Early Symptomatic Worsening During Treatment With Fluoxetine in Major Depressive Disorder: Prevalence and Implications

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Background: A subset of patients experience worsening of depressed mood after beginning antidepressant treatment, which could represent the natural history of the illness or a treatment-related effect. While patterns of response have been examined as possible predictors of outcome, the clinical correlates and implications of early worsening per se have not been investigated.

Method: In a post hoc analysis, we studied the clinical correlates of early worsening in a large sample of outpatients (N = 694) diagnosed with a DSM-III-R–defined major depressive episode and treated with fluoxetine (20 mg/day) for up to 12 weeks. We defined early worsening as an increase of at least 5 points on a modified 17-item Hamilton Rating Scale for Depression (mHAM-D, including reverse vegetative symptoms) compared to the previous visit, and occurring during the acute phase of treatment. The primary analysis compared remission and response at week 12 between those patients with and without worsening.

Results: In our sample, 211 patients (30.4%) experienced early worsening of depression. An increase in mHAM-D score at week 2, 3, 4, or 6 was associated with a significantly lower probability of remission and response at both week 8 and week 12, while no significant difference was observed in study discontinuation. Baseline features, including gender, age, mHAM-D score at entry, number of previous depressive episodes, and duration of illness were not associated with the development of early worsening during fluoxetine treatment.

Conclusion: Early clinical worsening is common and associated with a decreased likelihood of achieving remission.

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When clinicians prescribe an antidepressant to treat a depressive episode, they often expect a progressive and sustained improvement in depressive symptoms over the following 8 to 12 weeks. However, a subset of patients may report a worsening of mood during antidepressant treatment,[1,2] and it is not uncommon for depressed patients to discontinue treatment due to worsening of their condition.[3] To our knowledge, the clinical correlates and implications of such early worsening have not yet been investigated.

Specifically, while positive predictors of response have been identified by examining the relationship between early improvements and antidepressant treatment outcome, very little is known about possible links between early worsening and outcome in major depressive disorder (MDD).[4–7] The pattern of response itself has been reported to differentiate between the "true drug" response, which is delayed and persistent, and the "placebo pattern" of early or nonpersistent response.[8–12] Conversely, a recent meta-analysis of 47 double-blind, placebo-controlled studies questioned the validity of the delayed antidepressant response hypothesis,[13] showing that the time course of improvement with active medica-

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tion and placebo was nearly identical. Other investigators have examined the clinical significance of score change in psychotherapy outcome studies.[14–16] In the present study, we performed a post hoc analysis of a large, open clinical trial of fluoxetine 20 mg in outpatients with nonpsychotic major depressive episodes (MDEs) with the goal of assessing the frequency of clinical worsening during acute treatment with fluoxetine and examining whether this change predicts treatment outcome.

METHOD

Sample

The clinical sample consisted of 839 outpatients between 18 and 65 years of age. Inclusion and exclusion criteria were previously described elsewhere.[17] In brief, this was a multicenter, 12-week trial of fluoxetine 20 mg among outpatients with a nonpsychotic MDE as defined by DSM-III-R. After a run-in period of a week without medications, patients were treated with an open trial of 20 mg/day of fluoxetine for up to 12 weeks. Concomitant use of other psychotropic drugs was not allowed, except lorazepam and chloral hydrate through week 6.

Following a screening visit, patients were seen at baseline (1 week later) and weeks 1, 2, 3, 4, 6, 8, 10, and 12. At week 10, patients who had not shown adequate signs of improvement (i.e., at least a 50% reduction in mHAM-D score) were dropped from the study. All subjects signed informed consent statements approved by the institutional review boards of the participating institutions prior to study entry. The modified 17-item Hamilton Rating Scale for Depression (mHAM-D) was used as the outcome measure. This scale allows the substitution of hypersomnia and hyperphagia instead of insomnia, anorexia, and weight loss items in patients with reverse vegetative symptoms.[17]

