Reboxetine, a Unique Selective NRI, Prevents Relapse and Recurrence in Long-Term Treatment of Major Depressive Disorder

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Background: The long-term efficacy and tolerability of the antidepressant reboxetine, a unique selective norepinephrine reuptake inhibitor (selective NRI), were assessed in an international study.

Method: Two hundred eighty-three patients with recurrent DSM-III-R major depression who responded to 6 weeks of reboxetine treatment (≥ 50% decrease in Hamilton Rating Scale for Depression [HAM-D] total score) were randomly assigned to receive reboxetine or placebo for 46 weeks in a double-blind phase. Relapse (≥ 50% increase in HAM-D total score and/or a HAM-D total score ≥ 18) rate was the principal assessment criterion and included patients who experienced relapse or recurrence. Only patients who remained relapse-free at the end of the first 6-month treatment period were included in the relapse rate assessment at the end of the second 6-month treatment period.

Results: Reboxetine was associated with a markedly lower relapse rate than placebo (22% vs. 56%; $p < .001$) and a greater cumulative probability of a maintained response ($p = .0001$) during long-term treatment. Patients in remission (HAM-D total score ≤ 10) at the time of random assignment were less likely to relapse (16% reboxetine, 48% placebo; $p < .001$). The proportion of patients who were relapse-free and therefore remained in the study was significantly ($p \leq .001$) higher among those on reboxetine treatment than on placebo at the end of the first (61% vs. 40%) and second (88% vs. 59%) 6 months of treatment. Additional efficacy measures supported these findings. The incidence of adverse events with reboxetine was low and comparable with that for placebo. Discontinuation due to adverse events occurred infrequently.

Conclusion: Reboxetine treatment over 1 year is more effective than placebo in the prevention of relapse in patients with recurrent depression. The low relapse rates at the end of the second 6 months of treatment further suggest that reboxetine effectively prevents recurrence of depressive symptoms following episode resolution. Reboxetine is well tolerated in long-term treatment of depression, a finding that bodes well for long-term patient compliance.

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Lifetime prevalence rates for major depression may be as high as 17%.[1] The reemergence of depression after recovery from an episode appears to contribute significantly to the burden of depressive disorders, with as many as 75% to 80% of depressed patients experiencing a recurrence of depression at some point in their life.[2] In a review of studies on the course of depressive illness, Judd stated: "Among practicing psychiatrists, the most recent and important paradigm shift is the acceptance of unipolar major depressive disorder as primarily a chronic rather than an acute illness."[3]

Between episodes, patients may experience reduced quality of life owing to residual symptoms.[2] Depressive episodes and the intervening periods of partial remission may, therefore, have a substantial impact on caregivers and society in general, as well as on the individual. Antidepressant treatment for recurrent depression is intended to lower the probability and/or duration of future episodes and to confer pharmacoeconomic benefits in improved quality of life and reduced direct medical costs.[4]

A key question in the treatment of major depressive disorder is how long to continue pharmacotherapy. On average, a depressive episode can be expected to last for around 20 weeks,[5–7] and while antidepressants may suppress the symptoms of depression, they may not immediately correct the underlying disorder, so that there may be a gap of several weeks or months between symptom control and episode resolution.[8] Early discontinuation of an antidepressant is likely to result in relapse for about 50% of cases.[9,10]

Kupfer[11] summarized the potential course and treatment phases of depressive illness. Treatment can be considered in 3 phases: an acute phase of treatment to control disabling symptoms; a continuation phase, which may last for up to 6 months, to prevent relapse of an episode; and maintenance therapy established to stop recurrence or the incidence of new episodes. During the acute phase of treatment, patients would be expected to respond to treatment, i.e., experience a decrease in depressive symptoms, the goal being symptomatic remission. The aim of the second (continuation) phase of treatment, then, is to consolidate this response and prevent a relapse of the disorder, which is characterized by a rapid worsening of symptoms. By the end of the continuation phase, patients who have not relapsed can be considered to have recovered from the index episode, and after this point, subsequent worsening can be considered as a recurrence of depression, in other words, a new episode. The duration of the third phase, maintenance therapy, is a matter for clinical judgment and will be influenced by the patient's history of depression. Robinson et al.[12] found that a depressive episode can exceed 1 year, and they recommend continuing therapy for at least that length of time to prevent relapse. Maintenance therapy should also be considered to reduce long-term morbidity and increased mortality associated with major depressive disorder.[13]

