

Clinical Efficacy of Reboxetine in Major Depression

Alan F. Schatzberg, M.D.

The past decade has witnessed the advent of selective serotonin reuptake inhibitors (SSRIs) as first-line treatments for major depression. Still, there is considerable debate as to whether these agents are as effective or as potent as the first-generation tricyclic antidepressants (TCAs) or the mixed reuptake inhibitor, venlafaxine, all of which exert considerable effect on norepinephrine (NE) reuptake. Recently, reboxetine, a selective NE reuptake inhibitor (selective NRI), has been introduced in Europe. This drug has only a minimal affinity for muscarinic acetylcholine receptors and therefore causes less dry mouth, constipation, or other such effects than do the TCAs. Reboxetine does not block serotonin reuptake or α_1 receptors and, thus, does not appear to produce significant nausea, diarrhea, or hypotension. Unlike other antidepressants, reboxetine appears to be nonsedating. Data on acute and long-term clinical efficacy and safety from double-blind, placebo-controlled, and active comparator studies with reboxetine are reviewed. These studies indicate that reboxetine is significantly more effective than placebo and as effective as fluoxetine in reducing depressive symptoms. Improvements in social adjustments were reported to be more favorable with reboxetine than with fluoxetine. Further, data from controlled clinical trials have shown that the side effect profile for reboxetine is relatively benign. The clinical implications of studies on reboxetine are discussed with an eye toward understanding the potential role NE reuptake blockers may play in the treatment of patients with major depression.

(*J Clin Psychiatry* 2000;61[suppl 10]:31-38)

A wide range of antidepressants are now available, including the tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants, such as bupropion, mirtazapine, and nefazodone. Even with the wide array of antidepressants to choose from, clinicians still are uncertain which antidepressant is best for a given patient. TCAs are effective for a considerable number of patients, but have significant drawbacks in terms of their tolerability and safety. Consequently, they are associated with poor compliance and high lethality in overdose.^{1,2} One reason for adverse effects with the TCAs is their affinity for receptor sites other than those involved with antidepressant effects. Antidepressants such as the SSRIs have been developed with more selective affinities in their mode of action, thus offering treatment options that are safer and better tolerated by patients.³⁻⁵ However,

some concerns have been expressed as to whether SSRIs are as effective as TCAs across the range of depressive disorders.⁶ This concern has led to the hope that combining the antidepressant effects of the TCAs (predominantly on the noradrenergic system, although some have a dual action) with those of the SSRIs (predominantly on the serotonergic systems) might lead to a better antidepressant. Although the SNRIs (e.g., venlafaxine) and atypical antidepressants with serotonergic and noradrenergic properties (e.g., mirtazapine) have many beneficial properties, the combination drugs have their own limitations. To gain the benefits of the noradrenergic effects, high doses of venlafaxine are necessary, and adverse effects are often introduced. The use of mirtazapine is somewhat limited by sedation and weight gain.⁷

The development of reboxetine, a selective norepinephrine reuptake inhibitor (selective NRI), provides a new therapeutic alternative for the treatment of depression and a unique opportunity to study the effects of a well-tolerated selective noradrenergic drug.

Comprehensive placebo-controlled and active comparator clinical trials have shown that reboxetine is an effective and well-tolerated antidepressant when used in short- and long-term treatment. In analyses of special populations of patients such as those with severe depression, reboxetine has shown superior efficacy when compared with fluoxetine.⁸ Utilizing assessment scales designed to measure social functioning, Massana and colleagues⁹ have demonstrated that reboxetine is associated

From the Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, Calif.

Presented at the symposium "Norepinephrine: Neurotransmitter for the Millennium," held May 15, 1999, in Washington, D.C. This symposium was held in conjunction with the 152nd annual meeting of the American Psychiatric Association and was supported by an unrestricted educational grant from Pharmacia Corporation.

Reprint requests to: Alan F. Schatzberg, M.D., Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Room 300, Stanford, CA 94305-5717.

Table 1. Summary of Short-Term Placebo-Controlled Trials^a

Study Design	Sample Population	Age Range (y)	Duration (wk)	% Responders			p Value
				Reboxetine	Placebo	Comparator	
Reboxetine, 10 mg/d (N = 28) vs placebo (N = 28) ¹⁷	Inpatients	18–60	6	74	20	...	< .001
Reboxetine, 4–8 mg/d (N = 84) vs placebo (N = 89) vs desipramine, 100–200 mg/d (N = 89) ¹³	Inpatients	19–68	4	60	36	46	< .05 ^b
Reboxetine, 8 mg/d (N = 112) vs placebo (N = 112) vs imipramine, 150–200 mg/d (N = 115) ^c	Outpatients	18–72	6	59	52	62	NS ^d
Reboxetine, 8–10 mg/d (N = 126) vs placebo (N = 128) vs fluoxetine, 20–40 mg/d (N = 127) ^c	Outpatients	18–65	8	56	34	56	< .01 ^e

^aAdapted with permission from Montgomery.¹²
^bFor reboxetine vs. placebo; NS for desipramine vs. placebo.
^cData on file, Pharmacia & Upjohn Company, 1995.
^dNeither the reboxetine-placebo nor the imipramine-placebo comparison reached statistical significance.
^eFor both reboxetine vs. placebo and fluoxetine vs. placebo.

with greater improvement in social functioning, especially in terms of motivation toward action and negative self-perception, than fluoxetine. A summary of the reboxetine studies in major depressive disorder is presented in this article. Clinical findings that may suggest a role for reboxetine in the treatment of special patient populations and in panic disorder are also discussed.

