# Long-Term Treatment Outcomes of Depression With Associated Anxiety: Efficacy of Continuation Treatment With Fluoxetine

Melissa J. Joliat, Ph.D.; Mark E. Schmidt, M.D.; Maurizio Fava, M.D.; Shuyu Zhang, M.S.; David Michelson, M.D.; Nancy J. Trapp, B.A.; and Cherri M. Miner, M.D.

***Background:*** Severity of anxiety does not appear to influence the antidepressant response to fluoxetine during acute treatment of major depressive disorder (MDD). We report a retrospective pooled analysis of 2 studies to assess the effect of associated anxiety on the efficacy of fluoxetine in the continuation treatment phase of MDD.

***Method:*** Patients whose MDD remitted (study 1) or responded (study 2) after approximately 12 to 13 weeks of open-label treatment with fluoxetine 20 mg daily were randomly assigned in double-blind fashion to placebo, continued treatment with fluoxetine 20 mg daily, or, in study 2 only, treatment with enteric-coated fluoxetine 90 mg once weekly, for at least 25 weeks. Both studies included male and female outpatients who met criteria for MDD as assessed by DSM-III-R (study 1) or DSM-IV (study 2). Patients were categorized into high anxiety ($\geq 7$) or low anxiety ($< 7$) subgroups based on baseline Hamilton Rating Scale for Depression (HAM-D) anxiety/somatization subfactor scores. Subgroups were compared by therapy for time from randomization to relapse and change in efficacy scores.

***Results:*** No significant differences in time to relapse were observed between anxiety subgroups in either active treatment group. However, in patients switched to placebo for continuation treatment, the high anxiety subgroup had a significantly higher risk of relapse than those with low anxiety (risk ratio = 1.63, $p = .013$). Significant differences between anxiety groups were seen in change in HAM-D anxiety/somatization subfactor scores in the fluoxetine 20 mg and placebo treatment groups, and in change in HAM-D-17 scores in the placebo treatment group ($p < .05$).

***Conclusion:*** Although high baseline anxiety does not appear to impact the benefit of continuation therapy with fluoxetine, it does appear to predict increased risk of relapse in individuals who do not remain on antidepressant therapy for the duration of continuation treatment.

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*Corresponding author and reprints: Melissa J. Joliat, Ph.D., Eli Lilly and Company, P.O. Box 812, Northeast Harbor, ME 04662 (e-mail: joliat@lilly.com).*

Many patients with depressive illness also report prominent symptoms of anxiety.[1] Although anxious depression is not considered a separate classification according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), patients who present with both depressive and anxiety symptoms have been reported to have a poorer long-term prognosis[2] and an increased risk of suicidality[3,4] compared with patients who present with symptoms of only one of these illnesses. Patients with anxious depression exhibit greater functional impairment than patients with either disorder alone[5–7] and may require longer periods of treatment prior to achieving recovery from symptoms.[8]

Major depressive disorder with comorbid anxiety disorders has been found to be associated with poor response to antidepressant treatment.[9] This is consistent with the observation that depression with high ratings of anxiety symptoms is less likely to respond to antidepressant treatment in some,[10,11] but not all,[4,12] studies, regardless of the type of antidepressant used. The association between anxious depression and poor response to antidepressant treatment may account for the results of a recent study that demonstrated that the concomitant use of anxiolytics and/or hypnotics was a significant predictor of treatment resistance in older adults with depression.[13]

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Depressed patients who respond to acute treatment are advised to remain on antidepressant treatment for an additional 4 to 9 months.[14,15] This continuation treatment phase permits consolidation of the initial treatment gains achieved during acute treatment and prevents relapse. Although a number of studies have examined the acute response to antidepressants in patients with anxious depression,[16–18] few data exist concerning the relative value of maintenance treatment in these patients. To address this question, we have retrospectively examined data from 2 large relapse prevention trials, stratifying the sample using the anxiety/somatization subfactor of the modified 17-item Hamilton Rating Scale for Depression (HAM-D-17).[19] Patients were categorized as high anxiety (≥ 7) and low anxiety (< 7) on this subfactor.[4] Using data from 2 multicenter, double-blind, placebo-controlled trials of the long-term efficacy of fluoxetine (study 1[20] and study 2[21]), we analyzed the efficacy of both available fluoxetine dose regimens of 20 mg daily and enteric-coated 90 mg once weekly in the continuation treatment phase of major depressive disorder presenting with associated anxiety.