Problems of relapse, often due to noncompliance and poor tolerability, have been experienced with the use of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors, leading to increased health care service costs.[14] Selectively acting antidepressants provide better-tolerated alternatives,[15] an important factor in continued patient compliance with treatment. Reboxetine is a selective norepinephrine reuptake inhibitor (selective NRI).[16] Its efficacy has been demonstrated in placebo-controlled studies in comparison with desipramine,[17] fluoxetine, and imipramine.[18]

Reboxetine has negligible affinity for muscarinic or adrenergic receptors,[19] and no affinity for serotonin and dopamine uptake sites.[20] It is therefore expected to be free of the classical adverse effects associated with non-selective norepinephrine reuptake inhibitors (i.e., the TCAs). The improved tolerability profile of reboxetine compared with that of the TCA imipramine has already been demonstrated.[21]

Demonstration of acute antidepressant efficacy does not imply efficacy for long-term treatment.[22,23] Therefore, it is essential to assess the efficacy of new antidepressants in medium-term and long-term therapy, with long-term, placebo-controlled studies being conducted over periods of at least 1 year.[24]

Against this background, a placebo-controlled study was conducted to assess the long-term efficacy and tolerability of continuation therapy with reboxetine, 8 mg/day, in patients with a diagnosis of acute recurrence of major depressive disorder who had responded to an initial 6 weeks of treatment.

METHOD

Study Design

This was a randomized, placebo-controlled, double-blind, parallel-group, multicenter study conducted at 8 centers in Europe and South America. Following a washout period of up to 4 weeks, patients showing a response (≥ 50% decrease from baseline on the 21-item Hamilton Rating Scale for Depression [HAM-D][25]) to 6 weeks of open-label treatment with reboxetine, 8 mg/day, were randomly allocated to continue reboxetine treatment (4 mg twice daily) or to receive placebo for a further 46 weeks. During the study, the dosage of reboxetine could be reduced to 4 mg/day if the higher dose was poorly tolerated. Patients who experienced relapse (defined as an increase in the HAM-D total score of 50% or more and/or a HAM-D total score of ≥ 18 points) during the long-term phase were discontinued.

Patients

Patients aged 18 to 65 years with a diagnosis of acute recurrence of DSM-III-R major depressive disorder[26] attending outpatient clinics or having recently been hospitalized (within 2 weeks) were eligible for inclusion in this study. Patients were required to have a total score on the 21-item HAM-D of ≥ 18 points. Following the initial 6-week treatment period, those patients responding to treatment with reboxetine were eligible to participate in the long-term phase of the study. Written informed consent was obtained for all patients entering the study.

Patients with evidence of coexisting psychotic features (DSM-III-R[26]) and those with evidence of chronic depression (based on 3 of the Composite Diagnostic Evaluation of Depressive Disorders [CODE-DD] variables: acute or subacute onset and prolonged duration[27]) were not eligible for inclusion. Patients were also excluded if they were experiencing their first episode of major depression at the time of screening, if they had a history of major depression associated with an endocrinologic disorder, or if they had received electroconvulsive therapy in the previous 6 months. Those with a history of seizures, serious brain injury, or evidence of clinically significant hemopoietic or cardiovascular disease, urinary retention, or glaucoma were also excluded.