Analysis

Our analyses utilized a modified intent-to-treat (ITT) sample in which only subjects with at least 1 postbaseline visit available were considered (N = 830). To perform this analysis, we defined worsening as an increase of 5 or more points on the mHAM-D compared to the previous visit, and occurring after at least 1 week of treatment. This threshold was selected for consistency with reports suggesting that a difference greater than 4 points on the HAM-D is clinically significant.[18] We decided a priori to consider only those worsenings occurring after at least 1 week of treatment, to minimize the contribution of early adverse effects. We decided also to exclude those subjects with a worsening after the sixth week, as worsening at this point would lead to circular definitions of worsening and nonresponse. Response to fluoxetine was defined as a 50% decrease of the mHAM-D score from baseline, while remission was defined as an mHAM-D score of 7 or less.[19]

The 2 groups of patients, those with and without worsening, were compared with a log-rank test for response, remission, and dropout. Chi-square and unpaired T test were used for dichotomous and continuous clinical variables, respectively. Interactions between worsening and other sociodemographic variables were investigated in a Cox proportional hazards model of time to response. For all analyses, a 2-tailed p value < .05 was considered statistically significant. All calculations were performed with STATA/SE version 8 (StataCorp; College Station, Tex.). Given our sample size, we had 80% power to detect a difference in remission rates of 11% or more, considering an $\alpha = .05$.

RESULTS

Of 830 patients in the modified ITT sample, 22 dropped out after week 1 (2.7%), and 114 were excluded from the analysis because they experienced worsening at week 1 (N = 16 subjects, 1.9%) or after the sixth week of treatment (N = 90, 10.8%) or because they met criteria for a bipolar II diagnosis (N = 8, 1.0%). The subjects excluded were not significantly different from the analyzed sample in terms of sociodemographic variables (results not shown).

Among the 694 patients included in the analysis, 211 (30.4%) experienced a worsening between weeks 2 and 6 of treatment: 48 subjects experienced a worsening at week 2 (22.8%), 61 at week 3 (28.9%), 50 at week 4 (23.7%), and 52 at week 6 (24.6%) (Figure 1). For those 211 patients, the median worsening observed was 7 (range, 5–23) (Figure 2).

The baseline comparisons between the 2 groups (those with and without worsening) are presented in Table 1. No significant differences were observed when comparing for age, duration of illness, number of previous episodes, baseline mHAM-D score, difference between screening and baseline at mHAM-D, or plasma fluoxetine and norfluoxetine levels at week 6. Significant differences were observed for sex ($\chi^2 = 4.89$, p = .03) and screening mHAM-D score (T test = –2.12, p = .03); however, those results did not remain significant after correction for multiple testing.

We examined remission at week 12 using the conservative last-observation-carried-forward approach (i.e., patients prematurely terminating from the trial are assumed to experience no further improvement). In total, 102 subjects, out of 211 with worsening (48.3%), achieved remission at week 12, compared to 334 of 483 without worsening (69.2%, $\chi^2 = 27.23$, p = .0001). To remove the possible effect of early discontinuation, we used a Kaplan-Meier analysis in which dropout subjects were censored. No significant difference was observed when study discontinuation rates were compared (p = .09). Remission and response at week 12 were significantly less

Figure 1. Patients Experiencing a Worsening of 5 or More Points on the Modified Hamilton Rating Scale for Depression at Each Visit, Subdivided Into Remitted and Nonremitted at Week 12

