# Somatic Symptoms as Predictors of Time to Onset of Response to Fluoxetine in Major Depressive Disorder

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*Received June 25, 2003; accepted Sept. 15, 2003.* *From the Depression Clinical and Research Program, Massachusetts General Hospital, Harvard Medical School, Boston.*

*Supported by National Institute of Mental Health grant #R01-MH-48-483-05 (Dr. Fava), the American College of Neuropsychopharmacology/ GlaxoSmithKline Fellowship in Clinical Neuropsychopharmacology (Dr. Papakostas), and the Harvard Medical School/ Kaplen Fellowship in Depression Research (Dr. Papakostas).*

*Dr. Summergrad has received honoraria from and is on the speakers/advisory board of Eli Lilly. Dr. Nierenberg is an employee of Massachusetts General Hospital and has been a consultant for and/or received grant support or honoraria from Lilly, Wyeth, GlaxoSmithKline, Janssen, BMS, Pfizer, Innapharma, Cyberonics, and Lichtwer. Dr. Fava has received research support and/or honoraria from Abbott, Aspect, Bayer AG, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest, GlaxoSmithKline, GlaxoWellcome, Janssen, Knoll, Lichtwer, Lorex, Lundbeck, Novartis, Organon, Parke-Davis, Pfizer, Pharmacia & Upjohn, Pharmavite, Roche, Sanofi/Synthelabo, SmithKline Beecham, Solvay, Somerset, and Wyeth-Ayerst.*

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***Objective:*** In the present study we assessed the relationship between somatic symptoms and the time to onset of clinical response to fluoxetine in patients with major depressive disorder (MDD).

***Method:*** 87 outpatients (mean age = 41.4 ± 10.2 years; 59.8% women) with DSM-III-R MDD who had sustained acute response to fluoxetine completed the Symptom Questionnaire (SQ) at baseline. Onset of response was defined as a 30% decrease in the total score for the 17-item Hamilton Rating Scale for Depression that led to a 50% decrease by week 8. With the use of 2 separate multiple regressions, controlling for the severity of depression at baseline, we then assessed the relationship between the number of somatic symptoms as assessed by the SQ subscale for somatic symptoms (SQ-SS) and both the time to onset of clinical response and the time to clinical response. The study was conducted between November 1992 and January 1999.

***Results:*** A greater number of somatic symptoms at baseline predicted a greater amount of time to onset of clinical response to fluoxetine ($p = .0233$). The relationship between SQ-SS scores and time to response was not found to be statistically significant ($p > .05$).

***Conclusion:*** Somatic symptoms of depression were found to be associated with a delayed onset of antidepressant response to fluoxetine in MDD.

*(J Clin Psychiatry 2004;65:543–546)*

Even though many patients with major depressive disorder (MDD) may present with somatic symptoms rather than depressed mood as their chief complaint,[1] somatic/physical symptoms of depression are underrepresented in the current nosology relative to psychological and behavioral symptoms.[2] However, somatic symptoms, when systematically studied, seem prevalent in the overwhelming majority of MDD patients,[3,4] including those with treatment-resistant depression (TRD).[5] In addition, somatic symptoms of depression have been found to be related to a greater severity of depression.[6]

A growing number of studies also suggest that the number and severity of somatic symptoms of depression present immediately before initiation of pharmacotherapy for MDD to confer a poor outcome to treatment. In a previous study[7] conducted by our group, we reported that depressed patients who responded to an 8-week open trial of fluoxetine, 20 mg, but did not go on to achieve full remission had significantly more somatic symptoms than remitters. More recently, we reported[5] that the presence of somatic symptoms was found to confer a poor prognosis with respect to open treatment with nortriptyline in outpatients with TRD, an effect that was independent of the severity of depression or medical comorbidity at baseline.


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The purpose of this report was to test the relationship between the number of somatic symptoms of depression present immediately before initiation of pharmacotherapy for MDD and the time to onset of clinical response for outpatients enrolled in an 8-week, fixed-dose, open trial of fluoxetine, 20 mg.