## METHOD

### Patient Population

Details on the methods for both studies have been published previously (study 1,[20] study 2[21]). Both studies included male and female outpatients who met criteria for nonpsychotic major depressive disorder as assessed by the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III-R) (study 1) or DSM-IV (study 2) and had a single or recurrent episode of depression with a current duration of at least 1 month. In order to be enrolled in the study, patients in study 1 must have had a score of ≥ 16 on the HAM-D-17, while patients in study 2 must have had a HAM-D-17 score of ≥ 18 and a Clinical Global Impressions-Severity of Illness scale (CGI-S) score of ≥ 4. Written informed consent was obtained from all patients in accordance with the Helsinki convention. The study protocol was approved by the institutional review board of each of the study centers.

Baseline HAM-D anxiety/somatization subfactor scores (HAM-D items 10–13, 15, and 17) were used to categorize patients as high anxiety (≥ 7) or low anxiety (< 7) at entry into each study.

### Study Design

Both studies were multicenter, double-blind, placebo-controlled parallel trials conducted in the United States. Concise descriptions of study 1[20] and study 2[21] follow.

Study 1 consisted of 3 study phases: a 1-week, medication-free assessment/baseline phase, a 12- to 14-week acute treatment phase in which all patients received fluoxetine 20 mg daily (open label), and a double-blind continuation treatment phase in which patients who remitted while receiving acute treatment were randomly assigned to placebo or continued treatment with fluoxetine for 14 weeks, 38 weeks, or 50 weeks. Patients in the 14-week and 38-week fluoxetine treatment groups were switched to placebo after the allotted time for the duration of the study (50 weeks). For the purposes of the present analysis, only patients randomly assigned to receive placebo or fluoxetine for at least 38 weeks were included (N = 298: fluoxetine 20 mg daily, N = 202; placebo, N = 96). Remission was defined as no longer meeting the DSM-III-R criteria for major depression and having a HAM-D-17 score < 7 for 3 consecutive weeks. During the continuation phase, patients were monitored for relapse, which was defined as either meeting the DSM-III-R criteria for major depression for at least 2 weeks or having a HAM-D-17 score of ≥ 14 for 3 consecutive weeks (see details of methods in Reimherr et al.[20] or Stewart et al.[22]).

Study 2 also consisted of 3 phases. The initial assessment phase was followed by a 13-week open-label acute treatment phase in which all patients received fluoxetine 20 mg daily. Patients who responded to acute treatment were randomly assigned to 1 of 3 treatment groups for the continuation treatment phase. Patients received placebo, enteric-coated 90 mg fluoxetine weekly, or continued treatment with fluoxetine 20 mg daily for 25 weeks. Response was defined as no longer meeting diagnostic criteria for major depressive episode per DSM-IV and having a modified HAM-D-17 score ≤ 9 and CGI-S score ≤ 2. If patients had a significant reemergence of depressive symptoms during the continuation treatment phase (i.e., 50% or greater increase in HAM-D-17 score over the rating at the randomization visit and a HAM-D-17 score ≥ 12), they were seen at weekly intervals to monitor for relapse. Relapse was defined as meeting the criteria for major depressive episode (as determined by the Structured Clinical Interview for DSM-III-R, Patient Version, major depressive episode module) and having an increase in the CGI-S score of 2 or more relative to the rating before randomization for 2 consecutive visits (see details of methods in Schmidt et al.[21]). All patients randomly assigned to continuation therapy were included in this analysis (N = 501: fluoxetine 90 mg weekly, N = 190; fluoxetine 20 mg daily, N = 189; placebo, N = 122).

