Residual Symptoms in Depressed Patients Who Respond Acutely to Fluoxetine

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Background: Antidepressants have unequivocal efficacy as compared with placebo, but many patients have residual symptoms despite a robust response to antidepressant therapy. The purpose of this study is to assess residual symptoms in outpatients who respond acutely to fluoxetine.

Method: Two hundred and fifteen outpatients with major depressive disorder as assessed with the Structured Clinical Interview for DSM-III-R (SCID-P) were treated openly with fluoxetine 20 mg/day for 8 weeks. One hundred and eight (50.2%) were considered full responders (final 17-item Hamilton Rating Scale for Depression [HAM-D] score ≤ 7). Percentages of full responders who continued to have subthreshold or full major depressive disorder symptoms were calculated. The relationship between residual symptoms and Axis I and Axis II (assessed with SCID-II for personality disorders) comorbidity was assessed.

Results: Of the 108 responders, 19 (17.6%) had no subthreshold or threshold SCID-P major depressive disorder symptoms, while 28 (25.9%) had 1 symptom, and 61 (56.5%) had 2 or more symptoms. No statistically significant relationships were found between number of residual symptoms and selected Axis I comorbid conditions or total number of Axis II disorders.

Conclusion: Less than 20% of full responders to fluoxetine by HAM-D criteria were free of all SCID-P subthreshold and threshold major depressive disorder symptoms after 8 weeks of treatment. While depressed patients benefit from antidepressants, most continue to have some symptoms of depression. The high prevalence of residual symptoms among antidepressant responders suggests the need for further study including whether residual symptoms abate with longer treatment or increased dose of fluoxetine. Other strategies, such as cognitive behavioral therapy, may be needed to address residual symptoms.

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Antidepressants have unequivocal efficacy as compared to placebo,[1–3] but many patients continue to have residual symptoms despite a robust response to antidepressants.[4] In other words, patients may be much or very much improved after treatment, but fail to achieve symptom-free states. Rush and Trivedi[5] suggest that the ultimate clinical goal is to have all symptoms of depression resolve, but few investigations have examined how often complete resolution of symptoms occurs. Residual symptoms are important because if all symptoms of depression fail to resolve, patients may be at higher risk of developing future episodes of major depressive disorder compared with those without depressive symptoms.[6] Subsyndromal depressive symptoms that either persist after the resolution of major depressive episodes or exist without preexisting major depressive disorder are associated with more medical and psychiatric visits, emergency room use, psychiatric hospitalization, increased public assistance, disability benefits, thoughts of suicide, and attempted suicide.[6]

Traditionally, definitions of response to antidepressants have been heterogeneous, with many investigators using a drop of 50% in standard depression rating scales (most frequently the Hamilton Rating Scale for Depression [HAM-D][7]), and others using a threshold score to separate depressed patients from nondepressed patients. Using a threshold cutoff score (e.g., 17-item HAM-D score ≤ 7) to determine the absence of depression is a more conservative approach, but fails to take into account the severity of depression at baseline. Stassen and colleagues[8] found that while more severely depressed patients had the same percentage decrease in depression scores over time, it took those more severely depressed patients longer to cross a threshold score.

Frank et al.[9] found that definitions of remission, recovery, relapse, and recurrence are inconsistent between research reports. To rectify these inconsistencies, they suggested that full remission be defined as a 2-week or longer, but shorter than 6-month, period during which a depressed patient is asymptomatic, with the asymptomatic state defined as a 17-item HAM-D score of 7 or lower.[7] Recovery is then defined as being asymptomatic for 6 months or longer. The focus of our report is on the

acute remission phase, i.e., on those who have a full remission after a completed acute antidepressant trial. Patients who achieve the arbitrary HAM-D score of 7 or lower, as suggested for the cutoff point, may not be as asymptomatic as originally thought by Frank and colleagues.[9] Our clinical observation is that many patients who meet even the most conservative criteria for acute remission continue to have residual symptoms.