Assessments

Relapse rate and time were defined as the primary study endpoint. Additional separate analyses were conducted to examine relapse rates in the first and second 6 months of the double-blind phase. The following secondary measures of clinical efficacy were employed: HAM-D total score; Clinical Global Impressions (CGI) severity of

Table 1. Baseline Demographics of the Study Population[a]

Characteristic	Noncontrolled Phase: Reboxetine (N = 358)	Long-Term Phase: Reboxetine (N = 145)[b]	Long-Term Phase: Placebo (N = 141)[b]
Female, N (%)	263 (73.5)	115 (79.3)	95 (67.4)
Male, N (%)	95 (26.5)	30 (20.7)	46 (32.6)
Age, y, mean ± SD	43.2 ± 11.8	43.4 ± 11.6	42.3 ± 12.2
Height, cm, mean ± SD	165.6 ± 8.4	165.3 ± 7.5	165.4 ± 8.9
Weight, kg, mean ± SD	66.7 ± 13.0	67.2 ± 13.4	66.0 ± 11.8
Severity of depression			
HAM-D total score, mean ± SD	29.6 ± 5.6	29.1 ± 5.5	29.7 ± 5.7
MADRS, mean ± SD	18.4 ± 4.1	17.9 ± 4.0	18.6 ± 4.2
History of depression			
Age at onset, y, median (range)	34 (11–63)	34 (13–60)	32 (11–62)
Number of previous episodes, median (range)	3 (1–15)	3 (1–15)	3 (1–10)
Duration of the last episode, wk, median (range)	24 (2–364)	24 (3–364)	24 (2–360)
Duration of the present episode, wk, median (range)	8 (0.1–364)	8 (0.1–364)	10 (0.6–208)

[a]Abbreviations: HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.
[b]Three patients randomly assigned to receive reboxetine (N = 2) or placebo (N = 1) did not receive treatment and were therefore excluded from further analysis.

illness, global improvement scores, and efficacy index[28]; Montgomery-Asberg Depression Rating Scale (MADRS)[29]; and the Zung Self-Rating Depression Scale.[30]

Assessments were conducted at screening and baseline (day 0) and at weekly intervals during the first 6 weeks of treatment. During the subsequent double-blind phase, assessments were conducted every 2 weeks for the HAM-D and CGI and at monthly intervals for the MADRS and Zung. At the end of the first 6 weeks of treatment, the percentage of patients responding to treatment (HAM-D total score decreased ≥ 50% from baseline) and the percentage of patients in remission (HAM-D total score ≤ 10) were assessed. During the long-term phase, the percentage of patients in remission, the percentage of patients who relapsed, and the cumulative probability of maintained response and relapse were assessed.

Tolerability was assessed by evaluating the incidence, severity (mild, moderate, severe, or unknown), and seriousness of adverse events and by evaluating vital signs electrocardiograms (ECGs), laboratory tests, and ophthalmologic examinations. Adverse events and vital signs were recorded at weekly intervals during the 6-week noncontrolled phase and every 2 weeks during the double-blind phase. ECGs and laboratory tests were conducted every 2 weeks during the noncontrolled phase and every 2 months during the double-blind phase. Ophthalmologic examinations were performed at screening and at the end of the study. A follow-up visit was made to each patient 1 month after treatment discontinuation to monitor possible withdrawal reactions and collect information on adverse events.

Statistical Analyses

In designing this study, a 15% intergroup difference in relapse rate (the primary efficacy variable) was considered to be clinically significant. Based on an 80% response rate to reboxetine and a 50% relapse rate with placebo, 358 patients were required in the 6-week initial treatment phase of this study to ensure entry of at least 300 patients to the long-term phase.

With 135 patients in each group, the study had 80% power to detect an intergroup difference in relapse rate with an alpha level of .05. Response rates were analyzed using the chi-square test. Time to relapse and maintenance of response were described using the Kaplan-Meier method and compared by the log rank test.[31] Maintenance of response at the end of the first and last 6 months of the treatment period were compared using the chi-square test. The remission rate at the last assessment of the double-blind phase was calculated and the intergroup difference tested using the chi-square test. Analysis was carried out on the intent-to-treat population with the last observation carried forward. Descriptive statistics are presented for the additional efficacy assessments.