In study 1, only patients who remitted during the acute phase were randomly assigned to the continuation phase, whereas in study 2, patients who responded during the acute phase were randomly assigned to the continuation phase (Table 1). For purposes of this report, all patients who were randomly assigned to continuation treatment in either study will be considered as achieving a "response to acute treatment." Demographics and baseline characteristics for the 2 studies were similar and can be found in the original reports of these trials.[20,21]


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Table 1. Entry Criteria and Definition of Relapse for Continuation Phase of Long-Term Trials of Fluoxetine for Depression

| Variable | Study 1 | Study 2 |
|---|---|---|
| Score required for entry into the continuation phase | Remission during acute treatment: no longer meeting DSM-III-R criteria for major depression, plus HAM-D-17 score < 7 for 3 consecutive weeks | Response during acute treatment: no longer meeting DSM-IV criteria for major depressive disorder, plus a modified HAM-D-17 score ≤ 9 and CGI-S score ≤ 2 for the last 2 visits of the acute treatment phase |
| Definition of relapse | Either meeting the DSM-III-R criteria for major depression for at least 2 weeks or having a HAM-D-17 score of ≥ 14 for 3 consecutive weeks | Meeting the criteria for major depressive episode (SCID-P major depressive episode module) plus an increase in the CGI-S score of 2 or more relative to the rating before randomization for 2 consecutive visits |

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, SCID-P = Structured Clinical Interview for DSM-III-R, Patient Version.

### Assessments

In order to investigate the effects of comorbid anxiety on the outcome of continuation treatment for depression, data from study 1 and study 2 were pooled. For both studies, the primary efficacy measure was the categorical diagnosis of relapse. Additional efficacy measures included the HAM-D anxiety/somatization subfactor, the modified HAM-D-17, HAM-D item 1 (depressed mood), and CGI-S. The modified HAM-D-17 was defined as the combination of the following items from the HAM-D-28: for all patients, items 1 through 3, 7 through 11, 13 through 15, and 17 were combined with either items 4, 5, 6, 12, and 16 (for "typical" neurovegetative symptoms) or items 22, 23, 24, 25, and 26 (for "atypical or reversed" neurovegetative symptoms). The higher of the 2 combination scores was used to determine protocol eligibility, response, and relapse. This modification weights "atypical" symptoms equally with "typical" symptoms. The CGI-S rating scale was administered to assess the global severity of the disorder and its change over the course of the study.

Adverse events measurements and analysis have been published previously.[20,21]

### Statistical Methods

Efficacy analyses were conducted on an intent-to-treat basis. All statements of significance were based on a 2-sided test with an $\alpha = .05$, unless otherwise stated.

Patients were included in the analyses if they had both continuation phase baseline and postbaseline measurements. The baseline measurement for the continuation treatment analysis was the randomization-to-continuation visit for both studies. If this measurement was missing or incomplete at the specified baseline, then the baseline was considered the last visit with a non-missing measurement prior to randomization to continuation treatment. Total scores were considered missing if any one of the individual items within the total was missing.

To better understand the effects of severity of anxiety at the time of presentation for treatment (visit 2, at which patients began open-label treatment with fluoxetine 20 mg daily) on risk of relapse, we stratified the data using the anxiety/somatization subscores of < 7 (low anxiety) or ≥ 7 (high anxiety). For each treatment, the possible effect of baseline (prior to acute treatment) anxiety on risk of relapse was examined in a proportional hazard analysis of time to relapse using the Cox proportional hazard model with a term for anxiety level (high and low). Kaplan-Meier analysis of time to relapse was performed for each treatment group (to compare anxiety effect).

For each treatment group, analyses of change from baseline to endpoint (last observation carried forward) were conducted using an analysis of variance (ANOVA) model with a term for anxiety level for the HAM-D anxiety/somatization subfactor score, the modified HAM-D-17 total score, the HAM-D item 1 (depressed mood) score, and the CGI-S score. For purposes of this analysis, length of continuation therapy for both studies was approximately 25 weeks.