## METHOD

Outpatients, ages 18 to 65 years, who met criteria for a current major depressive episode according to the Structured Clinical Interview for DSM-III-R, Patient Edition, (SCID-P)[8] and who were medication free for at least 2 weeks, with a baseline 17-item Hamilton Rating Scale for Depression (HAM-D)[9] score ≥ 16, were eligible to enroll in an 8-week, fixed-dose, open-label trial of fluoxetine, 20 mg. The study was conducted at the Massachusetts General Hospital Depression Clinical and Research Program from November 1992 to January 1999. Patients were recruited through radio and newspaper advertisements and colleague referrals.

Exclusion criteria included pregnant women and women of childbearing potential who were not using a medically accepted means of contraception; lactating women; patients with serious suicidal risk or serious, unstable medical illness; patients with a history of seizure disorder; patients with the DSM-III-R diagnoses of organic mental disorders, substance use disorders (including alcohol, active within the last year), schizophrenia, delusional disorder, psychotic disorders not elsewhere classified, bipolar disorder, or antisocial personality disorder; patients with a history of multiple adverse drug reactions or allergy to the study drugs; patients with mood congruent or mood incongruent psychotic features; current use of other psychotropic drugs; patients with clinical or laboratory evidence of hypothyroidism; patients whose depression had failed to respond in the past to a trial of fluoxetine, the combination of fluoxetine and desipramine, or the combination of fluoxetine and lithium; patients who had failed to respond during the course of their current major depressive episode to at least 1 adequate antidepressant trial, defined as 6 weeks or more of treatment with either > 150 mg of imipramine (or its tricyclic equivalent) or > 60 mg of phenelzine (or its monoamine oxidase inhibitor equivalent).

During the screen visit, all enrolled patients signed an institutional review board–approved written informed consent form. A medical and psychiatric history, physical examination, serum chemistries, hematologic measures, electrocardiogram, and urine pregnancy test were then performed. The 31-item version of the HAM-D,[9] which allows the scoring of the HAM-D-17, was also administered during the screen visit and during all subsequent visits. The screen visit was conducted by experienced psychologists or psychiatrists extensively trained in the use of the HAM-D-31 through didactic sessions and periodic reviews of videotaped interviews. Interrater reliability for the use of the SCID-P mood module for the psychologists or psychiatrists involved in the study was estimated as kappa = 0.80.[10] At the conclusion of the screen visit, all enrolled patients were asked to return 1 week later for the baseline visit.

Patients (N = 384) who returned for their baseline visit were started on a 20-mg, fixed-dose regimen of fluoxetine. Visits subsequent to the screen occurred at baseline and then every other week for a total of 8 weeks. The HAM-D-31 was administered during all study visits.

### Assessment of Somatic Symptoms of Depression

The presence and number of somatic symptoms were assessed during the baseline visit with the Symptom Questionnaire (SQ).[11] Since this scale was introduced later in the study, it was administered to a subset of subjects enrolled. The SQ is a self-rated questionnaire containing 92 items, each scored dichotomously as true or false.

Our analysis focuses on the SQ subscale for somatic symptoms (SQ-SS), which consists of the following 18 items: feeling of not getting enough air, heavy arms and legs, poor appetite, tightness in the head or neck, choking feeling, feeling of pressure in the head or body, weak arms or legs, breathing difficult, parts of the body feel numb or tingling, heart beating fast or pounding, pressure on head, nauseated, sick stomach, upset bowels or stomach, muscle pains, headaches, cramps, and head pains. For the data analysis, the presence of a symptom was scored as a 1, and the absence of a symptom was scored as a 0. The SQ-SS score was defined as the sum of these 18 items.