CLINICAL EFFICACY

To date, a total of 1676 hospitalized patients or outpatients with a diagnosis of major depressive disorder according to DSM-III¹⁰ or DSM-III-R criteria¹¹ have participated in a total of 8 multinational clinical trials of reboxetine. These studies have compared the efficacy of reboxetine (4–6 mg/day in elderly; 8–10 mg/day in adults) with fluoxetine (20–40 mg/day), imipramine (150–200 mg/day), desipramine (150–200 mg/day), and placebo.

All placebo-controlled and active comparator studies of reboxetine followed a randomized, double-blind, parallel-group design. Male and female patients with major depressive disorder of at least moderate severity, as measured by the Hamilton Rating Scale for Depression (HAM-D), were evaluated. By design, patients were required to have a minimum score of 16 on the 17-item HAM-D (HAM-D-17) or 18 on the 21-item HAM-D (HAM-D-21), although the mean baseline scores for the 7 studies were in the mid-to-high twenties (moderately to severely depressed). Clinical efficacy of reboxetine was assessed using the HAM-D and the Clinical Global Impressions scale (CGI) and, in some studies, the Montgomery-Asberg Depression Rating Scale (MADRS), the Social Adaptation Self-evaluation Scale (SASS), and the Zung Self-Rating Depression Scale (SDS). In most studies, clinical response was defined as a

≥ 50% decrease from baseline in the HAM-D total score at last assessment.

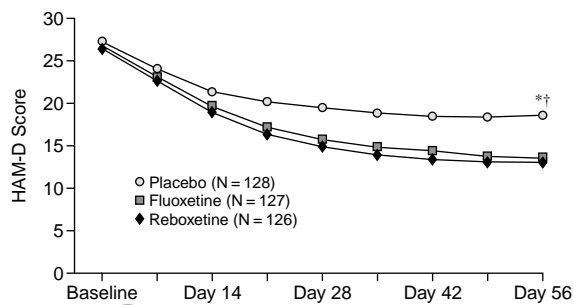
Short-Term Placebo-Controlled Trials of Reboxetine

Four short-term placebo-controlled studies were conducted over periods of 4 to 8 weeks in adult patients with major depressive disorder (Table 1).¹² Three of the 4 studies included an active comparator, either desipramine (100–200 mg/day),¹³ fluoxetine (20–40 mg/day), or imipramine (150–200 mg/day) (data on file, Pharmacia & Upjohn Company, 1995). Three of these studies demonstrated that reboxetine had a significantly superior efficacy to placebo in treating depression. The fourth study showed a pronounced placebo effect, so that although an improvement was seen for both reboxetine- and placebo-treated patients, no significant difference was seen between treatments. Similarly, no superiority over placebo was demonstrated for imipramine, the active comparator drug in this study.

Reboxetine versus placebo. A 6-week, multicenter, placebo-controlled study of reboxetine (6–10 mg/day) was carried out in 56 hospitalized patients with severe depression.¹⁴ Significant improvements were seen in patients taking reboxetine compared with those taking placebo in terms of the mean decrease in the HAM-D-21 total score and on the response rate at last assessment (percentage achieving a ≥ 50% decrease in HAM-D-21 total score from baseline to endpoint). Differences were also significant regarding the secondary efficacy assessment—the CGI—in which 78.6% and 25% of patients treated with reboxetine and placebo, respectively, achieved a “much to very much improved” rating.

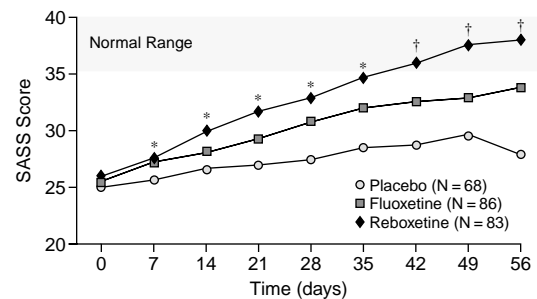
Reboxetine versus placebo versus desipramine. A multicenter, placebo-controlled comparison of reboxetine

Figure 1. Reboxetine Versus Fluoxetine Versus Placebo in Major Depressive Disorder^a



^aData on file, Pharmacia & Upjohn Company, 1995.
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.
*Reboxetine vs. placebo, $p = .01$.
†Fluoxetine vs. placebo, $p = .006$.