Patient characteristics, including demographics and severity of illness, were summarized for each of the 3 treatment groups at continuation treatment baseline by anxiety level. Differences between anxiety strata were assessed using Fisher exact test for categorical variables and ANOVA model with a term for anxiety level for continuous variables.

## RESULTS

### Demographics

Individual demographics for study 1 and study 2 have been previously reported.[20,21] Table 2 shows the pooled demographics and clinical characteristics for patients at the time of randomization to the continuation phase, stratified by high and low baseline anxiety and separated by treatment group. The overall low anxiety subgroup contained a statistically significantly lesser percentage of female patients. A statistically significantly higher percentage of patients in the overall low anxiety subgroup were white, but in individual treatment groups, the difference was significant only in the fluoxetine 20 mg group. In addition, mean scores on the HAM-D anxiety/somatization subscale were significantly higher in the high anxiety subgroup compared with the low anxiety group overall, even after patients achieved an antidepressant response to acute treatment. The difference in HAM-D anxiety/somatization subscale scores between high anxiety and low anxiety

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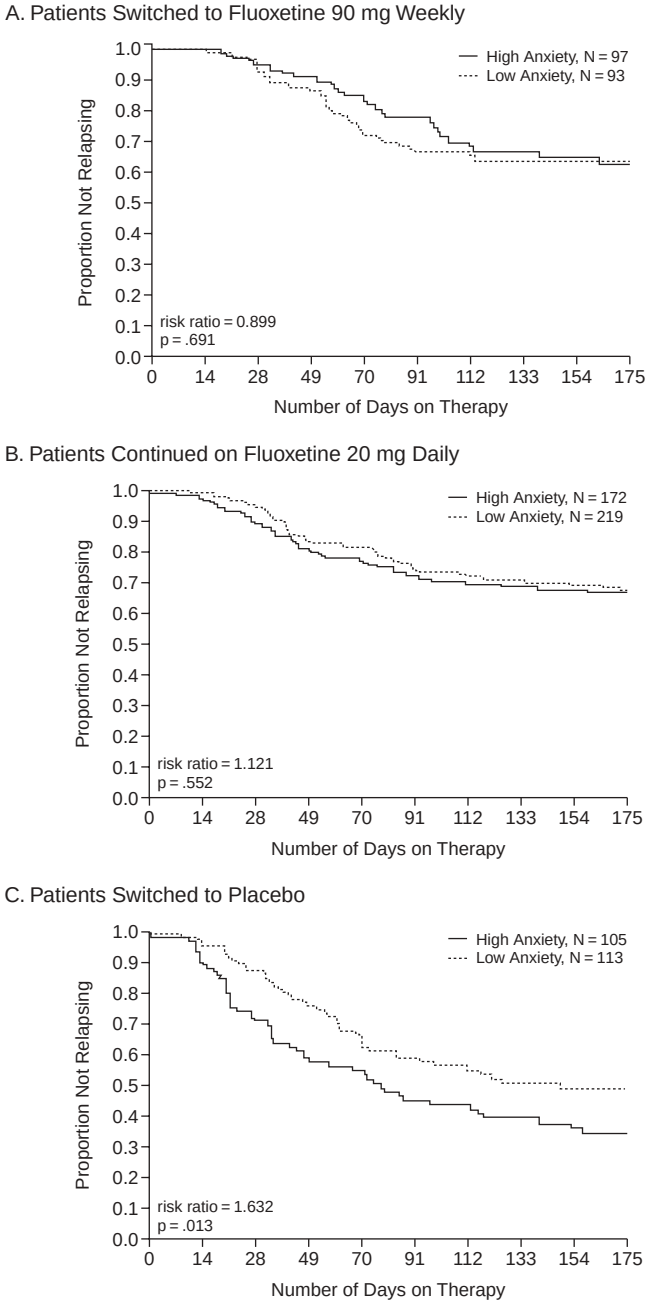
Table 2. Demographics and Clinical Characteristics for Patients at Randomization to Continuation Treatment in Long-Term Trials of Fluoxetine for Depression