RESULTS

Of the 358 patients who entered the 6-week noncontrolled phase of the study, 36 discontinued, primarily due to deterioration (N = 10), uncooperativeness (N = 11), or adverse events (N = 13). In addition, 1 patient committed suicide and another was lost to follow-up. Two hundred eighty-three patients were randomly assigned to treatment with reboxetine (N = 145) or placebo (N = 141) in the long-term phase of the study (3 patients randomly assigned to receive reboxetine [N = 2] or placebo [N = 1] did not receive treatment and were therefore excluded from further analysis). Demographic data, severity, and history of depression for these patients are shown in Table 1. The treatment groups were well matched and comparable to the population admitted to the noncontrolled phase.

Dose reductions or temporary treatment interruptions were rare and needed for only 7 patients in the noncontrolled phase and 5 patients in the long-term phase (reboxetine, N = 2; placebo, N = 3). Concomitant medications were administered infrequently. One hundred forty-four patients completed the study, with 64 discontinuing from the reboxetine group and 75 from the placebo group. The reasons for discontinuation are shown in Table 2. Discontinuation due to lack of efficacy occurred twice as frequently among placebo-treated patients as among reboxetine-treated patients (25.7% vs. 11.9%). The timings of discontinuations were comparable in the 2

Table 2. Reasons for Discontinuation Among Patients Treated in the Double-Blind Phase of the Study (N = 283)

Reason for Discontinuation	Reboxetine (N = 143) N	Reboxetine (N = 143) %	Placebo (N = 140) N	Placebo (N = 140) %
Adverse events	6	4.2	2	1.4
Lack of efficacy	17	11.9	36	25.7
Improvement	6	4.2	7	5.0
Protocol violation/ lost to follow-up	23	16.1	13	9.2
Uncooperative	12	8.4	17	12.1
Total	64	44.8	75	53.6

Figure 1. Mean HAM-D, MADRS, and Zung Self-Rating Depression Scale Total Scores During the 6-Week, Noncontrolled Phase of the Study

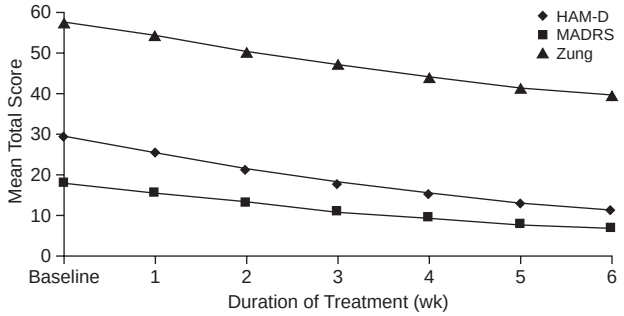
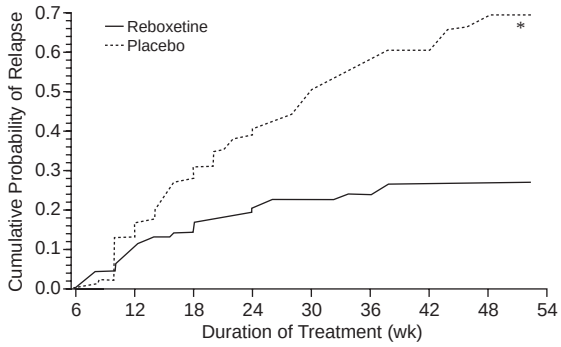


Figure 2. Cumulative Probability of Relapse During the Long-Term Phase in Patients Who Had Previously Responded to Treatment During the Noncontrolled Phase



*p = .0001.

treatment groups and, therefore, were not thought to affect the efficacy results.

Efficacy of Reboxetine During the 6-Week Noncontrolled Phase

During the noncontrolled phase, the mean HAM-D total score declined from 29.6 at baseline to 11.4 at week 6 (Figure 1). The MADRS and Zung scores confirmed improvement and are also shown in Figure 1. Two hundred seventy-two patients (76%) of the original 358 responded to treatment at week 6, with 179 (50%) classified as in remission. CGI severity of illness and global improvement scores reflected this improvement. While the majority of patients were initially assessed as being markedly to severely ill (90.8%), at the end of the noncontrolled phase, the majority of patients were judged to be normal or mildly ill (69.8%). The proportion of patients who were assessed as "very much improved" on the CGI global improvement scale increased from 0.8% at week 1 to 50.5% at week 6, while patients who were judged to be "much improved" increased from 10.3% at week 1 to 33.4% at week 6.

