Effects of Nefazodone on Body Weight: A Pooled Analysis of Selective Serotonin Reuptake Inhibitor– and Imipramine-Controlled Trials

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Background: Evidence suggests that the newer antidepressant drugs may differ with respect to their effects on body weight, especially during long-term treatment. However, the published data about treatment-emergent weight change with the newer antidepressants are limited. Most reports of unexpected selective serotonin reuptake inhibitor (SSRI)–associated weight gain are anecdotal or from small controlled trials. To determine if differences exist among the newer antidepressants, the authors retrospectively analyzed data from clinical trials comparing nefazodone with SSRIs and with imipramine.

Method: Weight change data supplied by Bristol-Myers Squibb from 6 completed clinical trials comparing the antidepressant nefazodone (N = 523) with 3 SSRIs, fluoxetine, sertraline, and paroxetine (N = 513), as well as 3 trials comparing nefazodone (N = 225) with the tricyclic antidepressant imipramine (N = 224) were analyzed. In all studies, nefazodone was found to be equal in efficacy to the comparator antidepressants. Studies that included both acute and long-term treatment phases were included in the analysis. Acute phases of the trials lasted either 6 or 8 weeks, and long-term phases varied in duration from 16 to 46 weeks. The analysis included summarizing the number and percentage of patients in each group with a ≥ 7% change in body weight from baseline at any point in the long-term and acute phases, at endpoint, and at week 16 of the long-term phases.

Results: Using 7% or greater weight change as the measure of clinical significance, 4.3% of SSRI-treated patients had lost weight at any point in the acute phase versus 1.7% of those treated with nefazodone ($p = .017$). However, at any point during the long-term phase, significantly more SSRI-treated patients than nefazodone-treated patients showed a significant increase in body weight (17.9% vs. 8.3%; $p = .003$). At any point in the acute phase, significantly more imipramine-treated patients than nefazodone-treated patients had a 7% or greater increase in body weight (4.9% vs. 0.9%; $p = .027$), and for the long-term phase the comparison yielded 24.5% versus 9.5%. The difference during the long-term phase was statistically significant in women ($p = .017$), but not in men ($p = .078$) due to the small numbers of men in each group.

Conclusion: SSRIs caused more weight loss during short-term treatment but more weight gain during long-term treatment. These results lend support to the observation that some antidepressants have a greater expected risk of weight gain than others during long-term therapy.

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Some recent reports suggest that the true incidence of weight gain associated with selective serotonin reuptake inhibitor (SSRI) treatment is higher than clinical trial reports indicate.[1–6] More specifically, there is uncertainty about whether unexpected increases in body weight occur during chronic as opposed to short-term treatment.[7] Since these reports are mainly anecdotal, involve small numbers of patients, or are not placebo controlled, caution has been urged in drawing conclusions about the risk of SSRI-associated weight gain.[8] The revised American Psychiatric Association Practice Guideline for the Treatment of Patients With Major Depressive Disorder[9(p27)] acknowledges the need for clarification of this issue, stating that "the literature differs as to whether patients taking SSRIs beyond the acute phase do or do not experience weight gain as a medication side effect."

One response to the emerging questions about the risk of SSRI-associated weight gain has been the reanalysis of data from completed clinical trials and pooled analyses of weight effects with newer antidepressants. Some of these analyses have already been published and include fluoxetine versus placebo,[8] citalopram versus placebo,[10] and fluoxetine versus sertraline and paroxetine.[11] These reports do not fully resolve the question of whether all SSRIs cause similar weight gain because at least one analysis did find a differential risk of weight gain among the SSRIs.[10] In addition, a large study[6] comparing sertraline and paroxetine found significant differences between these drugs in the incidence of weight gain and weight loss but failed to report the percentage of patients who exhibited at least a 7% change in weight, the accepted standard of clinical significance.