Fava et al.[4] found that after successful treatment with a variety of antidepressants, the most common residual symptoms in remitted patients were generalized and somatic anxiety and irritability. Only 12.2% of those patients were free of residual symptoms whatsoever after successful treatment. Thase and colleagues[10] found that relapse occurred in 52% of the patients who responded to treatment with HAM-D scores of 10 or lower for 2 consecutive weeks, whereas relapse occurred in only 9% of those who responded to treatment with HAM-D scores of 6 or lower for 2 consecutive months. Pava and colleagues[11] reported on the persistent difference between remitted depressed patients, who had a mean posttreatment HAM-D score of 3.7, and a comparison group of never-depressed normal volunteers. Remitted depressed patients had significantly more problems with social dysfunction, problem-solving abilities, and dysfunctional attitudes. Social dysfunction associated with depression may be an effect of the depression itself, the result of a comorbid disorder, or a long-term problem that reflects depression's interference with patients' ability to interact with others.

Residual depressive symptoms may be either the result of preexisting traits or problems that were caused by the depression. Residual symptoms caused by the persistence of preexisting traits are consistent with a "vulnerability" model. This model suggests that preexisting personality traits are a risk factor in the development of depression and would be expected to persist after the resolution of the depression. In contrast, the "scar" model suggests that depressive episodes cause lasting changes in personality.[12] Consistent with the vulnerability model, Shea et al.[12] found that personality traits remained relatively stable after a prospective depressive episode. Their findings suggest that personality traits may be a risk factor for the development of major depression. These personality traits persist after the depression resolves and may contribute to residual symptoms. Specifically, patients may have residual depressed mood, decreased interest, fatigue, poor concentration, psychomotor retardation (owing to low motivation) or agitation (owing to anxiety), feelings of worthlessness or guilt, and suicidal ideation associated with failures in occupational and interpersonal failure owing to a personality disorder. Alternatively, it is not likely that either insomnia or alterations in appetite could be attributed to a personality disorder.

The purpose of this study is to assess residual symptoms in outpatients in acute remission after treatment with fluoxetine and to examine the relationship between residual symptoms and Axis I and Axis II comorbidity.

POPULATION AND METHOD

Eligible subjects were consecutively enrolled in our Depression Clinical and Research Program (Boston, Mass.) for outpatient treatment in a clinical trial between July 1992 and January 1997. All subjects had a current episode of major depression, ascertained with the Structured Clinical Interview for DSM-III-R, Patient Edition (SCID-P),[13] and a 17-item HAM-D score of 16 or higher prior to treatment. Exclusion criteria included bipolar disorder, psychosis, alcohol or other substance use disorders active over the previous 12 months, significant antisocial personality disorder, active suicidal risk, unstable medical illness, organic mental disorder, history of intolerance or refractoriness to study drugs, concurrent use of psychotropic medications, pregnancy or breastfeeding, and clinical or laboratory evidence of hypothyroidism.

The current presence of major depressive disorder and the lifetime presence of other Axis I disorders, the age at initial major depressive disorder onset, and total number of depressive episodes were established by the SCID-P interview. Atypical depression was evaluated using the Atypical Depression Diagnostic Scale (ADDS),[14] which requires for the diagnosis of atypical depression the presence of mood reactivity as well as 2 of the following: leaden paralysis, hyperphagia, hypersomnia, or rejection sensitivity. Individuals were categorized as meeting criteria for definite atypical depression or probable atypical depression (mood reactivity and 1 of the additional 4 symptoms) or as not meeting criteria. Personality disorders were diagnosed using the Structured Clinical Interview for DSM-III-R, Personality Disorders (SCID-II).[15] The SCID-P, SCID-II, ADDS, and the 17-item HAM-D interviews were all conducted by psychiatrists affiliated with the Depression Clinical and Research Program who were fully trained in the use of these instruments through live and videotaped interviews.