### Definition of Outcome Measures

Treatment response was defined as a 50% decrease in score on the HAM-D-17 from baseline to endpoint. A completer analysis was used to define endpoint severity. Time until onset of response was defined as the first time point at which the score on the HAM-D-17 decreased by at least 30% from baseline (without a subsequent increase), leading to a 50% or greater decrease by week 8.[12]

By including only those patients without any increase in HAM-D-17 scores, we attempted to exclude those who had a placebo pattern of nonsustained response.[13] The responding group represented the best-case scenario: group members had a true drug pattern of response and responded or experienced remission by the end of the 8-week trial. The rationale for segregating responders was that if nonresponders were included in the same group, the time until onset of response would be delayed because of a reduced overall response rate and would lead to a false conclusion about the time until response for responders.[14]

### Statistical Analysis

Chi-square and t tests were used to compare sustained responders who did and did not have SQ-SS scores at baseline with respect to age, gender, age at onset of MDD, duration of current major depressive episode, severity of depression during the baseline visit, time to onset of clinical response, and time to clinical response. Using 2 separate multiple regressions and controlling for the severity of depression at baseline, we then assessed the relationship between the number of somatic symptoms as assessed by the SQ (SQ-SS) and both the time to onset of clinical response and the time to clinical response. For all analyses, statistical significance was set at $p \leq .05$.

## RESULTS

The results regarding the overall timing of the onset of antidepressant response are reported elsewhere.[12] In summary, a total of 324 (84.4%) of the 384 patients in the study completed the open trial; there were 60 dropouts (15.6%). Of the 384 patients, 193 (50.3%) responded, and 148 (38.5%) had acute remission with final HAM-D scores of 7 or lower. Of the 193 responders, 148 (76.7%) experienced remission of their symptoms. Of 324 who completed the study, 193 (59.6%) responded, and 148 (45.7%) experienced remission of their symptoms. A total of 182 (94.3%) of the 193 patients who met the criteria for response were included in the responder group; the criteria for inclusion were (1) all data points present, (2) a 30% decrease in baseline score on the HAM-D without subsequent exacerbation, and (3) a 50% reduction in baseline score on the HAM-D after 8 weeks of treatment with 20 mg/day of fluoxetine.

Of the 182 patients in the responder group, 87 had SQ-SS scores at baseline while 95 did not. There was no statistically significant difference between responders who did ($N = 87$) and did not ($N = 95$) have baseline SQ-SS scores in gender ratio (52/87 [59.8%] vs. 46/95 [48.4%] female, $p > .05$), years of age ($41.4 \pm 10.2$ vs. $39.7 \pm 9.2$, $p > .05$), severity of depression during the baseline visit as reflected by the HAM-D-17 total score ($19.0 \pm 2.7$ vs. $19.2 \pm 3.2$, $p > .05$), duration of the current major depressive episode in years ($3.2 \pm 5.1$ vs. $3.3 \pm 6.4$, $p > .05$), age at onset of MDD in years ($26.2 \pm 12.5$ vs. $27.2 \pm 15.1$, $p > .05$), time to onset of response in weeks ($3.6 \pm 1.8$ vs. $3.9 \pm 2.1$, $p > .05$), or time to response in weeks ($4.6 \pm 1.9$ vs. $5.1 \pm 2.0$, $p > .05$). The mean SQ-SS score at baseline for the sustained responder group was $8.5 \pm 5.0$. A greater number of somatic symptoms at baseline predicted a greater time to onset of clinical response to fluoxetine ($p = .0233$, coefficient = 0.090, standard error = 0.039). The relationship between SQ-SS scores and time to response was not found to be statistically significant ($p > .05$).

## DISCUSSION

The results of the present study reveal a significant relationship between the number of somatic symptoms of depression present immediately before the onset of treatment and the time to onset of clinical response to fluoxetine. Specifically, a greater number of somatic symptoms of depression were related to a later onset of clinical response to fluoxetine in MDD, regardless of depression severity at baseline. On the other hand, the relationship between the number of somatic symptoms and the time to response was not found to be significant.