To further clarify whether objective evidence substantiates the presence of differences in risk of drug-induced weight gain, the authors requested the data from double-blind studies that directly compare one of the newer antidepressants, nefazodone, with the SSRIs and with imipra-

Table 1. Duration of Treatment in Nefazodone-SSRI Comparative Studies (wk)

Comparator	Acute Phase Duration	Long-Term Phase Duration
Fluoxetine	8	44
Fluoxetine	6	46
Sertraline	6	46
Sertraline	6	20
Sertraline	8	16
Paroxetine	8	16

mine (data on file, Bristol-Myers Squibb, Princeton, New Jersey). Nefazodone represents a good comparator drug, since studies have found nefazodone to be comparable to the SSRIs and imipramine in antidepressant efficacy.[12–20] Nefazodone has also been shown to be effective in the long-term treatment of depression.[18–22] Being comparable in terms of efficacy eliminates the potential confounding variable of efficacy differences influencing body weight during treatment. In addition, unlike findings for the SSRIs, there have been no published reports of unusual rates of weight gain attributed to nefazodone.[23] Described below are the results of analyses of weight change data from the acute and long-term phases of 9 studies.

NEFAZODONE-SSRI STUDIES

Method

Weight data from 6 long-term studies that compared nefazodone with the SSRIs fluoxetine, sertraline, and paroxetine were analyzed. All data from the SSRIs were pooled. There were 523 subjects with weight measurements in the nefazodone group and 513 in the pooled SSRI group.

All 6 studies began as acute studies. After the acute phase, which lasted either 6 or 8 weeks (Table 1), patients who showed at least minimal improvement continued into the long-term phase for double-blind treatment. Typically, most patients (approximately 90% of those enrolling in the long-term phase) met Clinical Global Impressions-Improvement full response criteria of "very much improved" or "much improved."

Data Analysis

Analysis was done of all patients in nefazodone and SSRI groups in the acute phase. Then, an analysis was done of long-term data from patients who went into long-term phases of these studies, which varied in duration from 16 to 46 weeks.

The analysis included summarizing the number and percentage of patients in each treatment group (overall and by sex) who had at least a 7% change in body weight from baseline at any point during the acute and long-term phases of the studies and at endpoint. In addition, for the long-term data, an analysis was done on the latest weight measurement up to week 16 (the endpoint for the shortest trials). Increase and decrease were analyzed separately. For the endpoint and week 16 analyses, the distribution between treatments was compared using a stratified Cochran-Mantel-Haenszel test (stratified by protocol and sex for the overall comparison and by protocols only for the comparison within sex). For the analysis at any point in the acute and extension phases, time to first significant clinical change in weight was analyzed by treatment (overall and by sex). Since patients remaining on treatment for a long period of time are theoretically at a greater risk for a change in weight than patients on treatment for a short period of time, a log-rank test was used to account for possible differences in duration of exposure to drug. The log-rank test reflects the time to first ≥ 7% increase or decrease in weight. Since all analyses were stratified by protocol, the analyses accounted for the different durations of the SSRI studies.

Table 2. Acute Phase of Nefazodone-SSRI Studies: Patients With at Least a 7% Change in Weight by Treatment Group and Gender, N (%)[a]

	Any Point in Acute Phase			Endpoint of Acute Phase		
Weight Change	Nefazodone	SSRI	p Value	Nefazodone	SSRI	p Value
Overall	N = 523	N = 513		N = 523	N = 513	
Increase ≥ 7%	12 (2.3)	9 (1.8)	.558	12 (2.1)	8 (1.6)	.437
Decrease ≥ 7%	9 (1.7)	22 (4.3)	.017	7 (1.3)	18 (3.5)	.020
Women	N = 314	N = 294		N = 314	N = 294	
Increase ≥ 7%	7 (2.2)	5 (1.7)	.607	7 (2.2)	5 (1.7)	.720
Decrease ≥ 7%	7 (2.2)	15 (5.1)	.135	5 (1.6)	12 (4.1)	.058
Men	N = 209	N = 219		N = 209	N = 219	
Increase ≥ 7%	5 (2.4)	4 (1.8)	.763	5 (2.4)	3 (1.4)	.430
Decrease ≥ 7%	2 (1.0)	7 (3.2)	.033	2 (0.9)	6 (2.7)	.172

[a]p Values for endpoint of acute phase were obtained using the Cochran-Mantel-Haenszel test, stratified by protocol and sex for the overall group and by protocol for the gender groups. p Values for any point in the acute phase were obtained using the log-rank test, stratified by protocol and sex for the overall group and by protocol for the gender groups. Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Results

Analysis of both the acute and long-term phases of the studies found that there were differences between nefazodone and the SSRIs with respect to their effects on body weight. Table 1 shows the duration of the acute and long-term phases of each trial by individual SSRI. Table 2 shows the data on clinically significant weight gain at any point during treatment and at the endpoint of the acute treatment phase. Table 3 shows the data on clinically significant weight gain at any point during the long-term treatment phase, at week 16, and at study endpoint.

