Residual Symptoms in Depressed Patients After Treatment With Fluoxetine or Reboxetine

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Background: Residual symptoms are common and have a variety of consequences in depressed patients who respond to treatment, but seldom have specific residual symptoms been assessed. We examined the frequency and severity of residual depressive symptoms in 2 studies comparing the selective serotonin reuptake inhibitor (SSRI) fluoxetine with the norepinephrine reuptake inhibitor (NRI) reboxetine.

Method: Data from two 8-week, previously published, double-blind, random-assignment studies comparing fluoxetine and reboxetine were obtained. Both studies included men and women who met DSM-III-R criteria for unipolar nonpsychotic major depression. Symptoms were assessed with the 21-item Hamilton Rating Scale for Depression (HAM-D). The frequency and severity of residual symptoms were determined in the patients who completed treatment and responded (had at least 50% improvement on the HAM-D).

Results: In study 1, 117 patients completed treatment and responded. In study 2, 113 patients completed treatment and responded. The most frequent symptoms present after treatment were psychic anxiety, lack of interest, somatic anxiety, and depressed mood. No residual symptom differed significantly between treatment groups in both samples. Ordinal logistic regression, used to control for baseline symptom severity, revealed no other differences between drug groups except that decreased libido was significantly greater with fluoxetine in study 1 and study 2. Three composite scores for residual anxiety, sleep disturbance, and reduced drive did not differ between drug groups.

Conclusion: This study found no differences in residual symptoms in depressed patients who responded to treatment with the SSRI fluoxetine and the NRI reboxetine, with the exception that the fluoxetine group had a greater decrease in sexual interest, a likely side effect of that drug.

(J Clin Psychiatry 2005;66:1409–1414)

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No direct financial support for this study was received. The original studies (Andreoli et al.[15] and Massana et al.[16]) were conducted by Pharmacia.

Dr. Nelson has served as a consultant for or on the advisory boards of Abbott, Biovail, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Orexigen, Organon, Pfizer, Pharmacia, Sepracor, and Shire; has received grant/research support from Eli Lilly, Forest, and Pfizer; and has received honoraria from Abbott, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Organon, Pfizer, and Wyeth. Dr. Leon has served as a consultant for Cortex Labs and Cyberonics, Inc., and on the speakers or advisory boards of Pfizer. Ms. Portera reports no financial or other relationships relevant to the subject of this article.

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Recent emphasis on the need to treat depression to remission has raised awareness about the prevalence and importance of residual symptoms. Residual symptoms following major depression are common[1–5] and have been associated with a number of clinical consequences, including an increased risk of relapse,[6–8] a more chronic course of illness,[9] increased suicide risk,[1] and greater functional disability.[9,10] But the actual nature of residual symptoms has received relatively little attention.

To our knowledge, the only previous study to examine specific residual symptoms used the Structured Clinical Interview for DSM-III-R inventory to determine the presence or absence of symptom criteria for major depressive disorder after an 8-week course of fluoxetine.[11] Among patients who had remitted, more than 50% had 2 or more depressive symptoms present. The most common residual symptoms were sleep disturbance, fatigue, and loss of interest.

If different types of antidepressants have different effects on depressive symptoms, it might be expected that residual symptoms would reflect these differences. For example, a drug preferentially useful for anxiety but less effective for energy or drive might be expected to result in little residual anxiety but greater fatigue or lack of energy at the end of treatment. Although the question whether different classes of antidepressants treat differ-

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ent symptoms is controversial, Zimmerman and associates[12] conducted a recent survey and found that the presumed "symptom profile" of the antidepressant was the primary reason cited by clinicians for selecting an antidepressant. In that study, clinicians thought that the symptoms most important for drug selection were anxiety, insomnia, and fatigue.

In a previous study,[13] we found that the selective serotonin reuptake inhibitor (SSRI) fluoxetine and the selective norepinephrine reuptake inhibitor (NRI) reboxetine had similar effects on symptom change during treatment. Our findings were similar to those published by Trivedi et al.[14] who found that the SSRI sertraline and the catecholamine selective agent bupropion had similar effects on anxiety and insomnia. Both of these studies suggest that there may be a core group of depressive symptoms that improve together during treatment of depression. However, if agents selective for specific neurotransmitters have different but subtle effects on symptoms, these differences may become more apparent when the depression is treated and only residual symptoms remain.

In the current study, we examined residual symptoms, i.e., symptoms still present at the end of treatment, to determine which symptoms were most frequent and most severe, and if these symptoms differed following treatment with the selective NRI reboxetine or the SSRI fluoxetine.