Efficacy of Reboxetine During the Long-Term Phase

Of the patients who entered the long-term phase of the study and were eligible for efficacy analysis, 104 patients (78.2%) in the reboxetine group (N = 133) were classified as in remission at the last assessment, compared with only 59 patients (44.7%) in the placebo-treated group (N = 132) ($p < .001$). Fifty-six percent of patients relapsed in the placebo group compared with only 21.8% in the reboxetine group ($p < .001$).

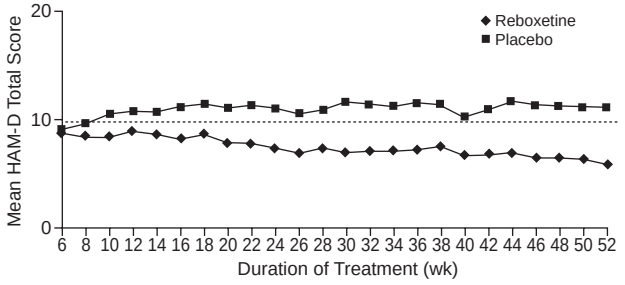
During the first 6 months of treatment, 61% of patients who received reboxetine (N = 133) remained relapse-free compared with 40% of patients who received placebo (N = 132; $p \leq .001$). The statistically significant difference between the treatment groups was maintained in the second 6 months of treatment, during which 88% of patients (66/75) who continued to receive reboxetine remained relapse-free compared with 59% of patients (29/49) who continued to receive placebo.

The cumulative probability of a maintained response was clinically and statistically greater with reboxetine than with placebo ($p = .0001$), and a greater proportion of patients maintained a response at the end of the first 6 months (60.9% vs. 40.2%; $p \leq .001$) and the last 6 months of the study (88.0% vs. 59.2%; $p \leq .001$). Furthermore, the cumulative probability of relapse was lower with reboxetine than with placebo ($p = .0001$) (Figure 2). Patients in the reboxetine group experienced relapse mainly in the first 3 to 4 months, but there was a steady increase in the number of patients experiencing relapse in the placebo group throughout the 12-month study (Figure 2).

The response criterion employed probably allowed admission to the long-term phase of patients with residual symptoms that would increase the likelihood of relapse. An analysis of the subset of patients classified as being in remission (HAM-D total score ≤ 10) at randomization was, therefore, carried out. As expected, these patients had a lower rate of relapse than those in the general study population: 15.9% in the reboxetine group compared with 48.3% in the placebo group ($p < .001$).

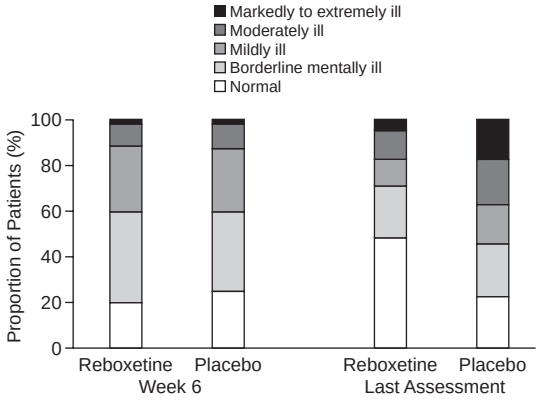
For patients randomly assigned to reboxetine treatment, the mean total HAM-D score decreased from 8.8 at week 6 (the end of the noncontrolled phase) to 7.9 at last assessment. Thus, the majority of patients treated with reboxetine

Figure 3. Mean HAM-D Total Score During the Long-Term Phase of the Study[a]



[a]A HAM-D score ≤ 10 represents remission.