In the short term, significantly more SSRI-treated patients experienced a significant decrease in body weight than did nefazodone-treated patients. Using a greater than 7% decrease as the measure of significance, 4.3% of SSRI-treated patients had lost weight at any point in the acute phase versus 1.7% of those treated with nefazodone. The decrease in weight was seen in both men and women.

Table 3. Long-Term Phase of Nefazodone-SSRI Studies: Patients With at Least a 7% Change in Weight by Treatment Group and Gender, N (%)[a]

	Week 16			Any Point During Long-Term Phase			Endpoint of Long-Term Phase		
Weight Change	Nefazodone	SSRI	p Value	Nefazodone	SSRI	p Value	Nefazodone	SSRI	p Value
Overall	N = 282	N = 313		N = 289	N = 319		N = 289	N = 319	
Increase ≥ 7%	10 (3.5)	19 (6.1)	.170	24 (8.3)	57 (17.9)	.003	20 (6.9)	44 (13.8)	.007
Decrease ≥ 7%	15 (5.3)	17 (5.4)	.911	27 (9.3)	35 (11.0)	.971	21 (7.3)	20 (6.3)	.566
Women	N = 156	N = 184		N = 161	N = 190		N = 161	N = 190	
Increase ≥ 7%	5 (3.2)	13 (7.1)	.117	14 (8.7)	36 (18.9)	.015	12 (7.5)	27 (14.2)	.041
Decrease ≥ 7%	8 (5.1)	13 (7.1)	.526	16 (9.9)	23 (12.1)	.759	12 (7.5)	16 (8.4)	.713
Men	N = 126	N = 129		N = 128	N = 129		N = 128	N = 129	
Increase ≥ 7%	5 (4.0)	6 (4.6)	.824	10 (7.8)	21 (16.3)	.079	8 (6.2)	17 (13.2)	.079
Decrease ≥ 7%	7 (5.5)	4 (3.1)	.294	11 (8.6)	12 (9.3)	.645	9 (7.0)	4 (3.1)	.122

[a]p Values for week 16 and endpoint of long-term phase obtained using the Cochran-Mantel-Haenszel test, stratified by protocol and sex for the overall group and by protocol for the gender groups. p Values for any point during the long-term phase obtained using the log-rank test, stratified by protocol and sex for the overall group and by protocol for the gender groups. Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Weight gain during long-term treatment was analyzed at 3 points: at week 16, at any point during the long-term phase, and at the endpoint of the long-term phase. The findings were as follows:

- At week 16, there was no significant difference in weight gain between nefazodone and the SSRIs (p = .170).
- At any point during the long-term phase, significantly more SSRI-treated patients than nefazodone-treated patients showed a significant increase in body weight (17.9% vs. 8.3%; p = .003).
- At the endpoint of the long-term phase, there was a significantly greater percentage of patients gaining weight while on treatment with the SSRIs (13.8% vs. 6.9%; p = .007).

Thus, during long-term treatment, the effect of SSRIs on weight reversed (as compared with acute treatment). This increase in weight was consistent among both men and women.

NEFAZODONE-IMIPRAMINE STUDIES

Method

Three studies in which nefazodone was dosed in the therapeutic range were looked at (the low-dose arm of nefazodone treatment [100–300 mg/day] in 1 study was not included). There were 225 subjects with weight measurements in the nefazodone group and 224 in the imipramine group.

Data Analysis

For each of the sets of studies, the same analysis was carried out as previously described for the SSRI analysis. Table 4 shows the data on clinically significant weight change at any point during acute-phase treatment and at endpoint of the acute phase by treatment group and gender. Table 5 shows the data on clinically significant weight change at any point during the long-term phase, at week 16, and at study endpoint.