Figure 2. Reboxetine Versus Fluoxetine Versus Placebo in Major Depressive Disorder: Improvement in Social Functioning^a



^aReprinted with permission from Dubini et al.¹⁸
Abbreviation: SASS = Social Adaptation Self-evaluation scale.
* $p < .05$ vs. placebo.
† $p < .05$ vs. fluoxetine.

(4–8 mg/day) and desipramine (100–200 mg/day) was conducted in 258 hospitalized patients with major depression.¹³ The primary efficacy assessment—frequency of antidepressant response (defined as $\geq 50\%$ decrease in HAM-D-17 total score)—showed a significant advantage for reboxetine (60% decrease with reboxetine vs. 36% with placebo) but not for desipramine (46% decrease with desipramine vs. 36% with placebo). The mean values of all scales used (total HAM-D-17, MADRS, and CGI) showed a significant difference between active treatments and placebo.

Results of this study indicate the superiority of reboxetine over placebo for the treatment of major depressive disorder.¹³ Further, the authors of the study concluded that reboxetine was at least as effective as desipramine in this 28-day trial and noted that the improvement in symptomatology was, on average, apparent a week sooner with reboxetine than with desipramine.

Reboxetine versus placebo versus imipramine. Another study evaluated the activity and tolerability of reboxetine (8 mg/day) versus imipramine (150–200 mg/day) and placebo in 339 patients with major depressive disorder (data on file, Pharmacia & Upjohn Company, 1995). Little difference was seen between the treatment groups in the mean change in the total HAM-D-21 score from baseline to endpoint (13.5 for reboxetine and 13.8 for imipramine). Owing to an exceptionally high placebo response rate (mean change = 11.3), the study failed to confirm the antidepressant efficacy of reboxetine or imipramine relative to placebo. The failure of this kind of study is not surprising. In placebo-controlled studies of TCAs, including imipramine, placebo response rates have frequently been reported to be high.¹⁵ Furthermore, the results of additional analyses that were conducted in the subpopulations of severe and melancholic patients support the antidepressant efficacy of both reboxetine and imipramine relative to placebo.¹⁶

Reboxetine versus placebo versus fluoxetine. A multi-center, placebo-controlled, 8-week study investigated the efficacy and tolerability of reboxetine with fluoxetine as the comparator drug in 381 patients with major depressive disorder (data on file, Pharmacia & Upjohn Company, 1995). The dose was fixed for reboxetine (8 mg/day) and fluoxetine (20 mg/day) for the first 4 weeks. Thereafter, titration was permitted up to 10 mg for reboxetine and up to 40 mg for fluoxetine. For the primary efficacy measure (improvement in the HAM-D-21 total score), there were significant advantages for reboxetine and fluoxetine compared with placebo (Figure 1). At last assessment, 56% of the patients in the reboxetine group were deemed responders ($\geq 50\%$ reduction in HAM-D-21 total score from baseline to endpoint) versus 56% in the fluoxetine group and 34% in the placebo group. The percentage of patients classified as “very much improved” as assessed on the CGI was higher in the reboxetine (39.5%) and fluoxetine (33.1%) groups compared with placebo (16.4%). Conversely, the percentage of “much to very much deteriorated” scores was higher in the placebo group (10.2%) than in groups treated with reboxetine (1.6%) and fluoxetine (3.9%).

Patient social motivation and behavior were investigated in this study with a newly developed 21-item self-rating scale, the SASS¹⁷ (Figure 2).¹⁸ That depression is accompanied by serious social maladjustment is well documented.^{19,20} In fact, when Hays and colleagues²¹ assessed global functioning status and well-being outcomes in a 2-year observational study of 1790 individuals with a variety of chronic medical illnesses, depression was considered the second most highly debilitating disease—above arthritis, diabetes, and heart and lung disease. For these reasons, the addition of measures of social adjustment, in particular of social motivation and behavior, was considered of interest for the evaluation of patient outcome following antidepressant treatment.

In the reboxetine-placebo comparison of the reboxetine versus fluoxetine versus placebo study, there were significant improvements favoring reboxetine for 20 of the 21 SASS items (all items except quality of spare time).²² Twelve of the 21 items reflected positive self-perception and environmental perception, interest, and appreciation. In the fluoxetine-placebo comparison, only 12 of the 21 items were associated with significant improvement. For 9 items, there was no discrimination between fluoxetine and placebo. In the reboxetine-fluoxetine comparison, 6 items significantly favored reboxetine compared with none favoring fluoxetine. Maximal correlation for reboxetine was present for community involvement, interest in hobbies, social compliance, rejection sensitivity, control of surroundings, and vainness. Further studies using this and other scales measuring social adjustment are warranted.