Figure 4. CGI Severity of Illness Score Distribution at the End of the Noncontrolled (Week 6) and Long-Term Phases of the Study[a]

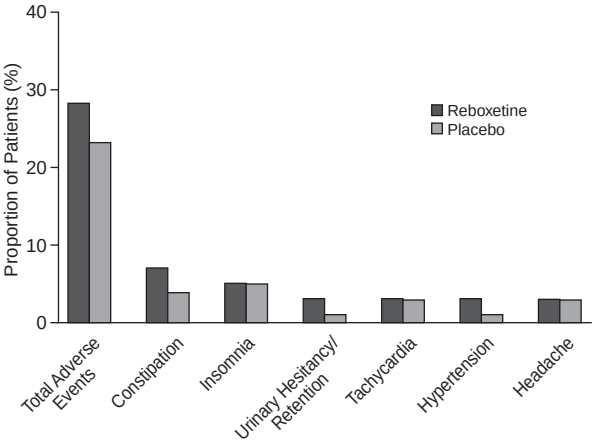


[a]Abbreviation: CGI = Clinical Global Impressions scale.

who did not experience relapse and therefore continued in the study remained in symptomatic remission. In contrast, the mean HAM-D total score increased from 9.1 at week 6 to 13.9 at last assessment in the placebo group, suggesting an overall worsening of symptomatology as the study progressed. The change in mean HAM-D total score over time is shown in Figure 3. The proportion of patients classified as "normal" at last assessment on the CGI severity of illness scale was higher with reboxetine than with placebo (Figure 4). The proportion of patients classified as "very much improved" at last assessment on the CGI global improvement scale steadily increased in the reboxetine group during the 1-year study period. The proportion of patients in the reboxetine group who were "very much improved" at last assessment was 72.9%. A lesser proportion of patients in the placebo group were classified as "very much improved" on the CGI global improvement scale (42.2% at last assessment).

The mean total MADRS score in the reboxetine-treated group decreased from 5.25 at week 6 to 4.47 at the last assessment. In contrast, an increase from 5.25 at week 6 to 8.58 at last assessment was seen in the placebo-

Figure 5. Adverse Events Occurring in > 2% of Patients During the Long-Term Phase of the Study



treated group. A similar trend was also observed using the Zung scale, with an improvement in the reboxetine-treated group (the mean total score decreased from 36.4 at week 6 to 35.9 at last assessment) and a worsening in the placebo-treated group (the mean total score increased from 38.8 at week 6 to 44.9 at last assessment).

Tolerability

Tolerability was assessed in 358 patients in the noncontrolled phase and 283 patients in the long-term phase. During the noncontrolled phase, 51.9% of patients reported adverse events, the majority of which did not require a change in the treatment dosage (89.6%) and were mild in severity (61.3%). The most frequently reported, newly emerged adverse events were dry mouth (19.0%), constipation (16.8%), increased sweating (8.1%), tachycardia and insomnia (6.1% each), urinary hesitancy/retention (5.6%), and decreased libido (5.0%). Urinary hesitancy/retention and decreased libido were reported more often by men than women. The majority of adverse events were short-lived, with a median duration of 22 days. Adverse events resulting in discontinuation were tachycardia (4 patients) and dry mouth, constipation, decreased libido, and urinary hesitancy/retention (2 patients each).

During the long-term phase, the frequency of newly reported adverse events was similar with reboxetine (28.0%) and placebo (22.8%). The majority of adverse events in both groups did not require modification of the study medication (87.5%) and were mild in severity (reboxetine, 72.5% vs. placebo, 81.3%). The most common events were constipation and insomnia (Figure 5). The median duration of these events was 28 days in the reboxetine group and 19 days in the placebo group. Adverse events resulting in discontinuations in the reboxetine group were dry mouth (2 patients), constipation (3 patients), decreased libido (2 patients), and urinary hesi-

tancy/retention (1 patient). One patient in the placebo group discontinued owing to constipation.

Two serious adverse events occurred in reboxetine-treated patients, but neither was considered to be drug related. One patient who had not responded to previous antidepressant treatment committed suicide by multiple-drug overdose 39 days after entering the study. The second patient experienced a generalized convulsive episode, probably due to discontinuation of benzodiazepine treatment, 3 days after entering the study. One patient in the placebo group experienced a hallucination that was judged by the investigator to be "probably" related to the study medication.