We treated 215 outpatients (mean age = 40.5 ± 10.3 years; 51.6% female) who met DSM-III-R criteria for major depressive disorder. Patients were treated with a fixed dose of fluoxetine 20 mg for 8 weeks. Of these 215 patients, 108 (50.2%) were considered to be full responders (final HAM-D score ≤ 7). We then assessed these 108 full responders for the presence or absence of subthreshold or threshold symptoms with the SCID-P mood disorders module at the end of the 8-week trial. Percentages of patients who continued to have subthreshold or full symptoms were calculated. Subthreshold symptoms are defined in the SCID-P as follows: "The threshold for the criterion is almost, but not quite met (e.g., subject has

Table 1. Characteristics of the Sample and Responders[a]

Characteristic	Total Sample (N = 215)	Responders (N = 108)
Age (y), mean ± SD	40.5 ± 10.3	39.7 ± 9.6
Gender (% female)	51.6	54.6
Duration of current episode (y), mean ± SD	3.3 ± 5.2	3.3 ± 5.4
No. of lifetime episodes, mean ± SD	3.3 ± 5.5[b]	3.7 ± 5.9[c]
Age at onset (y), mean ± SD	26.4 ± 12.9	25.4 ± 11.9
Baseline HAM-D, mean ± SD	19.5 ± 3.4	18.6 ± 2.9
No. baseline major depressive disorder symptoms, mean ± SD	7.8 ± .89	7.7 ± .81

[a]Abbreviation: HAM-D = Hamilton Rating Scale for Depression.
[b]N = 180; 35 subjects had either too many episodes to count or the number of prior episodes was indistinct.
[c]N = 94; 12 subjects had either too many episodes to count or the number of prior episodes was indistinct.

been depressed for only 10 days rather than the required 2 week minimum; subject reports loss of interest in only some activities, but not the required 'almost all activities')."[13] These subthreshold symptoms are important because they represent a dysfunctional change from what patients consider normal, but fall short of the arbitrary criteria used to define a threshold symptom. The persistence of subthreshold symptoms represents continued failure of patients to reach their normal, and perhaps premorbid, state. The prevalence of subthreshold symptoms in the general population is unknown. Subsyndromal depressive symptoms were defined as 2 or more threshold depressive symptoms that did not qualify for minor depression. Minor depression was defined as 2 to 4 threshold symptoms with at least 1 symptom that included either depressed mood or loss of interest or pleasure.[6]

The relationships between residual symptoms and both selected SCID-P diagnoses and the sum of the number of SCID-II baseline diagnoses were assessed with unpaired t tests. We used selected comorbid conditions to avoid excessive multiple comparisons and type I error.

The relationships between sum of subthreshold and threshold symptoms and baseline characteristics (age, gender, severity of depression, duration of current episode, age at onset, total number of Axis I and Axis II comorbid conditions) were assessed with multiple linear regression or chi-square analysis as appropriate. Analysis of variance (ANOVA) was used to assess differences between those patients free of any posttreatment SCID-P major depressive disorder symptoms and those with 1 or more symptoms. All analyses were performed using STATVIEW statistical software, version 4.0 (Abacus Concepts, Inc., Berkeley, Calif.).

RESULTS

Mean ± SD baseline HAM-D for all subjects (N = 215) was 19.5 ± 3.4, and the final mean ± SD HAM-D score for responders (N = 108) was 4.5 ± 2.2.

Figure 1. Frequency of Threshold and Subthreshold Residual Major Depressive Disorder Symptoms in Responders (N = 108)

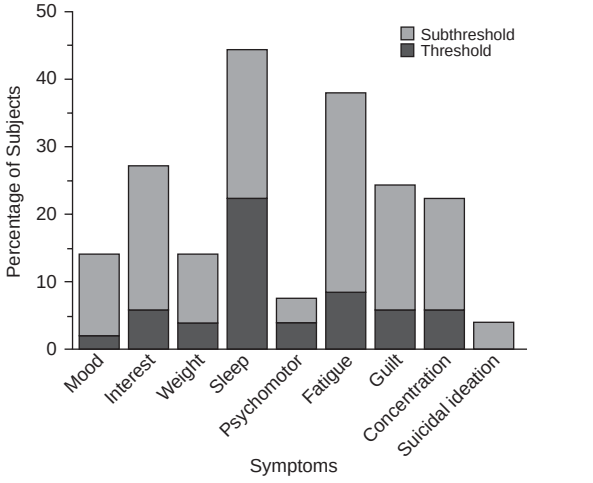
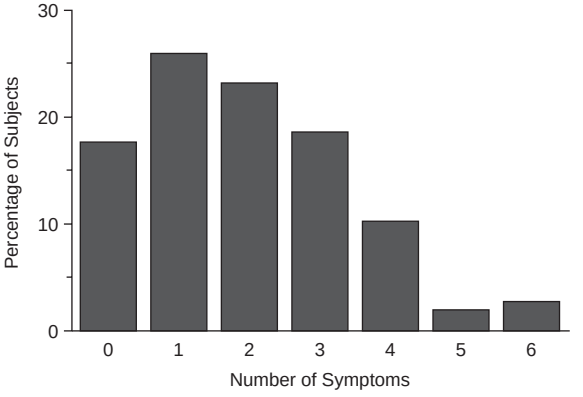