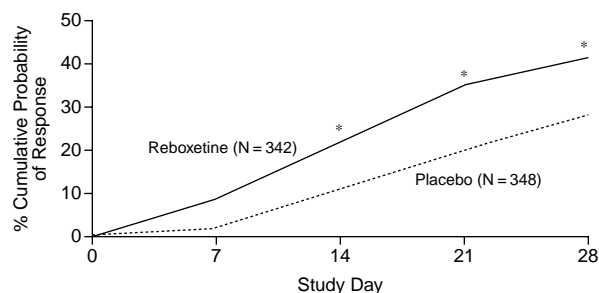
According to Dubini and colleagues,²² their findings on the SASS evaluations in this study support the hypothesis that a selective manipulation of the noradrenergic or serotonergic system in depression could have different effects on social functioning, with the noradrenergic agents being particularly effective on those aspects related to negative self-perception and lack of motivation toward action. Linking specific antidepressant actions with specific monoamine systems has long been discussed. However, specific involvement of serotonin in regulating mood and norepinephrine in sustaining drive have not been well supported as measured by syndromic clinical rating scales.²³⁻²⁵ The findings of Dubini and colleagues,²² however, suggest there may be validity to this hypothesis. The differential effects of these 2 antidepressants with respect to motivation and behavior would be in keeping with specific involvement of the noradrenergic system in sustaining drive. In this regard, the introduction of reboxetine, a selective NRI, should help to delineate such differences. Further evaluations along these lines are warranted and will be of interest to the field.

Summary. In each of the placebo-controlled studies, reboxetine had a rapid onset of action. Using pooled data, a significant difference ($p < .01$) in mean HAM-D total scores was seen after 10 days of treatment. The pooled between-treatment difference in HAM-D scores at last assessment favored reboxetine by 5.2 points (95% confidence interval = 3.8 to 6.6). The percentage of patients achieving "responder" status (defined as $\geq 50\%$ reduction in HAM-D total score) was greater for reboxetine-treated patients (56%–74%) than for placebo-treated patients (20%–52%). Analysis of the pooled data generated during the initial 4 weeks of treatment from all these studies showed that from day 14 onward, reboxetine-treated patients had a significantly greater cumulative probability of response than placebo-treated patients ($p < .001$) (Figure 3).¹²

Reboxetine Versus Placebo: Long-Term Trial

Because recurrent depression represents a major public health problem, the successful long-term treatment of in-

Figure 3. Cumulative Probability of Response in Short-Term Studies (4–8 weeks) Comparing Reboxetine (8–10 mg/day) With Placebo^a



^aReprinted with permission from Montgomery.¹² Kaplan-Meier analysis of results pooled from 4 studies. Response defined as $\geq 50\%$ reduction in Hamilton Rating Scale for Depression total score.

* $p < .001$, log-rank test.

dividuals who develop repeated episodes of depression has become highly relevant.²⁶ Even when patients experience control of their depressive symptoms, there is a 30% to 50% risk of relapse if treatment is discontinued too early.²⁷ Although symptom control may occur within a 6-week period, it may take 4 to 6 months for the depressive episode to resolve. Therefore, continued therapy is recommended for at least 4 months after a response to therapy is achieved.²⁸ For patients with recurrent depressive episodes, prophylactic treatment is generally recommended.²⁹⁻³¹ The basis for the latter recommendation stems from a number of long-term observational studies. In one 10-year follow-up study by Angst,³² episodes of symptoms were observed in 75% to 80% of patients. In a 15-year study by Mueller and colleagues,³³ an 85% cumulative rate of recurrence was found. Further evidence comes from a 2-year follow-up study of compliance and relapse by Melfi and colleagues.³⁴ Twenty-five percent of the patients in that study experienced a new episode of depression requiring antidepressant treatment, hospital admission for depression, electroconvulsive therapy, an emergency department visit for mental health, or attempted suicide. Moreover, it appears that patients are protected from recurrence only as long as they remain on treatment with antidepressants. Without this long-term management, depressive episodes occur more frequently.^{27,34,35}

To assess the suitability of an antidepressant for long-term use, it is therefore essential to assess efficacy and tolerability in long-term clinical trials. When such studies have been conducted with the TCAs, patients have reported experiencing significant adverse effects. As the incidence of adverse effects increases, so too does noncompliance, leading to increases in relapse and greater cost of care.¹ To this end, reboxetine was evaluated in a yearlong, placebo-controlled trial.

A 1-year, placebo-controlled study of reboxetine has shown that it is effective and well tolerated in the long-term

Table 2. Summary of Active Comparator–Controlled Trials of Reboxetine^a

Study Design	Sample Population	Age Range (y)	Duration (wk)	% Responders		p Value
				Reboxetine	Comparator	
Reboxetine, 8–10 mg/d (N = 79) vs fluoxetine, 20–40 mg/d (N = 89) ⁹	Outpatients	18–78	8	78	74	NS ^b
Reboxetine, 8–10 mg/d (N = 130) vs imipramine, 150–200 mg/d (N = 126) ³⁷	Hospitalized and outpatient	18–66	6	69	56	< .05
Reboxetine, 4–6 mg/d (N = 176) vs imipramine, 75–100 mg/d (N = 171) ³⁸	Elderly outpatients	56–94	8	52	52	NS