Table 4. Acute Phase of Nefazodone-Imipramine Studies: Patients With at Least a 7% Change in Weight by Treatment Group and Gender, N (%)[a]

	Any Point During Acute Phase			Endpoint of Acute Phase		
Weight Change	Nefazodone	Imipramine	p Value	Nefazodone	Imipramine	p Value
Overall	N = 225	N = 224		N = 225	N = 224	
Increase ≥ 7%	2 (0.9)	11 (4.9)	.027	1 (0.4)	11 (4.9)	.002
Decrease ≥ 7%	1 (0.4)	6 (2.6)	.016	1 (0.4)	4 (1.8)	.207
Women	N = 161	N = 133		N = 161	N = 133	
Increase ≥ 7%	2 (1.2)	8 (6.0)	.013	1 (0.6)	8 (6.0)	.008
Decrease ≥ 7%	1 (0.6)	4 (3.0)	.029	1 (0.6)	2 (1.5)	.467
Men	N = 64	N = 91		N = 64	N = 91	
Increase ≥ 7%	0 (0)	3 (3.3)	.090	0 (0)	3 (3.3)	.133
Decrease ≥ 7%	0 (0)	2 (2.2)	.200	0 (0)	2 (2.2)	.266

[a]p Values for endpoint of acute phase were obtained using the Cochran-Mantel-Haenszel test, stratified by protocol and sex for the overall groups and by protocol for the gender groups.
p Values for any point in the acute phase were obtained using the log-rank test, stratified by protocol and sex for the overall group and by protocol for the gender groups.

Results

Imipramine caused significantly more weight gain in the short-term and long-term compared with nefazodone. At any point in the acute phase, significantly more imipramine-treated patients than nefazodone-treated patients had a ≥ 7% increase in body weight (4.9% vs. 0.9%), and for the long-term phase the comparison yielded 24.5% versus 9.5%. The treatment differential with nefazodone at any point in the long-term phase was highly significant among women (p = .017). There was no difference in long-term weight gain between imipramine and nefazodone treatment in men; however, this was likely due to the small number of men in the studies (22 in each group).

With respect to weight loss, the treatments appear comparable in the short-term and the long-term. At any point in the long-term phase, nefazodone-treated patients had a numerically greater incidence of weight loss com-

Table 5. Long-Term Phase of Nefazodone-Imipramine Studies: Patients With at Least a 7% Change in Weight by Treatment Group and Gender, N (%)[a]

	Week 16			Any Point During Long-Term Phase			Endpoint of Long-Term Phase		
Weight Change	Nefazodone	Imipramine	p Value	Nefazodone	Imipramine	p Value	Nefazodone	Imipramine	p Value
Overall	N = 74	N = 60		N = 74	N = 61		N = 74	N = 61	
Increase ≥ 7%	2 (2.7)	5 (8.3)	.139	7 (9.5)	15 (24.5)	.161	2 (2.7)	12 (19.7)	.001
Decrease ≥ 7%	5 (6.8)	2 (3.3)	.393	10 (13.5)	5 (8.2)	.142	7 (9.5)	5 (8.2)	.918
Women	N = 52	N = 38		N = 52	N = 39		N = 52	N = 39	
Increase ≥ 7%	0 (0)	4 (10.5)	.019	4 (4.3)	12 (30.8)	.017	1 (1.9)	10 (25.6)	.001
Decrease ≥ 7%	4 (7.7)	2 (5.3)	.669	9 (17.3)	5 (12.8)	.235	6 (11.5)	5 (12.8)	.830
Men	N = 22	N = 22		N = 22	N = 22		N = 22	N = 22	
Increase ≥ 7%	2 (9.1)	1 (4.5)	.547	3 (13.6)	3 (13.6)	.078	1 (4.5)	2 (9.1)	.558
Decrease ≥ 7%	1 (4.5)	0 (0)	.280	1 (4.5)	0 (0)	.317	1 (4.5)	0 (0)	.317

[a]p Values for week 16 and endpoint of long-term phase obtained using the Cochran-Mantel-Haenszel test, stratified by protocol and sex for the overall group and by protocol for the gender groups. p Values for any point during the long-term phase obtained using the log-rank test, stratified by protocol and sex for the overall group and by protocol for the gender groups.

pared with imipramine-treated patients (13.5% vs. 8.2%). The treatment differential, although not statistically significant, was again greater among women.