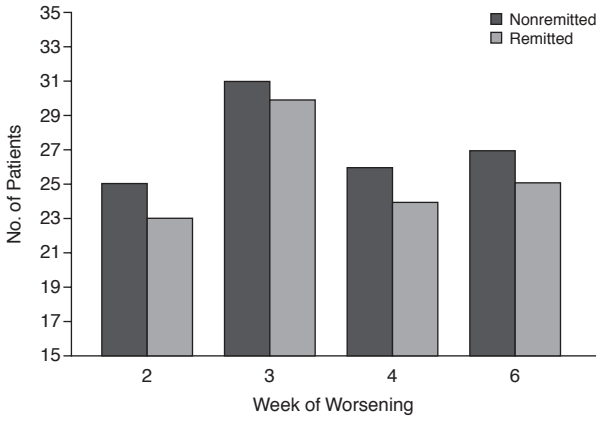
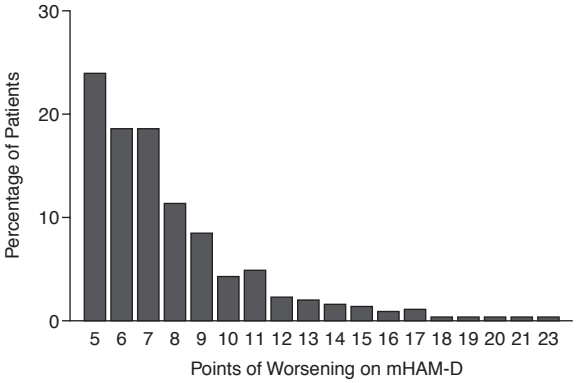


Figure 2. Distribution of the Extent of Worsening at Index Week[a]



[a]Only patients experiencing a worsening, as defined in the Method, were included.
Abbreviation: mHAM-D = modified Hamilton Rating Scale for Depression.

Table 1. Comparison Between Subjects With and Without Early Symptomatic Worsening During Fluoxetine Treatment[a]

Variable	No Worsening (N = 483)	Worsening (N = 211)	Test Result	p Value
Male sex, N (%)	167 (34.6)	55 (26.1)	$\chi^2 = 4.89$	.027
Age, y	39.6 ± 10.9	39.3 ± 10.2	T = 0.27	NS
Duration of MDD, mo	17.2 ± 23.7	16.8 ± 22.3	T = 0.20	NS
No. of previous episodes	3.4 ± 7.0	4.5 ± 9.1	T = –1.53	NS
mHAM-D				
Screening score	22.0 ± 4.0	22.7 ± 3.8	T = –2.12	.03
Baseline score	21.0 ± 3.7	21.5 ± 3.9	T = –1.59	NS
Change from screening to baseline	0.99 ± 2.8	1.18 ± 3.1	T = –0.79	NS
Plasma fluoxetine level, ng/mL[b]	84.9 ± 46.3	84.1 ± 39.4	T = 0.20	NS
Plasma norfluoxetine level, ng/mL[b]	111.0 ± 43.9	112.8 ± 43.3	T = –0.46	NS

[a]Data shown as mean ± SD unless otherwise noted.
[b]Plasma level data were available for 397 and 186 patients, respectively, for fluoxetine and norfluoxetine.
Abbreviations: MDD = major depressive disorder, mHAM-D = modified Hamilton Rating Scale for Depression, NS = nonsignificant.

likely in the group with early worsening (remission at week 12 $p < .0001$, log-rank test; response at week 12 $p < .0001$, log-rank test).

According to protocol, a total of 114 subjects were dropped from the study at week 10 for lack of improvement (13.7%). Among those, 29 patients were already excluded from our analysis, 43 did not experience worsening between weeks 2 and 6, and 42 did experience worsening. We then repeated the survival analysis excluding those subjects dropped from the study at week 10 for lack of improvement, and the difference in response and remission at week 12 remained significant (remission $p < .0001$, response $p = .003$, log-rank test).

A worsening of depressive symptoms between weeks 2 and 6 was significantly associated with a lower probability of response (crude OR = 1.24, 95% CI = 1.08 to 1.43 at week 8; OR = 1.30, 95% CI = 1.15 to 1.48 at week 12) and remission (OR = 1.38, 95% CI = 1.14 to 1.67 at week 8; OR = 1.43, 95% CI = 1.23 to 1.67 at week 12). Finally, we assessed the relationship between presence of worsening and remission at week 8 and at week 12, using a Cox regression model in which gender, mHAM-D score at screening, and severity of worsening in mHAM-D points were treated as covariates, but they did not significantly influence the observed association with outcome (p = NS).