^aReprinted with permission from Montgomery.¹²
^bSubset analysis of severely ill patients showed a between-treatment difference of 5.3 in favor of reboxetine on the Hamilton Rating Scale for Depression (95% confidence interval = 2.2 to 8.4).

management of depressed patients. In this study, conducted by Versiani and coworkers,³⁶ 286 depressed patients who had demonstrated a response to treatment (defined as a $\geq 50\%$ reduction from baseline in the HAM-D-21 total score) were randomly assigned to receive either reboxetine (8 mg/day) or placebo for 1 year or until relapse. The efficacy endpoint of the double-blind phase of the study was frequency of relapse. Patients were designated as having a relapse if they demonstrated a 50% or greater increase in their HAM-D-21 total score with respect to the end of the reboxetine run-in period (e.g., at the beginning of the double-blind, long-term study period) and a HAM-D-21 score ≥ 18 .

The therapeutic benefit of reboxetine was maintained for up to 12 months. At the last assessment, 78% of patients receiving reboxetine were in remission (HAM-D-21 total score ≤ 10) compared with 45% of patients receiving placebo ($p < .001$). The relapse rate with reboxetine treatment was also significantly less than for placebo. Reboxetine showed a significant advantage over placebo in the cumulative risk of relapse over the course of the treatment period ($p < .0001$). The proportion of relapse-free patients during both the first (61% vs. 40%) and the last 6 months of treatment (88% vs. 59%) was significantly higher for reboxetine-treated patients than among those taking placebo ($p < .001$). Throughout the 1-year study period, reboxetine was well tolerated. Little difference was found between the incidence of adverse events in patients receiving reboxetine compared with those receiving placebo. These results demonstrate that reboxetine is effective in both continuation and prophylactic treatment and that tolerability is maintained under those conditions.

Active-Comparator Studies

In addition to placebo-controlled studies, reboxetine has been evaluated against other antidepressant agents for its effectiveness in the treatment of major depressive disorder. Three double-blind, randomized, multicenter, multinational, active-controlled studies that did not include a concurrent placebo group have been completed (Table 2).¹²

Reboxetine versus tricyclic antidepressants. Two studies—one conducted in adult patients³⁷ and the other in elderly patients (> 65 years)³⁸—used imipramine as the comparator agent. These studies employed methodologies similar to that used in the placebo-controlled study of imipramine. The lack of a placebo group in a patient population in which a relatively high placebo response rate might be expected limits the usefulness of these studies for the establishment of efficacy. However, the studies do serve to compare agents for efficacy and tolerability.

In the first of the 2 studies, the efficacy of reboxetine, as measured by improvement in the HAM-D-21, MADRS, and CGI, was similar to that of imipramine.³⁷ Of the patients in the reboxetine group, 68.5% were classified as responders ($\geq 50\%$ reduction in HAM-D-21 total score versus baseline), compared with 56.2% in the imipramine group, whereas 52.0% and 45.5%, respectively, were deemed to be in remission (HAM-D-21 total score ≤ 10). The between-treatment difference in the proportion of response was 12.3% in favor of reboxetine, which, although it is not significantly different, suggests that reboxetine is at least as effective as imipramine in the extent of improvement of major depression.

Reboxetine was compared with imipramine in an 8-week study of 347 elderly patients.³⁸ Although the study was primarily a safety assessment of reboxetine compared with imipramine, efficacy measures were also monitored. At last assessment, 54.1% of the reboxetine-treated patients and 56.5% of the imipramine-treated patients were classified as responders ($\geq 50\%$ reduction in HAM-D-21 score vs. baseline). With respect to remission, 42.4% of the reboxetine group and 49.4% of the imipramine group were deemed in remission (HAM-D-21 total score ≤ 10). At last assessment, the proportion of patients who were “much to very much improved” was slightly higher with reboxetine than with imipramine (58.9% vs. 42.3%). Overall, the efficacy of reboxetine therapy in elderly patients with major depressive disorder, as evaluated by the improvement of HAM-D-21, CGI, MADRS, and Global Depression Scale scores, appeared to be no different from that seen with imipramine.

Reboxetine versus fluoxetine. Another research team investigated the therapeutic potential of reboxetine (8 mg/day) versus fluoxetine (20 mg/day) in 168 patients with major depressive disorder.⁹ No significant differences were seen between reboxetine and fluoxetine on the mean improvement in HAM-D-21 total score (the primary efficacy endpoint) or in the secondary efficacy measurements (CGI and MADRS).

At last assessment, 78% of the patients treated with reboxetine and 74% of the fluoxetine-treated patients were classified as responders ($\geq 50\%$ reduction in HAM-D-21 total score vs. baseline), while 67% in each group were seen to be in remission (HAM-D-21 total score ≤ 10). The 4% mean between-treatment difference in the proportion of response with reboxetine did not reach statistical significance.