The present findings are particularly important in light of a recent study[7] in which we reported that depressed patients who responded to fluoxetine but did not go on to achieve full remission had significantly more somatic symptoms than remitters. Thus, it is quite possible that slower response rates may, in part, explain the adverse impact of somatic symptoms on the likelihood of a responder going on to achieve full remission. Alternatively, patients who present with prominent somatic symptoms may have been less likely to comply with their antidepressant regimen, although we have previously found no impact of somatic symptoms on the risk of prematurely discontinuing treatment with fluoxetine.[7] We also have not found any relationship between the degree of somatic symptoms before treatment with fluoxetine and the risk of developing side effects.[15]

An implication of the present finding of the relationship between somatic symptoms of depression and later onset of response to fluoxetine in MDD is that identifying treatments particularly effective in alleviating somatic symptoms of depression may prove advantageous in helping MDD patients achieve early clinical response and remission. A number of studies suggest that dual-acting antidepressants such as most tricyclic antidepressants,[16] mirtazapine,[17] and duloxetine[18] may be particularly effective in treating somatic symptoms of depression as opposed to predominantly serotonergic[7] or noradrenergic[5] agents. Therefore, studies are warranted to further explore the role of dual-acting antidepressants in MDD patients who present with prominent somatic symptoms or in patients also presenting with syndromes often associated with chronic depression and a prominent somatic component such as irritable bowel syndrome, fibromyalgia, and chronic fatigue. In parallel, preliminary analyses suggest an early onset of clinical response with dual-acting antidepressants such as duloxetine.[19] Further exploration of the role of dual-acting antidepressants such as venlafaxine, mirtazapine, and duloxetine in hastening antidepressant response by way of targeting physical symptoms of depression is warranted.

One limitation of the present study is that the analysis was done post hoc. Another limitation is that follow-up visits were performed every other week rather than every

week, and more frequent visits may have improved our ability to measure the timing of response. In addition, treatment was open, without blinding of the subjects or evaluators, and no placebo group was included. Furthermore, the HAM-D may have been insufficiently sensitive to measure the changes in depression associated with the time to onset of response, and perhaps an instrument such as the Montgomery-Asberg Depression Rating Scale (MADRS)[20] may have been more sensitive in detecting an earlier onset of response. In addition, since the MADRS relies less than the HAM-D does on somatic symptoms, the use of the former instrument in conjunction with the HAM-D would also help limit any confounding effects of somatic symptoms and outcome.

There are also some limitations associated with the use of the SQ to measure somatic symptoms of depression. In particular, the SQ-SS subscale does not include all the somatic symptoms of MDD described in the DSM-IV (for instance, poor appetite is mentioned but increased appetite is not, nor are sleep symptoms). Furthermore, certain somatic symptoms seem to be more heavily weighed in the SQ-SS subscale than others (i.e., 3 items closely resemble each other in eliciting shortness of breath: feeling of not getting enough air, choking feeling, breathing difficult). The present study also did not assess the relationship between certain comorbid conditions frequently associated with chronic depression such as irritable bowel disorder, chronic fatigue, and fibromyalgia and time to onset of response.

A separate limitation is that of sampling bias. Clinical trials have a number of inclusion and exclusion criteria and, as a result, patients in clinical trials do not directly reflect the typical outpatient population of MDD patients. The latter is particularly important for the present study, since depressed patients with severe or unstable medical conditions were excluded. Patients with comorbid depression and medical illness are theoretically more likely to present with somatic complaints. The degree to which these findings generalize to a more heterogeneous population of depressed patients including those with severe medical illness, suicidality, psychosis, bipolar disorder, or substance abuse remains to be determined. In addition, in order to accurately estimate time to onset of response, we have limited the present analysis to completers as in a previous report.[12] Thus, the degree to which these findings generalize to patients who discontinued the study also remains to be determined.

## CONCLUSION

The results of the present study reveal a significant relationship between the number of somatic symptoms of depression present immediately before the onset of treatment and the time to onset of clinical response to fluoxetine. Specifically, a greater number of somatic symptoms of depression were related to a later onset of clinical response to fluoxetine in MDD, regardless of depression severity at baseline. Identifying treatments effective in improving both depressive and somatic symptoms may prove particularly useful in helping MDD patients achieve early clinical response and remission.

*Drug names:* desipramine (Norpramin and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), lithium (Eskalith and others), mirtazapine (Remeron), nortriptyline (Aventyl and others), phenelzine (Nardil), venlafaxine (Effexor).

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