Figure 2. Distribution of Total Subthreshold and Threshold Residual Symptoms in Responders (N = 108)



Other baseline characteristics of the full sample are presented in Table 1. Only 19 (17.6%) of those with a final HAM-D score of 7 or lower were free of SCID-P major depressive disorder symptoms, while 28 (25.9%) had 1 symptom, 25 (23.2%) had 2 symptoms, 20 (18.5%) had 3 symptoms, 11 (10.2%) continued to have 4 symptoms, 2 (1.9%) had 5 symptoms, and 3 (2.8%) had 6 symptoms, most of which were subthreshold according to the SCID-P (Figures 1 and 2). Distribution of combinations of subthreshold and threshold symptoms is presented in Table 2. Of the full responders, 10.2% continued to have at least 2 threshold symptoms, with 5.6% who met criteria for subsyndromal depression and 4.6% who met criteria for minor depression.[6]

The 3 most common symptoms were sleep disturbances (44%), fatigue (38%), and diminished interest or pleasure (27%). Two patients (1.9%) had threshold de-

Table 2. Distribution of Threshold and Subthreshold Symptoms for Residual Symptoms (N = 108)

Subjects With Residual Symptoms	1 Residual Symptom (N = 28)	2 Residual Symptoms (N = 25)	3 Residual Symptoms (N = 20)	4 Residual Symptoms (N = 11)	5 Residual Symptoms (N = 2)	6 Residual Symptoms (N = 3)
No. of subjects with threshold symptoms only	1 threshold (N = 25)	2 threshold (N = 2)	3 threshold (N = 0)	4 threshold (N = 0)	5 threshold (N = 0)	6 threshold (N = 0)
No. of subjects with subthreshold symptoms only	1 subthreshold (N = 3)	2 subthreshold (N = 8)	3 subthreshold (N = 8)	4 subthreshold (N = 4)	5 subthreshold (N = 0)	6 subthreshold (N = 0)
Distribution of subjects with both subthreshold and threshold symptoms		1 threshold and 1 subthreshold (N = 15)	2 threshold and 1 subthreshold (N = 3)	3 threshold and 1 subthreshold (N = 1)	4 threshold and 1 subthreshold (N = 1)	5 threshold and 1 subthreshold (N = 1)
			1 threshold 2 subthreshold (N = 9)	2 threshold and 2 subthreshold (N = 2)	3 threshold and 2 subthreshold (N = 0)	4 threshold and 2 subthreshold (N = 0)
				1 threshold and 3 subthreshold (N = 4)	2 threshold and 3 subthreshold (N = 0)	3 threshold and 3 subthreshold (N = 0)
					1 threshold and 4 subthreshold (N = 1)	2 threshold and 4 subthreshold (N = 1)
						1 threshold and 5 subthreshold (N = 1)

Table 3. Differences Between Responders With and Without Residual Symptoms: Baseline Severity and Number of Comorbid Axis I and II Disorders[a]