The analysis of a subset of patients with severe depression on trial entry revealed advantages for reboxetine. In severely depressed patients, the between-treatment difference in mean HAM-D-21 score from baseline was 5.3 points (21.5 vs. 16.2). In this subpopulation, there was a statistically significant difference favoring reboxetine.⁸

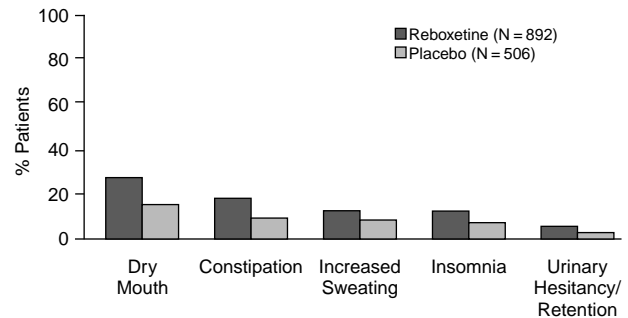
ADVERSE EVENTS

The tolerability profile of reboxetine was evaluated in 1622 patients who were treated in 7 phase 2 and 3 depression clinical studies (data on file, Pharmacia & Upjohn Company, 1999). The vast majority of adult patients (76.4%) received mean daily dosages of > 6 mg/day in divided doses for more than 4 weeks, but less than 12 weeks. The remaining patients received less than 6 mg/day, which is consistent with the overall exposure of patients who were 65 years of age and older in the clinical trials and with the recommendation of a lower initial dose (4 mg/day) for elderly patients.

Placebo-Controlled Studies

At least one treatment-emergent symptom was reported for 67.2% (269/400) of the reboxetine-treated patients, 56.2% (226/402) of the placebo-treated patients, 69.1% (141/204) of the TCA-treated patients, and 63.8% (81/127) of the fluoxetine-treated patients (data on file, Pharmacia & Upjohn Company, 1999). Most of the adverse events were reported as mild or moderate. Among the most frequently reported adverse events (i.e., events reported by $\geq 5\%$ of patients), the following events had a statistically significantly higher risk of occurring with reboxetine than placebo: dry mouth (27% vs. 15%), constipation (18% vs. 9%), increased sweating (12% vs. 8%), insomnia (12% vs. 7%), and urinary hesitancy/retention (5% vs. 2%, of which retention constituted 2% and 1%, respectively) (Figure 4). Side effects commonly associated with the SSRIs such as nausea (8% with reboxetine vs. 7% with placebo), anxiety/agitation (6% vs. 7%), and daytime somnolence (3% vs.

Figure 4. Frequency of Adverse Events Occurring in $> 5\%$ of Patients With a Statistically Significantly Higher Risk of Development on Reboxetine Treatment Than on Placebo^a



^aData on file, Pharmacia & Upjohn Company, 1999. Values represent physician ratings during clinical trials.

7%) were no more common in patients treated with reboxetine than in those treated with placebo.

The majority of the adverse events in the reboxetine group were mild to moderate in severity. Within the recommended dosage range of 4 to 10 mg/day, there appear to be no significant dose-related increases in adverse events. No apparent gender- or age-related differences have been reported. In fact, the number of patients older than 65 years who reported at least one treatment-emergent side effect in the short-term studies was lower than in younger cohorts (64.4% vs. 72.0%, respectively). Across the reboxetine database, elderly patients tolerated reboxetine as well as or better than younger patients. Discontinuations because of adverse events were low and were comparable between treatment groups (11.8% for reboxetine vs. 9.0% for placebo).

Active-Controlled Studies

In the direct comparison of reboxetine with fluoxetine, adverse events were more frequently reported as mild in the groups treated with reboxetine and placebo and as being of moderate severity in the fluoxetine group. Across all fluoxetine studies, the tolerability of reboxetine was similar to that of fluoxetine, with a similar number of patients reporting adverse events. However, the tolerability profile of reboxetine differs from that of fluoxetine, with less associated nausea and related symptoms, headache or migraine, tremor, diarrhea, and somnolence. Patients on fluoxetine treatment reported less dry mouth, constipation, hypotension, and urinary hesitancy.

In the study comparing reboxetine with imipramine,³⁷ tolerability of reboxetine was high, as shown by the results of patient reports, laboratory tests, electrocardiogram (ECG) recordings, and other physical parameter measurements. Serious adverse events were infrequently reported in both groups. The newly emerged adverse event rate was

high, as expected, when using a checklist to record adverse events. However, in only a minority of cases were these judged “probably or definitely” related to study medications. A significant difference was found in the cumulative risk of individual adverse events (dry mouth, hypotension and/or related symptoms, and tremor), with reboxetine producing fewer side effects. When the investigators were asked to weigh efficacy versus side effects according to the CGI-Efficacy Index, more of the reboxetine group (33.9%) compared with the imipramine group (22.3%) were judged to show evidence of marked efficacy in the absence of side effects at the last assessment.³⁷