We compared our definition of "worsening ≥ 5 points at the HAM-D" with a definition of worsening based on a Clinical Global Impressions-Severity of Illness scale (CGI-S)[20] increase of 1 point between 2 consecutive visits. Out of 211 patients defined as worsened on the HAM-D, 163 (77.3%) were worsened on the CGI-S, and 104 were considered worsened on the CGI-S but not with the HAM-D criteria. The results were nonetheless quite similar: patients with worsening according to the CGI-S were also less likely to show remission at weeks 8 and 12

(remission at week 8 p = .015, remission at week 12 p = .011).

Finally, to investigate whether the worsening phenomenon was confined to patients who had not yet responded, we examined 95 patients who met criteria for remission (mHAM-D score ≤ 7) and subsequently experienced a worsening of at least 5 points. Of this subsample, 57 (60%) were still in remission at week 12. Moreover, 63 subjects worsened by 3 points or more compared to the baseline mHAM-D score, and only 13 (20.6%) of them were remitted at week 12.

To investigate the predictive value for a different cutoff of worsening, we performed a sensitivity and specificity analysis with a different cutoff (3 to 6 points). As expected, the sensitivity tends to decrease with higher thresholds (i.e., greater number of points of worsening), and the predictive value of poor prognosis (i.e., no remission at week 12) remains relatively low (46%–50%).

DISCUSSION

In the present study, we investigated the worsening of depression severity score during antidepressant treatment in a large sample of depressed outpatients treated with fluoxetine. We observed that a worsening of 5 or more points on the mHAM-D occurred in 30.4% of the patients. This worsening was slightly more frequent in men and associated with a marginally more severe baseline mHAM-D score, even if, given the number of comparisons for baseline variables, these results may represent false-positives. The more interesting result was that the presence of a worsening between weeks 2 and 6 of treatment was significantly associated with a poorer outcome. Worsenings may have different possible explanations. For example, worsenings during the first few weeks of treatment may not be etiologically related to antidepressant therapy, but may simply represent a correlate of the natural history of the illness. Worsenings may also correspond to treatment-related side effects or be due to drug-induced anxiety, agitation, or insomnia; the loss of an initial placebo effect; or the influence of adverse life events. Less likely but still possible causes are the loss of an initial therapeutic effect of the antidepressant or a fluctuation in plasma levels. Another possibility is that discontinuing the concomitant sedative-hypnotic after week 6 may be related to an increased HAM-D score in following weeks; however, our definition of worsening included only an increase in HAM-D score between weeks 2 and 6.

As an alternate hypothesis, worsening may represent instead a marker for treatment-related side effects. These patients may be predisposed to antidepressant side effects, such as anxiety, agitation, or insomnia, and those side effects may contribute to a poorer global response or a higher dropout rate.[21,22] In recent years, a number of studies have focused on the possible side effects or paradoxical reactions to antidepressants, in particular the emergence of suicidal ideation[23,24] and severe psychomotor agitation[25] and how side effects may lead to discontinuation of antidepressant.[26] Moreover, in psychotherapy studies, researchers have also investigated the clinical significance of score change.[14–16]

Furthermore, worsening might be related to the loss of an initial placebo effect. In 1993, Quitkin and colleagues[27] observed that among 507 patients randomly assigned to placebo, imipramine, and phenelzine, 31% of the patients who were taking placebo, 12% who were taking imipramine, and 9% who were taking phenelzine had relapsed between weeks 7 and 12. The authors concluded that a large proportion of "early relapses" in patients taking antidepressant drugs might be attributable to the loss of nonspecific placebo effects. The same group presented the data on pattern analysis of response in a large sample of patients treated with active drug and placebo.[8] For the purpose of comparison, we calculated from Table 2 of that article[8] the rate of subjects who had a week rated as improved (CGI-I score = 1) followed by an unimproved week (CGI-I score = 0), between week 2 and week 6 of treatment. In their sample, 60 (42.9%) of 140 patients treated with placebo and 43 (24.2%) of 178 treated with active drug exhibited worsening between weeks 2 and 6. Those rates are very similar to the rates we observed in our sample, in which all patients were treated with fluoxetine (30.4%). Moreover, a relevant percentage of patients, after an early worsening, reached a clinical remission (38.4% at week 8 and 48.3% at week 12), while out of 211 patients, 42.7% exhibited worsening and subsequently did not reach an improvement of at least 50% of their baseline mHAM-D score at week 12. Although it is not possible to separate drug response from placebo response, we can hypothesize that in this latter group of patients an initial placebo response may have waned after a few weeks of treatment.

