Reboxetine Versus Fluoxetine: An Overview of Efficacy and Tolerability

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Serotonin selective reuptake inhibitors (SSRIs) are widely used to treat depression and offer the advantage of being better tolerated compared with tricyclic antidepressants, which inhibit both serotonin and norepinephrine reuptake. Against this background, 2 clinical studies were conducted comparing the efficacy and tolerability of reboxetine, a selective norepinephrine reuptake inhibitor, with fluoxetine, an SSRI. Both studies were of double-blind, randomized, parallel-group, multicenter design. One included a placebo control group. Five hundred forty-nine patients with major depression, under inpatient care or attending outpatient or day hospital clinics, received reboxetine (8–10 mg/day) or fluoxetine (20–40 mg/day) over 8 weeks. The overall efficacy of reboxetine and fluoxetine was similar, and superior to placebo, as assessed by the mean reduction in Hamilton Rating Scale for Depression total score. Reboxetine demonstrated superior efficacy compared with fluoxetine in severely ill patients and was associated with greater improvement in social functioning, especially in terms of motivation toward action and negative self-perception. Both treatments were well tolerated. In summary, reboxetine is an effective and well-tolerated antidepressant and is superior to fluoxetine in the treatment of severely ill patients and in terms of improving social functioning.

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The serotonin selective reuptake inhibitor (SSRI) fluoxetine is a widely used alternative to tricyclic antidepressants (TCAs) in the treatment of depression. The specificity of action of fluoxetine is associated with better tolerability compared with the TCAs,[1] which, as well as inhibiting norepinephrine and serotonin reuptake to varying degrees, have affinity for muscarinic, α_1-adrenergic, and histaminergic receptors.[2] Fluoxetine, however, may not be as effective as the TCAs in some patient subtypes such as those with severe depression.[3]

Reboxetine is a selective norepinephrine reuptake inhibitor with potent antidepressant activity[4,5] and weak affinity for dopamine uptake sites or for muscarinic or adrenergic receptors.[6] In comparison with placebo, reboxetine, 8–10 mg/day, was found to be effective and well tolerated in the treatment of major depression.[7] Reboxetine was also demonstrated to be as effective as imipramine and desipramine in the treatment of major depression and was better tolerated.[8,9] Furthermore, reboxetine was shown to be as effective as imipramine in severely ill patients.[8] Against this background, 2 randomized double-blind studies (1 placebo-controlled) were conducted to compare the efficacy and tolerability of reboxetine (8–10 mg/day) with fluoxetine (20–40 mg/day) over 8 weeks in patients with major depression. Analyses of the response included an assessment of social functioning and efficacy in severe depression.

DESIGN

A total of 549 patients with a diagnosis of a major depressive episode were recruited to 2 multicenter, multinational, double-blind studies (Table 1). Patients were under inpatient care or attending outpatient or day hospital clinics and were required to have a pretreatment, 21-item Hamilton Rating Scale for Depression (HAM-D)[10] total score of ≥ 22. After an initial washout period of up to 4 weeks, patients were randomly assigned to treatment for 8 weeks with either 8 mg/day of reboxetine, 20 mg/day of fluoxetine, or placebo (placebo group in 1 study only). Dosage could be increased to 10 mg/day for reboxetine or to 40 mg/day for fluoxetine after 4 weeks if necessary. The primary endpoint for efficacy analysis was the decrease in HAM-D total score from baseline to last assessment. Other efficacy measures were the Clinical Global Impressions (CGI) scale,[11] the Montgomery-Asberg Depression

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Table 1. Disposition of Patients in 2 Multicenter, Multinational, Double-Blind Studies

Study	Received Treatment	Completed Study	Discontinued Treatment
Study 1 (N = 381)			
Reboxetine	126	88	38 (30%)
Fluoxetine	127	97	30 (24%)
Placebo	128	76	52 (41%)
Study 2 (N = 168)			
Reboxetine	79	59	20 (25%)
Fluoxetine	89	69	20 (22%)

Rating Scale (MADRS),[12] and the Social Adaptation Self-Evaluation Scale (SASS).[13] Response to treatment was defined as ≥ 50% decrease in HAM-D total score from baseline. Adverse events were reported and assessments were made of vital signs, laboratory tests, and ECG.