| Characteristic | High Anxiety | | | | Low Anxiety | | | | p Values, High vs Low Anxiety | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Weekly 90 mg (N = 97) | Daily 20 mg (N = 172) | Placebo (N = 105) | Overall (N = 374) | Weekly 90 mg (N = 93) | Daily 20 mg (N = 219) | Placebo (N = 113) | Overall (N = 425) | Weekly 90 mg | Daily 20 mg | Placebo | Overall |
| Age, mean ± SD, y | 40.8 ± 12.1 | 40.6 ± 10.8 | 41.5 ± 11.4 | 40.9 ± 11.2 | 41.0 ± 12.8 | 41.3 ± 11.0 | 41.2 ± 10.4 | 41.2 ± 10.8 | .903 | .531 | .831 | .705 |
| Female, % | 70.1 | 72.1 | 76.2 | 72.7 | 66.7 | 65.8 | 66.4 | 66.1 | .642 | .190 | .135 | .046 |
| White, % | 91.8 | 84.3 | 86.7 | 86.9 | 91.4 | 95.9 | 92.0 | 93.9 | 1.000 | < .001 | .270 | < .001 |
| Recurrent depression, % | 75.3 | 69.8 | 70.5 | 71.4 | 68.8 | 71.2 | 69.0 | 70.1 | .337 | .823 | .883 | .698 |
| HAM-D-17 score, mean ± SD | 4.01 ± 2.55 | 3.78 ± 2.55 | 3.57 ± 2.50 | 3.78 ± 2.53 | 4.25 ± 2.51 | 3.44 ± 2.47 | 3.15 ± 2.41 | 3.54 ± 2.49 | .519 | .183 | .206 | .175 |
| HAM-D item 1 score, mean ± SD | 0.20 ± 0.49 | 0.29 ± 0.54 | 0.28 ± 0.49 | 0.28 ± 0.52 | 0.32 ± 0.55 | 0.25 ± 0.48 | 0.27 ± 0.48 | 0.27 ± 0.50 | .562 | .446 | .871 | .721 |
| HAM-D anxiety/ somatization subfactor score, mean ± SD | 1.40 ± 1.24 | 1.35 ± 1.12 | 1.19 ± 1.22 | 1.32 ± 1.18 | 1.26 ± 1.17 | 1.08 ± 1.04 | 0.89 ± 0.82 | 1.07 ± 1.02 | .411 | .014 | .035 | .001 |
| CGI-S score, mean ± SD | 1.36 ± 0.48 | 1.37 ± 0.52 | 1.29 ± 0.45 | 1.34 ± 0.49 | 1.38 ± 0.49 | 1.34 ± 0.49 | 1.28 ± 0.47 | 1.33 ± 0.48 | .826 | .562 | .968 | .755 |

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression, HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

**Figure 1. Kaplan-Meier Relapse Graphs for High and Low Anxiety Patients on Continuation Therapy After Achieving an Acute Response to Antidepressant Therapy With Fluoxetine 20 mg Daily[a]**




[a]p Values derived from log-rank test.

subgroups at randomization was statistically significant in the fluoxetine 20 mg group and the placebo group, individually, but not in the 90 mg weekly group.

## Efficacy Results

***Kaplan-Meier time to relapse.*** There were no significant differences in distribution of days to relapse between the high anxiety subgroup and low anxiety subgroup for either of the fluoxetine treatment groups (Figures 1A