Another possible explanation for these clinical worsenings is a fluctuation in plasma levels, in which pharmacokinetic differences between subjects or poor compliance may play a role. Given the pharmacokinetic profile and long half-life of fluoxetine, it seems unlikely that plasma level variations play a major role. In the absence of a serial evaluation of plasma levels, however, we cannot exclude this possibility.

Finally, worsening may be secondary to stressful life events, particularly in MDD with atypical features,[28] since the core feature of this subtype is mood reactivity. We cannot assess this hypothesis with the present dataset.

In clinical practice, the presence of mood worsening during antidepressant treatment can strongly influence the decision-making process,[29] because the clinician may interpret an increase in HAM-D score as a lack of sustained response to antidepressants and decide to modify the medication regimen. Some psychotherapy researchers

have examined the clinical significance of score change in outcome studies[14–16]; however, at present no clear guidelines are available for patients undergoing worsening during acute antidepressant treatment. On the basis of the results of a survey among participants in a psychopharmacology course, the most common strategy is to raise the dosage of antidepressant (in about 80% of the cases), both for partial response during the acute phase and for relapse during long-term maintenance therapy.[30] The issue of which is the best clinical approach for a patient with a worsening during the acute phase has not yet been addressed. Nevertheless, we observed in our study that a substantial proportion of subjects experiencing a worsening could still reach remission at week 12 (48.3%), supporting the view that the therapy should be maintained. In our study, the global remission rate was 62.8% among the 694 subjects included in the analysis and 57.3% in the ITT sample.

The major limitations of the present study are the post hoc nature of the analyses and the absence of a placebo double-blind control. Another important limitation arises from the fluoxetine dosage, fixed at 20 mg/day. While it could be considered a very common dosage for moderately severe depression, this is also a dose that many clinicians would raise if worsening occurs. At present, no data are available regarding the prevalence of worsenings at different drug dosages or with antidepressant drugs different from fluoxetine.

In most clinical trials, only baseline and final scores at established endpoints are taken into consideration to define patient outcome. In our analysis, we were able to identify a depressive worsening during antidepressant treatment in a substantial proportion of the subjects, which was related to a reduced probability of remission. The degree to which this finding is generalizable to other depressive populations and to other antidepressants will require examination of other large, prospective clinical trials.

Drug names: fluoxetine (Prozac and others), imipramine (Tofranil and others), lorazepam (Ativan and others), phenelzine (Nardil).