There were no significant effects on laboratory parameters, ophthalmologic parameters, ECG variables, or vital signs in any group, except for an increase in heart rate in 10% to 15% of reboxetine-treated patients. This finding was not thought to be clinically significant, and there was no difference between reboxetine- and placebo-treated patients in the incidence of tachycardia (see Figure 5). There was a slightly higher frequency of diseases of the circulatory system in the reboxetine group at the start of the long-term phase.

DISCUSSION

Depression is a chronic, recurrent illness that can be effectively treated with antidepressants. However, early termination of therapy incurs a high risk of relapse.[9,10] It is important, therefore, to assess the efficacy of new antidepressants not only in the short-term acute phase, but also over longer time periods, including a continuation period to assess relapse prevention and a maintenance period to assess recurrence prevention.

Reboxetine, a selective NRI, was significantly more effective than placebo in the prevention of relapse and recurrence in patients who had shown a response to an initial 6 weeks of treatment. The majority of reboxetine-treated patients remained relapse-free at last assessment compared with just under half of the placebo-treated patients. The majority of patients who received reboxetine and did not experience symptomatic relapse during the long-term phase of the study remained in symptomatic remission, as reflected by the mean HAM-D total score. However, those who received placebo did not. Indeed, patients in the placebo group appeared to worsen slightly during the long-term phase.

In the present study, the response criterion (≥ 50% decrease in HAM-D total score), reflecting a change in score rather than an absolute level, may have allowed admission of patients with residual symptoms to the double-blind phase, thus increasing the subsequent chance of relapse.[22] A subset analysis of patients classified as in remission at the end of the noncontrolled phase, however, confirmed the results of the whole patient population and demonstrated an even lower relapse rate for both the reboxetine and placebo groups during the long-term phase.

In this study, slightly more patients discontinued treatment in the placebo group compared with the reboxetine group, but the reasons for discontinuation were different. Lavori et al.[32] highlighted the fact that patients discontinuing or deviating from the protocol may affect the overall results of an investigation. In our study, the time to discontinuation was recorded, and there was no difference in this measure between treatment groups. Discontinuation, therefore, did not affect the findings of the efficacy analysis.

Most relapses during treatment with placebo occur within the first 6 months of stopping antidepressant therapy.[8,33] The duration of further treatment to consolidate the response will vary from patient to patient,[34] but is generally recommended to be between 4 and 6 months.[13] A reappearance of symptoms after 6 months is generally regarded as a recurrence[22] and may affect between 75% and 80% of patients with major depressive disorder.[2]

For patients who entered the second 6-month period of the study (i.e., remained relapse-free), relapse after the first 6 months of treatment may be more appropriately thought of as a recurrence of a depressive episode in accord with established treatment recommendations.[22] Therefore, the analysis of patients who remained relapse-free after 6 months provides an estimate of the efficacy of reboxetine in preventing recurrence. The results of this study showed reboxetine to be significantly more effective than placebo in this respect, with 88.0% of reboxetine-treated patients versus 59.2% of placebo-treated patients who entered the last 6 months of treatment remaining relapse-free at all observations. However, longer term studies over several years are required to clearly assess the role of reboxetine in the prevention of recurrence.

While the use of TCAs over extended periods may be effective, patient support is needed if tolerability is to be maintained. Better tolerated antidepressants will, therefore, be a major advance in the long-term treatment of recurrent depression.[35] Reboxetine was well tolerated, with the majority of adverse events during both phases of the study reported as being of mild intensity, short duration, and not requiring modification of the treatment regimen. In the long-term phase, the incidence of adverse events was low and similar in the reboxetine and placebo groups. Discontinuation due to adverse events occurred at a low rate (4.2%), which has favorable implications for compliance. The tolerability of reboxetine is therefore maintained in the long term.

CONCLUSION

Reboxetine effectively prevents relapse of major depressive disorder following response to acute therapy and is well tolerated when administered in the long term. Furthermore, the maintained response by reboxetine-treated

patients at the end of the second 6 months of treatment suggests reboxetine may effectively prevent recurrence of depression. The use of reboxetine for maintenance and prophylactic therapy of depressive illness is supported by this study.

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

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