METHOD

Symptom data from 2 previously published, similar, 8-week, double-blind, parallel comparison studies of fluoxetine and reboxetine were examined.[15,16] The symptom data were provided by the manufacturer of reboxetine, Pharmacia. We did not pool the data. Rather, we examined each sample independently, anticipating using the second sample to cross-validate any significant findings.

Details of study design have been described previously.[15,16] Briefly, subjects in each study were between the ages of 18 and 65 years and met DSM-III-R criteria for unipolar nonpsychotic major depression. Duration of depression of at least 1 month and a 21-item Hamilton Rating Scale for Depression (HAM-D)[17] score of 22 or higher were required. Patients were randomly assigned to treatment with fluoxetine 20–40 mg/day or reboxetine 8–10 mg/day for 8 weeks. The 21-item HAM-D was used to assess symptoms prior to treatment and at weeks 1, 2, 3, 4, 6, and 8 thereafter. For the purposes of this study, we examined the first 17 HAM-D items.

In addition to the individual symptoms, 3 composite scores for anxiety, sleep disturbance, and drive were generated based on the previous literature and the findings reported by Zimmerman et al.[12] that anxiety, fatigue, and insomnia were the symptoms that were most likely to influence the clinicians' selection of an antidepressant. The composite score for anxiety included HAM-D items 9, 10, and 11. The composite score for sleep included items 4, 5, and 6, and the composite drive score included item 7 (loss of interest), item 8 (retardation), and item 13 (lack of energy).

Table 1. Characteristics of Depressed Patients Treated With Fluoxetine or Reboxetine

Characteristic	Reboxetine	Fluoxetine
Study 1[a]		
Randomized, N	126	127
Sex (female), N (%)	85 (67)	83 (65)
Age, mean (SD), y	40.0 (12.0)	40.2 (11.5)
HAM-D-21 score, mean (SD)	26.8 (3.4)	26.9 (3.6)
Completed the trial, N (%)	84 (67)	90 (71)
50% improvement, N (%)	53 (42)	64 (50)
Study 2[b]		
Randomized, N	79	89
Sex (female), N (%)	57 (72)	64 (72)
Age, mean (SD), y	44.0 (12.6)	43.6 (11.8)
HAM-D-21 score, mean (SD)	28.6 (5.3)	27.4 (4.1)
Completed the trial, N (%)	60 (76)	68 (76)
50% improvement, N (%)	53 (67)	60 (67)

[a]Data from Andreoli et al.[15]
[b]Data from Massana et al.[16]
Abbreviation: HAM-D-21 = 21-item Hamilton Rating Scale for Depression.

Statistical Analysis

Because we were interested in residual symptoms present in responders, we examined those patients who completed 8 weeks of treatment and had at least 50% improvement on the HAM-D. The number and percentage of patients who had residual symptoms were determined, as well as the severity of the symptoms. Because individual items on the HAM-D are scored on ordinal but not interval scales, the Mann-Whitney U test was used to compare residual symptom scores between groups. Mean scores for the composite items were compared with t tests. We also performed ordinal logistic regression with the residual symptom as the dependent variable and the baseline symptom score as a covariate to determine if differences between treatment groups were influenced by the initial symptom severity. With a similar aim, analysis of variance (ANOVA) was employed for the final composite scores to control for the baseline score. We were aware of the potential problem resulting from multiple comparisons (a type I error) but wished to minimize the possibility of failing to find a true difference. In addition, we planned to use the second sample to cross-validate any differences found.

RESULTS

Table 1 indicates the number of patients starting treatment in each drug group in both studies and their characteristics. Table 1 also displays the number of patients who

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Table 2. Frequency and Severity of Specific Residual Symptoms After Treatment With Fluoxetine or Reboxetine in Study 1[a]