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REFERENCES

1. Damluji NF, Ferguson JM. Paradoxical worsening of depressive symptomatology caused by antidepressants. J Clin Psychopharmacol 1988;8:347–349
2. Beasley CMJ, Dornseif BE, Bosomworth JC, et al. Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. BMJ 1991;303:685–692
3. Lin EH, Von Korff M, Katon W, et al. The role of the primary care physician in patients' adherence to antidepressant therapy. Med Care 1995;33:67–74
4. Nierenberg AA, Farabaugh AH, Alpert JE, et al. Timing of onset of antidepressant response with fluoxetine treatment. Am J Psychiatry 2000;157:1423–1428
5. Stassen HH, Delini-Stula A, Angst J. Time course of improvement under antidepressant treatment: a survival-analytical approach. Eur Neuropsychopharmacol 1993;3:127–135
6. Stassen HH, Angst J, Delini-Stula A. Delayed onset of action of antidepressant drugs? survey of results of Zurich meta-analyses. Pharmacopsychiatry 1996;29:87–96
7. Moller HJ, Muller H, Volz HP. How to assess the onset of antidepressant effect: comparison of global ratings and findings based on depression scales. Pharmacopsychiatry 1996;29:57–62
8. Quitkin FM, Rabkin JD, Markowitz JM, et al. Use of pattern analysis to identify true drug response: a replication. Arch Gen Psychiatry 1987;44: 259–264
9. Quitkin FM, Rabkin JG, Ross D, et al. Identification of true drug response to antidepressants: use of pattern analysis. Arch Gen Psychiatry 1984;41:782–786
10. Fieve RR, Goodnick PJ, Peselow ED, et al. Pattern analysis of antidepressant response to fluoxetine. J Clin Psychiatry 1986;47:560–562
11. Dunlop SR, Dornseif BE, Wernicke JF, et al. Pattern analysis shows beneficial effect of fluoxetine treatment in mild depression. Psychopharmacol Bull 1990;26:173–180
12. Nierenberg AA, Quitkin FM, Kremer C, et al. Placebo-controlled continuation treatment with mirtazapine: acute pattern of response predicts relapse. Neuropsychopharmacology 2004;29:1012–1018
13. Posternak MA, Zimmerman M. Is there a delay in the antidepressant effect? a meta-analysis. J Clin Psychiatry 2005;66:148–158
14. Bauer S, Lambert MJ, Nielsen SL. Clinical significance methods: a comparison of statistical techniques. J Pers Assess 2004;82:60–70
15. Thompson MG, Thompson L, Gallagher-Thompson D. Linear and nonlinear changes in mood between psychotherapy sessions: implications for treatment outcome and relapse risk. Psychother Res 1995;5:327–336
16. Wise EA. Methods for analyzing psychotherapy outcomes: a review of clinical significance, reliable change, and recommendations for future directions. J Pers Assess 2004;82:50–59
17. Stewart JW, Quitkin FM, McGrath PJ, et al. Use of pattern analysis to predict differential relapse of remitted patients with major depression during 1 year of treatment with fluoxetine or placebo. Arch Gen Psychiatry 1998;55:334–343
18. Montgomery SA, Bech P, Blier P, et al. Selecting methodologies for the

evaluation of differences in time to response between antidepressants. J Clin Psychiatry 2002;63:694–699
19. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse, and recurrence. Arch Gen Psychiatry 1991;48:851–855
20. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
21. Amsterdam JD, Maislin G, Potter L. Fluoxetine efficacy in treatment resistant depression. Prog Neuropsychopharmacol Biol Psychiatry 1994; 18:243–261
22. Perlis RH, Mischoulon D, Smoller JW, et al. Serotonin transporter polymorphisms and adverse effects with fluoxetine treatment. Biol Psychiatry 2003;54:879–883
23. Grunebaum MF, Ellis SP, Li S, et al. Antidepressants and suicide risk in the United States, 1985–1999. J Clin Psychiatry 2004;65:1456–1462
24. Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. JAMA 2004;292:338–343
25. Tollefson GD, Sayler ME. Course of psychomotor agitation during pharmacotherapy of depression: analysis from double-blind controlled trials with fluoxetine. Depress Anxiety 1996–1997;4:294–311
26. Beasley CM Jr, Koke SC, Nilsson ME, et al. Adverse events and treatment discontinuations in clinical trials of fluoxetine in major depressive disorder: an updated meta-analysis. Clin Ther 2000;22:1319–1330
27. Quitkin FM, Stewart JW, McGrath PJ, et al. Loss of drug effects during continuation therapy. Am J Psychiatry 1993;150:562–565
28. Farabaugh AH, Mischoulon D, Fava M, et al. The potential relationship between levels of perceived stress and subtypes of major depressive disorder (MDD). Acta Psychiatr Scand 2004;110:465–470
29. Rush AJ, Fava M, Wisniewski SR, et al. Sequenced Treatment Alternatives to Relieve Depression (STAR*D): rationale and design. Control Clin Trials 2004;25:119–142
30. Fredman SJ, Fava M, Kienke AS, et al. Partial response, nonresponse, and relapse with selective serotonin reuptake inhibitors in major depression: a survey of current "next-step" practices. J Clin Psychiatry 2000; 61:403–408