a main effect for marital status was observed in the previously reported ANOVA that included all the SAS scores, the interaction of marital adjustment and long-term outcome was further assessed. Moderate and severe SAS scores were used to define a problematic marriage. Although there was a strong statistical relationship between outcome and marital functioning, a stable marriage did not ensure that patients would do well among married patients: 3 of 10 experiencing a full relapse and 4 of 6 experiencing subsyndromal symptoms were in good marriages. However, the data suggest that a problematic marriage was almost never associated with a full recovery. Only 1 of the 18 married patients experiencing a stable recovery was in an unstable marriage. The chi-square test comparing the 3 marital states with the outcome groups [$\chi^2 = 20.17$, $df = 4$, $p < .001$] was significant. Subjects in satisfactory marriages did fairly well, those in problematic marriages did poorly, and single patients fell in between.

DISCUSSION

Several conclusions can be drawn from these data. Half of these patients (53%, N = 29) showed little evidence of depression 1 year after treatment in a double-blind study for depression. Although the remission these patients experienced was long lasting, there were no differences in baseline levels of depressive symptoms, history of chronic symptoms, or social maladjustment between those who were doing well and those who had a return of symptoms at the long-term evaluation.

Psychosocial factors were associated with the return of depressive symptoms at the long-term assessment. Among the patients who experienced a recurrence of symptoms, the most common coincident factors were the presence of significant life stresses and marital problems. Life stresses have been associated with depression,[44,59] as has the combination of life stresses and marital problems.[60] Additional factors identified in this study included medication failure, personality disorder, and a decision not to continue medication. With the exception of medication failure, these factors may respond to nonpharmacologic intervention. Despite the encouragement given to patients to continue treatment with medication and/or psychotherapy at the end of the double-blind treatment phase, only 3 patients decided to pursue psychotherapy. Most of these factors occurred more frequently in patients with full relapses. Conversely, the existence of significant personal problems was highest for the patients experiencing subsyndromal symptoms.

At the long-term evaluation, one quarter of patients (25%, N = 14) experienced mood-related symptoms at a subsyndromal level. This phenomenon of partial continuing symptoms has been reported previously in another long-term follow-up study[43] and in community surveys.[29,45] The subsyndromal level of symptoms reported here was generally associated with at least moderate impairment in social adjustment, suggesting that this level of symptomatology is clinically significant. Similar findings of social impairment among patients with subsyndromal depressive symptoms have been found in other studies.[11,12,35,36]

Reasonable marital adjustment was shown to be more strongly related to success than other factors. Almost all patients who did well were single or in satisfactory marriages, although a positive marriage was not always connected with a successful outcome. These findings are similar to those of an earlier study of patients treated with psychotherapy.[61] Although that study showed some resolution of depressive symptoms, marital dysfunction persisted. Alternatively, another report has suggested that marital adjustment and other psychosocial factors do not influence long-term outcome in recurrent, severe major depression.[55]

The presence of subsyndromal symptoms during the double-blind phase was found to be predictive of poor long-term outcome. Partial antidepressant responders have been shown in a number of studies to be at particular risk of relapse.[11,40,41] However, the observations in this study differ from those studies in 2 important aspects. First, the patients in this study had a complete and sustained remission of depressive symptoms prior to developing subsyndromal symptoms. Second, included within this group of patients with subsyndromal symptoms were those who experienced only brief episodes of elevated HAM-D scores as well as those with high average HAM-D scores. Earlier studies appear to have included only the second group.

Although statements of causality cannot be made, the poor outcome in only 6 cases was attributed to failure of antidepressant medication to sustain its effectiveness. In 5 of these cases, the presence of additional confounding factors complicates interpretation of the relative importance of medication failure. Even though these 6 cases represent a small portion of the study population, psychiatric practices can become collection points for "difficult to treat" patients, thus skewing the perception of some professionals regarding the long-term efficacy of antidepressant medications. However, we suspect that many treatment-resistant patients exhibit the confounding variables cited in our list of relapse factors.

CONCLUSION

In summary, long-lasting remission of depression was found in about half (53%) of patients over a period of up to 2 years. The importance of continued monitoring of both mood and overall psychosocial adjustment was demonstrated, i.e., initial measures of social functioning and depression did not predict outcome as well as later measures. The study findings also suggest that after successful acute antidepressant treatment, the need for psychotherapy should be carefully considered, particularly as it relates to dealing with issues such as marriage and handling significant life stresses. This is especially important since the reappearance of symptoms was generally associated with the presence of psychosocial factors, most commonly marital adjustment. Additionally, the quality of the treatment response may indicate a need for more extended treatment, since patients experiencing subsyndromal symptoms during the double-blind period were more likely to exhibit depressive symptoms at the long-term evaluation.

Medication failure was associated with poor outcome in only a small number of patients, most of whom also experienced significant life stressors. The efficacy of antidepressant medications in the long-term management of depression has been well established in controlled trials. Naturalistic long-term treatment of depression may improve by continuing patients on antidepressant therapy while also assisting them to deal better with life stresses.

Drug names: citalopram (Celexa), fluoxetine (Prozac), mirtazapine (Remeron), paroxetine (Paxil), sertraline (Zoloft).

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