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**Table 3. Change From Randomization to Endpoint During Continuation Treatment in Long-Term Trials of Fluoxetine for Depression**

| Assessment Scale | Anxiety Level | Fluoxetine 90 mg Weekly | | | | | | Fluoxetine 20 mg Daily | | | | | | Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Baseline | | Change to Endpoint | | p | | Baseline | | Change to Endpoint | | p | | Baseline | | Change to Endpoint | | p |
| | | N | Mean | (SD) | Mean | (SD) | Value[a] | N | Mean | (SD) | Mean | (SD) | Value[a] | N | Mean | (SD) | Mean | (SD) | Value[a] |
| HAM-D anxiety/ somatization subscale score | High | 96 | 1.43 | (1.25) | 1.93 | (2.75) | .546 | 171 | 1.36 | (1.12) | 1.92 | (2.87) | .027 | 103 | 1.17 | (1.22) | 3.12 | (2.65) | .009 |
| | Low | 92 | 1.37 | (1.29) | 1.77 | (2.34) | | 214 | 1.09 | (1.05) | 1.33 | (2.32) | | 112 | 0.90 | (0.82) | 2.19 | (2.45) | |
| HAM-D-17 score | High | 96 | 4.17 | (2.77) | 6.94 | (8.70) | .480 | 171 | 3.79 | (2.56) | 6.66 | (8.42) | .264 | 103 | 3.45 | (2.34) | 0.65 | (8.72) | .030 |
| | Low | 92 | 4.23 | (2.51) | 6.11 | (7.26) | | 214 | 3.45 | (2.48) | 5.72 | (7.84) | | 112 | 3.18 | (2.40) | 8.08 | (8.53) | |
| HAM-D item 1 depressed mood score | High | 96 | 0.30 | (0.46) | 1.05 | (1.38) | .921 | 171 | 0.29 | (0.54) | 0.87 | (1.21) | .698 | 103 | 0.28 | (0.49) | 1.51 | (1.23) | .380 |
| | Low | 92 | 0.31 | (0.55) | 1.03 | (1.30) | | 214 | 0.24 | (0.47) | 0.82 | (1.20) | | 112 | 0.27 | (0.48) | 1.36 | (1.38) | |
| CGI-S score | High | 96 | 1.39 | (0.51) | 1.02 | (1.47) | .872 | 170 | 1.36 | (0.51) | 1.04 | (1.42) | .375 | 103 | 1.29 | (0.46) | 1.74 | (1.34) | .092 |
| | Low | 92 | 1.37 | (0.49) | 1.05 | (1.38) | | 214 | 1.34 | (0.48) | 0.92 | (1.33) | | 112 | 1.29 | (0.47) | 1.42 | (1.41) | |

[a]p Values derived from analysis of variance model with a term for anxiety level, comparing high vs. low anxiety.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression.

and 1B). However, high anxiety patients assigned to the placebo treatment arm had a statistically higher risk of relapse than low anxiety patients assigned to placebo treatment (Figure 1C). Relapse rates for the high anxiety subgroup were 27.8%, 28.5%, and 53.3% for 90 mg weekly, 20 mg daily, and placebo treatment groups, respectively. Relapse rates for the low anxiety subgroup were 31.2%, 27.2%, and 40.7% for 90 mg weekly, 20 mg daily, and placebo treatment groups, respectively.

***Changes in HAM-D and CGI-S values.*** Table 3 summarizes the changes in the HAM-D and CGI-S values from baseline to endpoint for each treatment group by anxiety level. There was a statistically significantly greater increase in HAM-D anxiety/somatization subscale scores and HAM-D-17 total scores in high anxiety patients compared with low anxiety patients in the placebo treatment group. In the fluoxetine 20 mg daily group, high anxiety patients had a statistically significantly greater increase in HAM-D anxiety/somatization subscale scores than low anxiety patients. Change in scores was comparable between high anxiety patients and low anxiety patients in the fluoxetine 90 mg weekly treatment group.

Statistical comparisons of efficacy between treatment groups are not presented in this analysis because only study 2 contained a 90-mg arm, and evaluation of the pooled data may lead to inaccurate conclusions in regard to between-treatment differences.