	Fluoxetine, N = 64			Reboxetine, N = 53			Comparison of Fluoxetine Versus Reboxetine[b]
Symptom	N	%	Mean Score	N	%	Mean Score	
Depressed mood	29	45.3	0.578	23	43.4	0.547	z = 0.23, p = .82
Guilt	12	18.8	0.188	11	20.8	0.208	z = 0.27, p = .79
Suicidal thinking	2	3.1	0.031	1	1.9	0.019	z = 0.42, p = .67
Difficulty falling asleep	24	37.5	0.453	23	43.4	0.566	z = 0.79, p = .43
Midnight awakening	26	40.6	0.453	12	22.6	0.302	z = 1.81, p = .07
Early morning awakening	15	23.5	0.250	12	22.7	0.264	z = 0.03, p = .97
Lack of interest	40	62.5	0.781	32	60.4	0.774	z = 0.40, p = .69
Retardation	11	17.2	0.172	14	26.4	0.283	z = 1.25, p = .21
Agitation	21	32.8	0.406	12	22.7	0.283	z = 1.19, p = .23
Psychic anxiety	43	67.2	0.922	37	69.8	0.887	z = 0.22, p = .83
Somatic anxiety	36	56.3	0.703	29	54.7	0.660	z = 0.29, p = .77
Somatic symptoms, gastrointestinal	15	23.4	0.266	12	22.6	0.226	z = 0.19, p = .85
Somatic symptoms, general	27	42.2	0.422	15	28.3	0.302	z = 1.46, p = .14
Decreased libido	31	48.5	0.531	18	34.0	0.358	z = 1.62, p = .10
Hypochondriasis	18	28.1	0.313	13	24.6	0.283	z = 0.40, p = .69
Weight loss	5	7.8	0.109	4	7.6	0.113	z = 0.04, p = .97
Lack of insight	0	0.0	0.0	4	7.5	0.075	z = 2.23, p = .03
Anxiety composite score	51	79.7	2.031	41	77.4	1.830	t = 0.75, p = .46
Sleep composite score	36	56.3	1.156	29	54.7	1.132	t = 0.10, p = .92
Drive composite score	44	68.8	1.375	37	69.8	1.358	t = 0.08, p = .94

[a]Data from Andreoli et al.[15]
[b]Tests of significance: Mann-Whitney U test except for comparison of factor scores, which employed t tests (df = 115).

completed treatment and the number of responders in each group.

The frequency and mean severity of residual symptoms are shown for study 1 in Table 2 and for study 2 in Table 3. In both samples and in both drug groups, the symptoms most often present and having the greatest severity following treatment were psychic anxiety, lack of interest (in work and activities), somatic anxiety, and depressed mood. These symptoms were present in 40% or more of the patients in each study.

There were no significant differences in the severity of residual symptoms between drug treatment groups with 2 exceptions. In study 1, lack of insight was more frequent in the reboxetine group; however, in study 2, there was no suggestion of a difference. In study 2, decreased libido was present in 51.7% of the patients receiving fluoxetine versus 32.1% of those taking reboxetine and was significantly more severe (Mann-Whitney U test, z = 2.39, p = .02). In study 1, this symptom was also more frequent (48.5% vs. 34.0%) and more severe in the fluoxetine group, but the latter difference failed to reach significance (z = 1.62, p = .10). The only other item with a suggestive difference was midnight awakening. In study 1, this symptom was more frequent with fluoxetine (40.6% vs. 22.6%, z = 1.81, p = .07); however, in study 2, midnight awakening was more frequent with reboxetine (37.7% vs. 28.3%).

Comparison of the residual composite scores for anxiety, sleep disturbance, and drive revealed no significant between-group differences in these variables.

Ordinal logistic regression analyses were performed for 5 key symptoms—depressed mood, lack of interest, psychic anxiety, somatic anxiety, and somatic symptoms, general (lack of energy/aches and pains). When baseline scores were accounted for, no significant differences remained between drug groups. The only item for which a difference was suggested was the rating of somatic symptoms, general (lack of energy/aches and pains). In study 1, the independent association of drug group with the residual rating of somatic symptoms, general was z = 1.78, p = .07. In study 2, the association of the residual rating for somatic symptoms, general and drug group was z = 1.59 and p = .11. ANOVAs for the 3 composite scores were also performed. None of these scores differed significantly between treatment groups in either study.

Because of the significant finding for differences in decreased libido, ordinal logistic regression analysis was also performed for this item. As before, decreased sexual interest was significantly greater in the fluoxetine group in study 2. However, when baseline sexual interest was taken into account, the difference in sexual interest was significant in study 1 as well (z = 2.02, p = .04).

DISCUSSION

In this examination of residual symptoms, patients treated with an SSRI and a selective NRI experienced similar residual symptoms. The only difference noted was greater decreased libido after fluoxetine treatment,

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Table 3. Frequency and Severity of Specific Residual Symptoms After Treatment With Fluoxetine or Reboxetine in Study 2[a]