In the Ban et al. study,¹³ several side effects were significantly different among patients treated with desipramine, reboxetine, and placebo (e.g., dry mouth, blurred vision, urinary hesitancy). Dry mouth was reported more commonly with desipramine (46%) than with placebo (22%) or reboxetine (25%). Blurred vision was also more common with desipramine (17%) than with reboxetine (3.8%) or placebo (3.6%). Urinary hesitancy was more common with reboxetine (11%) than with placebo (1.2%), but not significantly greater than with desipramine (4.5%). When the investigators restricted their observations to side effects of at least moderate severity, dry mouth and constipation were both seen more commonly with desipramine (21% and 18%, respectively) and reboxetine (13% and 17%, respectively) than with placebo (3.7% and 1.2%, respectively). Taken together, these data suggest noradrenergic antidepressants can produce anticholinergic-like side effects by increasing norepinephrine levels. Of note is that urinary hesitancy can occur and should be monitored both in individual patients and in wider release. Still, in the Ban et al. study,¹³ severe forms of this side effect were not observed.

In the study comparing reboxetine with imipramine in an elderly population, the occurrence of newly reported adverse events was similar in both groups; however, the prevalence of adverse events was higher in the imipramine group than in the reboxetine group.³⁴ Discontinuation due to a newly emerged adverse event was more frequent with imipramine (15.8%) than with reboxetine (11.4%). In this study, there was no indication of modifications in laboratory test results that were of clinical significance.

PANIC DISORDER

In an 8-week, double-blind study of reboxetine versus placebo in 75 patients with a diagnosis of panic disorder, reboxetine at a dose of 6 to 8 mg/day proved to be effective in reducing the number of panic attacks ($p < .0002$) and Phobic Scale scores ($p < .004$). On the basis of the results obtained, the therapeutic effects on number of panic attacks were noted by week 2 or 3, whereas the reduction in phobic symptomatology did not occur until week 6. Statistically significant differences favoring reboxetine were noted for occupational functioning, family adjustment, and

social adjustments. Adverse effects, laboratory test results, vital signs, and ECG findings for reboxetine were no different than for placebo.

SUMMARY

A comprehensive series of clinical trials has compared reboxetine with placebo, the TCAs imipramine and desipramine, as well as the SSRI fluoxetine. Compared with placebo, reboxetine has been shown to be effective in both short- and long-term studies. Against comparator antidepressants, reboxetine is at least as effective in the treatment of patients with major depressive disorder in the adult and elderly populations as desipramine, imipramine, and fluoxetine. In one study that included severely depressed patients, reboxetine was significantly more effective than fluoxetine in this subgroup. Reboxetine also offers significant advantages over fluoxetine in terms of social functioning and in patients' perception of their recovery and has a significantly improved adverse event profile compared with TCAs. In comparison with fluoxetine, reboxetine has a different adverse event profile, but shows advantages in terms of less agitation, nervousness, anxiety, somnolence, and gastrointestinal events. Overall, reboxetine often offers a significant safety advantage over TCAs in the treatment of the depressed population and an efficacy that is comparable to that of fluoxetine.

Drug names: bupropion (Wellbutrin), desipramine (Norpramin and others), fluoxetine (Prozac), mirtazapine (Remeron), nefazodone (Serzone), reboxetine (Vestra), venlafaxine (Effexor).

REFERENCES

- Roose SP. Tolerability and patient compliance. *J Clin Psychiatry* 1999;60 (suppl 17):14-17
- Montgomery SA. The place of reboxetine in antidepressant therapy [chairman's overview]. *J Clin Psychiatry* 1998;59(suppl 14):26-29
- Montgomery SA, Henry J, McDonald G, et al. Selective serotonin reuptake inhibitors: meta-analysis of discontinuation rates. *Int Clin Psychopharmacol* 1994;9:47-53
- Montgomery SA, Kasper S. Comparison of compliance between serotonin reuptake inhibitors and tricyclic antidepressants: a meta-analysis. *Int Clin Psychopharmacol* 1995;9(suppl 4):33-40
- Anderson IM. SSRIs versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. *Depress Anxiety* 1998;7 (suppl 1):11-17
- Brunello N, Racagni G. Rationale for the development of noradrenaline reuptake inhibitors. *Hum Psychopharmacol* 1998;13:S13-S19
- Roose SP. Tolerability and patient compliance. *J Clin Psychiatry* 1999;60 (suppl 17):14-17
- Massana J. Reboxetine versus fluoxetine: an overview of efficacy and tolerability. *J Clin Psychiatry* 1998;59(suppl 14):8-10
- Massana J, Moller HJ, Burrows GD, et al. Reboxetine: a double-blind comparison with fluoxetine in major depressive disorder. *Int Clin Psychopharmacol* 1999;14:73-80
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*. Washington, DC: American Psychiatric Association; 1980
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*. Washington, DC: American Psychiatric Association; 1987
- Montgomery SA. Reboxetine: additional benefits to the depressed patient.