## DISCUSSION

The results of this study suggest that patients who present with major depressive disorder with high levels of anxiety may have a greater risk of relapse if they do not receive adequate continuation therapy after achieving an acute response to antidepressant treatment. While a number of studies have examined the efficacy of fluoxetine in the acute treatment of depression with associated anxiety,[4,9–11] few studies have focused on the effect of anxiety on the outcome of continuation treatment. Our findings are consistent with the results of a prospective follow-up study by Ramana and colleagues[23] that reported that higher baseline anxiety was predictive of a greater risk of relapse in patients with major depression.

A number of studies have reported that patients with higher levels of baseline anxiety may be less responsive to acute antidepressant treatment than those with lower levels of baseline anxiety.[9–11] Although not all studies report such differences,[4] even subtle disparities in acute response might predict a greater risk of relapse for patients with high baseline anxiety while continuing on active treatment, especially if the dose is reduced from that used to achieve an acute response. However, this study indicates that patients who respond to acute treatment with fluoxetine 20 mg daily are offered significant protection against relapse when continued on fluoxetine 20 mg daily or even switched to the lower dose of fluoxetine 90 mg weekly, regardless of anxiety level at baseline. On the other hand, the higher relapse rates seen in high anxiety patients switched to placebo for continuation treatment suggest that patients presenting with higher anxiety may have a greater risk of relapse than those presenting with lower anxiety, should they terminate long-term antidepressant treatment too soon. While completion of an adequate course of antidepressant therapy is an appropriate treatment goal for all patients, this analysis suggests that there may be baseline markers and/or symptoms that are helpful in predicting risk of relapse in patients not continuing a full course of treatment.

Patients with high levels of baseline anxiety who were judged to have responded in these 2 trials on the basis of clinician impression and modified HAM-D-17 total score continued to have higher residual anxiety symptoms in the overall patient group at the time of randomization (Table 2). This difference is consistent with previous reports and recommendations regarding the acute treatment of depression with comorbid anxiety.[24] Residual symptoms of

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anxiety have been reported to be associated with greater risk of relapse in patients with major depressive disorder.[23,25] Our analysis is supportive of this theory, but suggests that continuation treatment with an antidepressant (in this case, fluoxetine) may provide protection against relapse despite the existence of residual anxiety symptoms.

It is interesting to note that the fluoxetine 90 mg weekly group, which was the only treatment group with no significant differences in residual anxiety at randomization, was also the only group with no significant differences in change in any measure between high and low anxiety subgroups during continuation treatment. While the similarity between anxiety subgroups at randomization, in this treatment group only, is most likely a consequence of differences in randomization criteria between the 2 pooled studies, the possible correlation between differences in residual anxiety after acute treatment and differences in response to continuation treatment emphasizes the importance of taking residual anxiety into account during the management of depression.

One of the foremost limitations of the current analysis lies in the pooling of 2 studies, which, while similar in design, are not identical. Despite the similarities in baseline patient characteristics between the 2 studies,[20,21] differences in the criteria for randomization to continuation therapy and the definition of relapse restrict the conclusions that may be drawn from this analysis. In particular, we could not provide accurate comparisons of efficacy between treatment groups. The objective of this investigation was to examine the effect of baseline anxiety on the outcome of continuation therapy and on the risk for relapse after achieving an acute response to antidepressant treatment; by limiting our analysis to anxiety strata within treatment groups, we were able to accomplish this assessment. However, the results of this analysis must be considered with respect to the limitations imparted by the differences in diagnostic and outcome criteria between the 2 pooled studies.

Our analysis suggests that patients with major depressive disorder who present with high anxiety may have a higher risk of relapse than patients with lower anxiety levels following treatment discontinuation after achieving an acute response to antidepressant therapy. This finding may, in part, be related to residual symptoms of anxiety after acute treatment. While all patients should be encouraged to commit to an adequate course of antidepressant therapy, this analysis suggests that baseline characteristics of patients may be helpful in predicting risk of relapse with early treatment discontinuation. Appropriate education and monitoring of such patients may be helpful in their full participation in long-term treatment, early recognition of relapse, and timely intervention. Future work looking at other factors that may correlate with risk of relapse is warranted.

*Drug name:* fluoxetine (Prozac and others).

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