	Fluoxetine, N = 60			Reboxetine, N = 53			Comparison of Fluoxetine Versus Reboxetine[b]
Symptom	N	%	Mean Score	N	%	Mean Score	
Depressed mood	34	56.7	0.600	23	43.4	0.434	z = 1.47, p = .14
Guilt	18	30.0	0.300	14	26.4	0.283	z = 0.35, p = .72
Suicidal thinking	5	8.3	0.083	1	1.9	0.019	z = 1.52, p = .13
Difficulty falling asleep	18	30.0	0.333	20	37.7	0.396	z = 0.78, p = .43
Midnight awakening	17	28.3	0.317	20	37.7	0.396	z = 0.97, p = .33
Early morning awakening	13	21.7	0.217	6	11.3	0.113	z = 1.46, p = .14
Lack of interest	37	61.7	0.717	25	47.2	0.528	z = 1.58, p = .11
Retardation	9	15.0	0.150	8	15.1	0.151	z = 0.01, p = .99
Agitation	11	18.3	0.217	13	24.5	0.264	z = 0.74, p = .46
Psychic anxiety	37	61.6	0.650	35	66.0	0.717	z = 0.49, p = .63
Somatic anxiety	29	48.4	0.550	25	47.2	0.547	z = 0.07, p = .95
Somatic symptoms, gastrointestinal	5	8.3	0.083	6	11.3	0.113	z = 0.53, p = .59
Somatic symptoms, general	27	45.0	0.517	18	34.0	0.396	z = 1.14, p = .25
Decreased libido	31	51.7	0.650	17	32.1	0.340	z = 2.39, p = .02
Hypochondriasis	15	25.0	0.317	16	30.2	0.340	z = 0.48, p = .63
Weight loss	2	3.4	0.050	1	1.9	0.019	z = 0.48, p = .63
Lack of insight	0	0.0	0.0	0	0.0	0.0	z = 0, p = 1.000
Anxiety composite score	42	70.0	1.417	44	83.0	1.528	t = 0.52, p = .61
Sleep composite score	31	51.7	0.867	35	66.0	0.906	t = 0.22, p = .83
Drive composite score	44	73.3	1.383	34	64.2	1.075	t = 1.49, p = .14

[a]Data from Massana et al.[16]
[b]Tests of significance: Mann-Whitney U test except for comparison of factor scores, which employed t tests (df = 111).

which likely reflects the sexual dysfunction associated with the use of an SSRI.[18] The symptoms most often present following treatment—psychic anxiety, lack of interest (in work and activities), somatic anxiety, and depressed mood—were among those HAM-D symptoms most frequently present prior to treatment in the 2 samples described here[13] and in another sample of depressed patients.[19] This finding would appear to suggest that the initial symptoms of depression are a more important determinant of residual symptoms than differences in the antidepressants used to treat the depression.

These data are consistent with previous findings of similar symptom change during treatment with agents selective for different neurotransmitters.[13] In that study, we examined the magnitude of symptom change during treatment with reboxetine or fluoxetine and found similar symptom change during treatment in 2 patient samples. There was no evidence to suggest that anxiety, lack of interest, or lack of energy was more responsive to one agent than another.

We have also previously reviewed studies comparing serotonergic (5-HT) and noradrenergic (NE) antidepressants.[20] Most of these studies found no differences in the symptoms responding to these different selective agents. A few studies reported greater change with one agent than another, but the findings were not consistent.

A related question is whether there are differences in the symptoms that predict response to selective agents, but these data are also inconsistent. Filteau et al.[21] performed a post hoc analysis of patients who had participated in 9 double-blind trials at their center and examined the characteristics of responders to selective 5-HT agents (N = 28) and selective NE agents (N = 29). They found that SSRI responders had higher initial scores on an anxiety-agitation factor derived from the HAM-D and higher scores on a depression factor. Rampello et al.[22] reported somewhat similar findings in 74 patients with poststroke depression. They created 2 composite scales, 1 composed of symptoms associated with anxiety and thought to be mediated by serotonin and the other composed of symptoms associated with retardation and fatigue and thought to be mediated by catecholamines. They found citalopram more effective in anxious depression and reboxetine more effective in retarded depression. These 2 studies, however, differed from others reported.

Rush et al.,[23] in a meta-analysis of 439 patients treated with bupropion or sertraline, found that anxiety did not predict response to these different agents. Alternatively, Burns et al.,[24] in a study comparing lofepramine and fluoxetine, found that baseline anxiety predicted a positive response to the NE agent lofepramine and a negative response to fluoxetine. Further, psychomotor retardation and lack of energy predicted poor response to a NE selective agent but did not predict response to fluoxetine. In a similar manner, Bowden et al.[25] found a trend for high anxiety to be associated with poor response to fluoxetine but anxiety was not associated with response to desipramine. The studies of predictors of response have found inconsistent findings.