- J Psychopharmacol 1997;11(suppl 4):S9-S15
13. Ban TA, Gaszner P, Aguglia E, et al. Clinical efficacy of reboxetine: a comparative study with desipramine—with methodological considerations. *Hum Psychopharmacol* 1998;13:S29-S39
 14. Versiani M, Amin M, Chouinard G. Double-blind, placebo-controlled study with reboxetine in inpatients with severe major depressive disorder. *J Clin Psychopharmacol* 2000;20:28-34
 15. Quitkin FM, Rabkin JG, Gerald J, et al. Validity of clinical trials of antidepressants. *Am J Psychiatry* 2000;157:327-337
 16. Massana J, Möller H-J, on behalf of the Reboxetine Study Group. In severe depression, reboxetine is as effective as imipramine and more effective than fluoxetine. Presented at the 11th annual meeting of the European College of Neuropsychopharmacology; November 1-5, 1998; Paris, France
 17. Bosc M, Dubini A, Polin V. Development and validation of a social functioning scale, the Social Adaptation Self-evaluation Scale. *Eur Neuropsychopharmacol* 1997;7(suppl 1):S57-S70
 18. Dubini A, Bosc M, Polin V. Noradrenaline-selective versus serotonin-selective antidepressant therapy: differential effects on social functioning. *J Psychopharmacol* 1997;11(suppl 4):S17-S23
 19. Leader JB, Klein DN. Social adjustment in dysthymia, double depression, and episodic major depression. *J Affect Disord* 1996;37:91-101
 20. Kasper S. From symptoms to social functioning: differential effects of antidepressant therapy. *Int Clin Psychopharmacol* 1999;14(suppl 1):S27-S31
 21. Hays RD, Wells KB, Sherbourne CD. Functioning and well-being outcomes of patients with depression compared with chronic general medical illnesses. *Arch Gen Psychiatry* 1995;52:11-19
 22. Dubini A, Bosc M, Polin V. Do noradrenaline and serotonin differentially affect social motivation and behaviour? *Eur Neuropsychopharmacol* 1997;7(suppl 1):S49-S55
 23. Burns RA, Lock T, Edwards DR, et al. Predictors of response to amine-specific antidepressants. *J Affect Disord* 1995;35:97-106
 24. Montgomery SA, James D, Montgomery DB. Pharmacologic specificity is not the same as clinical selectivity. In: Dahl SG, ed. *Clinical Pharmacology in Psychiatry*. Berlin, Germany: Springer Verlag; 1987:179-183
 25. Nystrom C, Hallstrom T. Double-blind comparison between a serotonin and a noradrenaline reuptake blocker in the treatment of depressed outpatients. *Acta Psychiatr Scand* 1985;78:384-390
 26. Keller MB, Klerman GL, Lavori PW, et al. Long-term outcome of episodes of major depression: clinical and public health significance. *JAMA* 1984;252:788-792
 27. Montgomery SA. Antidepressants in long-term treatment. *Ann Rev Med* 1994;45:447-457
 28. Impact of neuropharmacology in the 1990s: strategies for the therapy of depressive illness. Task Force of the Collegium Internationale Neuro Psychopharmacologicum (CINP). *Eur Neuropsychopharmacol* 1993;3:153-156
 29. Hirschfeld RMA. Guidelines for the long-term treatment of depression. *J Clin Psychiatry* 1994;55(12, suppl):61-69
 30. Hirschfeld RM. Long-term drug treatment of unipolar depression. *Int Clin Psychopharmacol* 1996;11:211-217
 31. Keller MB, Boland RJ. Implications of failing to achieve successful long-term maintenance treatment of recurrent unipolar major depression. *Biol Psychiatry* 1998;44:348-360
 32. Angst J. How recurrent and predictable is depressive illness? In: Montgomery SA, Rouillon F, eds. *Long-Term Treatment of Depression*. Chichester, England: Wiley Press; 1992:1-14
 33. Mueller TI, Leon AC, Keller MB, et al. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. *Am J Psychiatry* 1999;156:1000-1006
 34. Melfi CA, Chawla AJ, Croghan TW, et al. The effects of adherence to antidepressant treatment guidelines on relapse and recurrence of depression. *Arch Gen Psychiatry* 1998;55:1128-1132
 35. Kasper S. The rationale for long-term antidepressant therapy. *Int Clin Psychopharmacol* 1993;8:225-235
 36. Versiani M, Mehilane L, Gaszner P, et al. Reboxetine, a unique selective NRI, prevents relapse and recurrence in long-term treatment of major depressive disorder. *J Clin Psychiatry* 1999;60:400-406
 37. Berzowski H, Van Moffaert M, Gagiano CA. Efficacy and tolerability of reboxetine compared with imipramine in a double-blind study in patients suffering from major depressive episodes. *Eur Neuropsychopharmacol* 1997;7(suppl 1):S37-S47
 38. Katona C, Bercoff E, Chiu E, et al. Reboxetine versus imipramine in the treatment of elderly patients with depressive disorders: a double-blind randomised trial. *J Affect Disord* 1999;55:203-213