Variable	No Post–Major Depressive Disorder Symptoms (N = 19)	1 or More Post–Major Depressive Disorder Symptoms (N = 89)	Analysis Test Statistic	df	p
Age (y), mean ± SD	40.3 ± 10.3	39.6 ± 9.5	F = 0.09	106	.77
Gender, % female	63	53	χ^2 = 0.68	1	.41
Never married, %	21.1	52.8	NA	1	.02[a]
Unemployed, %	36.8	25.8	NA	1	.40[a]
Age at onset (y), mean ± SD	25.4 ± 13.2	25.4 + 11.7	F = 0.00003	106	1.0
Duration of current episode (y), mean ± SD	3.4 ± 6.9	3.3 ± 5.1	F = 0.0016	106	.97
No. of lifetime episodes, mean ± SD[b]	3.6 ± 5.7[c]	3.7 ± 6.0[d]	F = 0.0018	92	.97
HAM-D (baseline), mean ± SD	19.0 ± 3.1	18.5 ± 2.9	F = 0.40	106	.53
Sum of Axis I, mean ± SD	1.9 ± 1.4	1.6 ± 1.3	F = 0.60	106	.44
Sum of Axis II, mean ± SD	1.1 ± 1.5	1.4 ± 1.4	F = 0.53	106	.47

[a]Fisher exact test. Abbreviation: NA = not applicable.
[b]N = 94; 12 subjects had either too many episodes to count or the number of prior episodes was indistinct; when these 12 patients were included in the analysis, no statistical significance was found.
[c]N = 17.
[d]N = 77.

pressed mood and 4 patients (3.7%) continued to have subthreshold suicidal ideation. No statistically significant relationships were found between number of residual symptoms and selected Axis I comorbid conditions (history of alcohol or substance abuse, any anxiety disorder, and eating disorder) or total number of Axis II disorders. Furthermore, no relationship was noted between any Axis II disorder, current anxiety disorders, atypical depression subtype, melancholic subtype, comorbid dysthymia, and residual symptoms with a Bonferroni correction. No differences in demographic variables were detected between those free of any posttreatment major depressive disorder symptoms and those with 1 or more symptoms (Table 3).

DISCUSSION

The principal finding is that even among subjects who are considered full responders to fluoxetine 20 mg for 8 weeks, more than 80% had 1 or more residual DSM-III-R symptoms of major depressive disorder, more than 30% had 3 or more symptoms, and 10.2% met formal criteria for either minor or subsyndromal depression. Thus, "remission," as stringently defined by a HAM-D cutoff score of 7 or lower, cannot be equated with an asymptomatic state.

Presence of residual symptoms was not predicted by any of the baseline characteristics (age, gender, marital status, employment status, baseline severity of depression, number of prior episodes, duration of current episode, or Axis I and Axis II comorbid conditions). Alternative contributory factors may include medication side effects, premorbid social functioning, and social support, in addition to the persistence of major depressive disorder symptoms. Medication side effects that could be misinterpreted as residual symptoms include insomnia and fatigue. We found, however, that 91.7% (44/48) of those

with posttreatment threshold or subthreshold insomnia had pretreatment insomnia and 92.7% (38/41) of those with posttreatment threshold or subthreshold fatigue had pretreatment fatigue. Insomnia and fatigue appear to persist, and therefore should be considered residual symptoms.

Epidemiologically, 2 depressive symptoms that last for 2 weeks in people without a prior history of depression compared with those without any depressive symptoms are associated with an adjusted odds ratio of 4.4 for subsequent first onset major depression in the next year.[16] These findings imply that minimal depressive symptoms are prodromal and increase the risk of developing an initial full-blown episode of major depression. For those who may or may not have had previous episodes of major depression, the presence of subsyndromal depressive symptoms is associated with an odds ratio of 2.8 and the presence of minor depression with an odds ratio of 2.9 for the risk of lifetime major depression compared to those with no symptoms.[6] Judd and colleagues[6] reported that 3.9% of the general population met criteria for subsyndromal depression and 1.5% met criteria for minor depression. We found that 5.6% of acute full responders met criteria for subsyndromal depression and 4.6% met criteria for minor depression. The proportion of full responders with subsyndromal depression and minor depression was substantially higher than would be expected among the general population.

The high prevalence of residual symptoms among antidepressant responders suggests the need for further study, including whether residual symptoms abate with longer treatment or increased dose of fluoxetine, the impact of residual symptoms on quality of life, the relationship between residual symptoms and risk of relapse and/or recurrence, and the cost-effectiveness of specific treatments, including focused psychotherapies, aimed at further resolution of residual symptoms.

Drug name: fluoxetine (Prozac).

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