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The findings of our current study and the literature reviewed above suggest that antidepressants may act through a final common pathway. This hypothesis appears to be supported by recent brain imaging studies. Using positron emission tomography, Bremner and colleagues[26,27] found that tryptophan depletion and administration of alpha-methyl-paratyrosine (AMPT) both produced decreases in cerebral blood flow in the same brain areas—the orbitofrontal cortex, the dorsolateral prefrontal cortex, and the thalamus. These data suggest that antidepressants acting on NE and 5-HT mechanisms may affect similar neuroanatomic areas of the brain.

We examined residual symptoms using the HAM-D. It is possible that other dimensions not assessed on the HAM-D might show greater differences with different selective antidepressants. For example, Fava and colleagues[28–30] have reported that the SSRI fluoxetine had a beneficial effect on anger and irritability, a dimension not well assessed on the HAM-D. To our knowledge, the utility of noradrenergic or dopaminergic agents has not been reported for this dimension. The literature suggests that impulsivity—another symptom not assessed on the HAM-D—may be more responsive to serotonergic drugs.[31] Dubini et al.[32] reported that social functioning was more responsive to the NE selective agent reboxetine than fluoxetine, but this finding has not been replicated.

Another area of interest has been the study of positive and negative affect. Of interest in relation to residual symptoms, positive and negative affect has been studied in subjects without depression as well as in those with depression. Negative affect has been found to correlate with a measure of serotonin functioning.[33] The SSRI paroxetine has been shown to reduce negative affect in medically and psychiatrically healthy volunteers.[34] Studies have suggested that the emotional blunting sometimes seen with SSRIs might represent inhibition of positive affect. Opbroek et al.[35] reported that 15 patients with SSRI-induced sexual dysfunction demonstrated a reduction in emotional intensity relative to controls. In addition, Harmer and associates[36] found that even a single dose of the NE agent reboxetine shifted perception of affect in a positive direction. These findings suggest a possible difference between 5-HT and NE agents on positive affect; however, 2 recent studies[37,38] failed to confirm this hypothesis.

Furlan and associates[37] compared the effects of 2 SSRIs with placebo in older volunteers. They found that SSRIs reduced negative affect in relation to negative events but found no evidence of emotional blunting. In another recent study, Harmer et al.[38] compared the effects of a 7-day course of citalopram and reboxetine on positive and negative emotional information processing in 42 healthy volunteers. Both drugs had similar effects on emotion-related tasks, namely reducing negative in relation to positive emotional material. To our knowledge, selective 5-HT and NE antidepressants have not been shown to have different effects on either positive or negative affect.

The current study has limitations. As mentioned above, the symptoms assessed were limited to those assessed by the HAM-D scale. Other dimensions were not assessed. In addition, the HAM-D was not designed for the assessment of individual symptoms. Although previous work has found that individual items on the HAM-D can be reliably rated by different investigators,[39] it is not clear that the training required to achieve this level of reliability was provided in these clinical trials. In addition, the HAM-D varies with respect to the quality of individual items. For example, some items such as depressed mood, psychic anxiety, and lack of interest are assessed on a 0- to 4-point scale. Anchor points are defined, and nonpsychotic depressed patients will commonly score across the range of these items. Loss of energy, however, is a poorly designed item. The item rates both aches and pains and lack of energy and is only scored from 0 to 2. In fact, in the current study, it might be argued that the failure to find a significant difference between drug groups for residual lack of energy reflects the limitations of that HAM-D item. This limitation is a possibility; however, we note that there was no suggestion of a difference between groups in the composite score for lack of drive (sum of lack of energy, lack of interest, and motor retardation).

Another possible limitation of the study is that we studied residual symptoms in patients with 50% improvement after 8 weeks of treatment, and it might be questioned if differences would be found with a more stringent criterion for remission. To address this question, we examined residual symptoms in patients who completed treatment and remitted (HAM-D score ≤ 7). Because symptom scores were generally low in remitting patients, we limited this analysis to the 5 most common residual symptoms (depressed mood, lack of interest, psychic and somatic anxiety, and lack of energy/aches and pains) and the 3 composite scores for anxiety, sleep disturbance, and reduced drive. In fact, there were no significant between-group differences in patients who remitted in either study for these 5 individual residual symptoms or for the 3 composite scores.

In summary, our findings are at odds with the common clinical lore that antidepressant drug selection might be based on the "symptom profile" of the drug.[12] Zimmerman and colleagues[12] noted that there was little empirical evidence to support that view, as we[20] had concluded in a prior review. Our present findings extend this observation. Not only do 5-HT and NE selective antidepressants have similar effects on symptoms, but residual symptoms also appear to be similar following treatment with different selective agents.

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Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), paroxetine (Paxil and others), sertraline (Zoloft).

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