DISCUSSION

Differences in side effects represent a major consideration in drug selection. Recently, there has been increasing interest in possible differences between the newer antidepressants in terms of one side effect: weight gain.[7] For obvious reasons, unwanted, excessive weight gain has an adverse impact on appearance and physical health. It can also lead to noncompliance with treatment.

Among the newer antidepressants, only mirtazapine has been found to cause clinically significant weight gain among patients enrolled in short-term placebo-controlled trials.[21] Reports of unexpected weight gain involving the SSRIs have been anecdotal or from small controlled trials. Reports on nefazodone have shown weight gain similar to that with placebo.[23] Analysis of the data from long-term trials that compare nefazodone with imipramine and SSRIs shows a consistent incidence of weight gain with nefazodone: 8.3% in the SSRI trials and 9.5% in the imipramine trials.

The 6 controlled studies that were direct comparisons between nefazodone and 3 SSRIs revealed that with long-term treatment the incidence of clinically significant weight gain was twice as great with the SSRIs as it was with nefazodone. These results support the observations in some controlled studies and anecdotal reports that SSRIs are associated with significant weight gain in some patients, especially during long-term treatment.

Understandably, it is difficult to characterize the precise incidence of weight gain with a specific drug. In most studies, up to 10% of patients taking placebo may experience clinically significant weight gain during long-term treatment. From a clinical perspective, the long-term effects of a drug on body weight may be more significant than its acute effects, mainly because antidepressant therapy typically involves treatment for months or years rather than weeks. Data from controlled studies indicate that SSRIs cause more short-term weight loss than does nefazodone, whereas more patients treated with SSRIs than nefazodone are likely to experience significant weight gain during long-term therapy. These findings argue against the idea that weight gain during antidepressant therapy can be fully explained as a recovery effect.[24] In addition, a recent study[25] has demonstrated clinically significant weight gain in SSRI-treated patients with panic disorder, a condition not usually associated with weight loss and therefore not susceptible to patients' regaining lost weight or to a recovery effect. Moreover, patients with atypical depression experience increased appetite and weight gain as part of their illness. For them, recovery would imply weight loss, not weight gain.

Our analysis also compared the effects on weight of nefazodone and imipramine. Imipramine and other tricyclic antidepressants have long been known to cause significant weight gain. Yet, paralleling the apparent situation with the SSRIs, there appears to be a tendency for controlled trials to report a lower incidence of weight gain than seems to be experienced in clinical practice and to fail to detect drug-placebo differences. For example, a long-term maintenance trial of full-dose imipramine (200–300 mg/day) for recurrent unipolar disorder found minimal weight gain (average gain of 5.8 lb [2.6 kg] during an average treatment period of 725 days) associated with active treatment and no differences between individuals receiving active medication versus those randomly assigned to the "no drug" cells (average gain of 2.8 lb [1.2 kg] during an average treatment period of 422 days).[26] On the other hand, a review of outpatients taking amitriptyline, nortriptyline, and imipramine for an average of 6 months found that patients experienced a mean weight increase of 1.3 to 2.9 lb (0.6–1.3 kg)/month.[27] This led to an average total weight gain of 3 to 16 lb (1.4–7.2 kg), depending on drug, dose, and treatment duration. Weight gain was linear over time and was accompanied by marked increases in the preference for sweets. Excessive weight gain was the most common cause of discontinuation of treatment, occurring in one half of the patients.

Because of the extensive use of antidepressant drugs in our society and the possibility that there may be meaningful differences between antidepressant drugs with respect to their effects on body weight, it is important to improve the quality of available data addressing this issue. In the absence of new studies providing information about drug-associated weight gain, it could prove useful and cost-effective to analyze archived data to see what insights they may yield.

Drug names: amitriptyline (Elavil and others), citalopram (Celexa), fluoxetine (Prozac), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), sertraline (Zoloft).

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