EFFICACY OF REBOXETINE COMPARED WITH FLUOXETINE AND PLACEBO

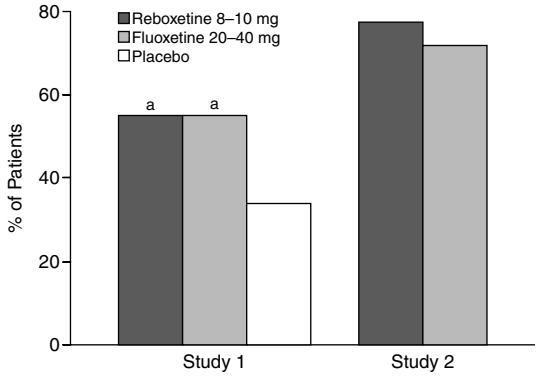
Overall Study Population

Both reboxetine and fluoxetine were effective in reducing the severity of depression. In the placebo-controlled study, the decrease in mean HAM-D total score from baseline to last assessment was greater ($p < .024$) for reboxetine (13.4, 95% CI = 11.8 to 15.0) and fluoxetine (13.3, 95% CI = 11.7 to 14.9) compared with placebo (8.6, 95% CI = 7.1 to 10.2). The percentage of patients who responded to treatment (≥ 50% reduction in HAM-D total score from baseline) was comparable for both active treatments in each study (Figure 1). As expected, the response rates were lower in the placebo-controlled study than in the comparator-controlled study. In the placebo-controlled study, 56% of both reboxetine- and fluoxetine-treated patients responded to treatment compared with 34% of patients in the placebo group. Both active agents were significantly superior to placebo ($p < .01$). In the second study, 78% of reboxetine-treated patients and 74% of fluoxetine-treated patients responded to treatment. Results from other rating scale assessments showed a similar pattern of results with similar improvements noted for reboxetine and fluoxetine, and both active treatments superior to placebo. Deterioration was the reason for discontinuation in more of the placebo-treated patients (29/128) than reboxetine- or fluoxetine-treated patients (19/205 and 19/216, respectively) when data from the 2 studies were combined.

Severely Depressed Patients

Sixty-nine percent of patients in the placebo-controlled trial and 72% of patients in the active comparator trial were classified as markedly to severely ill according to the CGI-Severity of Illness scale. In all active treatment groups, there was a significant decrease in mean HAM-D total scores from baseline in severely ill patients, but there were significantly greater improvements in the reboxetine groups compared with the fluoxetine groups (Table 2).

Figure 1. Response to Treatment (≥ 50% reduction in HAM-D total score) in the 2 Clinical Studies Comparing Reboxetine With Fluoxetine



[a]$p < .01$.

Table 2. Efficacy of Reboxetine Versus Fluoxetine in Severely Ill Patients

Study	Mean Decrease in HAM-D Total Score From Baseline to Last Assessment: Reboxetine	Mean Decrease in HAM-D Total Score From Baseline to Last Assessment: Fluoxetine	Between-Treatment Difference[a]: Mean (95% CI)
Study 1	14.0 (N = 83)	13.6 (N = 86)	0.4 (–2.3 to 3.2)
Study 2	21.5 (N = 55)	16.2 (N = 66)	5.3 (2.2 to 8.4)

[a]Weighted between-treatment difference: mean = 2.6 (95% CI = 0.5 to 4.6).

Social Functioning

The SASS results from the placebo-controlled study have been reported in detail by Dubini et al. (1997).[14] Seventy-nine percent of patients (reboxetine, N = 103; fluoxetine, N = 100; placebo, N = 99) in the placebo-controlled study and 88% of patients (reboxetine, N = 69; fluoxetine, N = 78) in the non–placebo-controlled study provided self-evaluation at baseline and last assessment. In the placebo-controlled study, there was no difference in baseline scores between treatment groups and there was a mean improvement to last assessment of 10.3 points with reboxetine, 7.6 points with fluoxetine, and 3.4 points with placebo. There was a significant difference in mean SASS total score at last assessment between each of the treatments ($p < .0001$). In the comparator study, the results were not so clear, with no statistically significant differences in improvement of mean SASS total scores. This was probably due to the relatively low level of impairment of social functioning at admission and to fewer patients providing SASS data. The baseline mean SASS total scores were 27.3 for reboxetine and 27.9 for fluoxetine in

Table 3. Cumulative Analysis of Adverse Events Occurring in > 10% of Patients in at Least 1 Group

Adverse Event	Percentage of Patients Treated		
	Reboxetine (N = 205)	Fluoxetine (N = 216)	Placebo (N = 128)
Nausea and related symptoms	15	25	13
Constipation	17	5	7
Insomnia	16	11	6
Dry mouth	27	6	14
Sweating	12	7	4
Headache/migraine	14	20	15
Hypotension and related symptoms	13	6	5

the non–placebo-controlled study compared with 25.1 for reboxetine, 24.5 for fluoxetine, and 23.9 for placebo in the placebo-controlled study.

In the placebo-controlled study, point-biserial correlation analysis of SASS individual items revealed significant differences between the response to reboxetine and to fluoxetine. There was no significant positive association with fluoxetine compared with reboxetine for any of the items. There was a significant positive association with reboxetine compared with fluoxetine for 9 items and maximal association with reboxetine (r_{bis} = 0.10–0.14) for improvement in community involvement, interest in hobbies, social compliance, rejection sensitivity, control of surroundings, and vainness. These items describe motivation toward action and negative self-perception.

TOLERABILITY OF REBOXETINE COMPARED WITH FLUOXETINE

The frequency of newly reported adverse events (data from 2 studies combined) was similar for reboxetine-treated patients (67%) and fluoxetine-treated patients (66%) compared with 61% in the placebo group. The majority of adverse events were mild to moderate in severity. The type of adverse event reported in more than 10% of patients in any group is shown in Table 3. For the 2 studies combined, adverse events were the reason for discontinuation in a similar proportion of placebo- and reboxetine-treated patients (12% and 12%, respectively) and in a slightly lower proportion of fluoxetine-treated patients (7%). The lower level of discontinuations due to adverse events in the fluoxetine-treated patients may have been due to the dosage used. There were no clinically significant alterations in vital signs, ECG, or laboratory parameters in either study.

CONCLUSIONS

Reboxetine is as effective and well tolerated as fluoxetine in the treatment of depressed patients and is significantly more effective in the severely ill. Furthermore, social functioning, especially in the areas of lack of motivation and negative self-perception, is improved to a greater extent with reboxetine than with fluoxetine. The results indicate that reboxetine is a useful therapeutic option for the treatment of major depression.

Drug names: desipramine (Norpramin and others), fluoxetine (Prozac), imipramine (Tofranil and others).

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