

Antidepressant Efficacy and Tolerability of the Selective Norepinephrine Reuptake Inhibitor Reboxetine: A Review

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Reboxetine is a unique selective norepinephrine reuptake inhibitor (NRI) with proven antidepressant efficacy in pharmacologic and biochemical tests predictive of antidepressant properties. Comprehensive clinical trials, including 8 placebo-controlled and/or active treatment-controlled studies, plus 4 open studies, have assessed the short-term and long-term efficacy and tolerability of reboxetine in patients with major depressive disorders and dysthymia. Results from a total of 690 patients who entered 5 open or placebo-controlled studies are summarized in this paper. Four hundred forty-nine patients with a diagnosis of either major depressive disorder or dysthymia were treated with reboxetine in these clinical studies of 4 weeks' to 12 months' duration. In a 6-week placebo-controlled study, clinically significant improvement ($\geq 50\%$ reduction in Hamilton Rating Scale for Depression total score) was observed at last assessment in 74% of reboxetine-treated patients compared with 20% of patients in the placebo group. Similar results were observed in the 6-week run-in phases of the 3 long-term studies, where the efficacy of reboxetine was maintained over the 12-month study period. Reboxetine was well tolerated; adverse events reported were mainly mild to moderate in severity, and there were no clinically significant changes in vital signs or laboratory parameters. The first in its class, reboxetine, a selective NRI, will provide a valuable addition to the existing armamentarium of agents used in the treatment of depression. *(J Clin Psychiatry 1998;59[suppl 14]:4-7)*

Dysfunction of either the noradrenergic or serotonergic neurotransmitter systems is the most widely accepted basis for depression. The serotonergic system has been the focus of much research over recent years, leading to the introduction of serotonin selective reuptake inhibitors (SSRIs), which offer an additional choice of drug with a reduced side effect profile compared with older tricyclic antidepressants (TCAs). Research focused on the role of the noradrenergic system has led to the development of reboxetine, the first in the class of selective norepinephrine reuptake inhibitors (selective NRIs), and marks a milestone in antidepressant therapy.¹

Reboxetine is highly potent in pharmacologic and biochemical tests predictive of clinical antidepressant efficacy.² It is free from the typical side effects associated

with the older TCAs, since it not only lacks affinity for serotonin or dopamine uptake sites, but is also devoid of any affinity for muscarinic, histaminergic, or adrenergic receptors.³

A comprehensive series of clinical trials have been conducted assessing the efficacy and tolerability of reboxetine in uncontrolled conditions, in comparison with placebo and with active comparator agents.⁴⁻⁷ A summary of 5 of these trials is presented in this paper.

SUMMARY OF CLINICAL TRIALS

A total of 690 patients (hospitalized patients and outpatients aged 18-68 years or > 65 years) entered the 5 studies summarized in this paper; of these, 449 patients received treatment with reboxetine (Table 1) (data on file, Pharmacia & Upjohn). Patients with a diagnosis of major depressive disorder (MDD) or dysthymia⁸ were assessed during either short-term (4-6 weeks' treatment) or long-term therapy (up to 12 months).

Primary measures of therapeutic efficacy were the reduction in the Hamilton Rating Scale for Depression (HAM-D) total score⁹ and the percentage of patients showing a $\geq 50\%$ reduction in HAM-D total score from baseline to last assessment. The Montgomery-Asberg Depression Rating Scale (MADRS)¹⁰ and the Severity of Illness and

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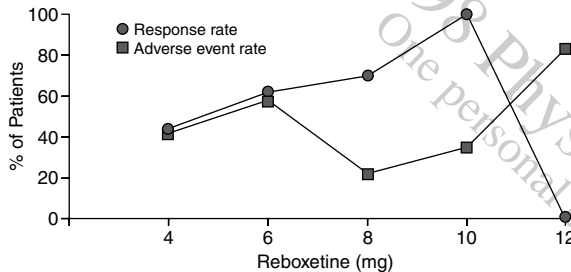
Table 1. Summary of Open and Placebo-Controlled Studies With Reboxetine*

Design	Length of Study	Diagnosis	Number of Patients		Population
			Total Entering the Study	Reboxetine (Daily Dose)	
Open, multicenter, multinational (dose range-finding study)	4 wk	MDD	98	98 (4–12 mg)	Hospitalized (aged 23–65 y)
Open, multicenter, multinational	≤ 12 mo	MDD or dysthymia	209	140 ^a (8 mg)	Outpatients (aged 25–68 y)
Open, multicenter, multinational	≤ 12 mo	MDD or dysthymia	Interim analysis: 44	Interim analysis: 40 ^a (4–8 mg)	Hospitalized/outpatients (aged 65–94 y)
Placebo-controlled, double-blind, randomized, multicenter, multinational	6 wk	MDD	56	28 (6–10 mg)	Hospitalized (aged 18–60 y)
Placebo-controlled, double-blind, randomized, multicenter, multinational	≤ 12 mo	MDD	283 ^a	143 ^a (8 mg)	Outpatients (aged 18–65 y)

*Data on file, Pharmacia & Upjohn. Abbreviation: MDD = major depressive disorder.

^aPatients entering long-term treatment.

Figure 1. Comparison of Efficacy Versus Tolerability of Reboxetine in Hospitalized Patients to Assess the Frequency of Response ($\geq 50\%$ Decrease of HAM-D Total Score) and Frequency of Adverse Events of at Least Moderate Severity by Treatment Dose*



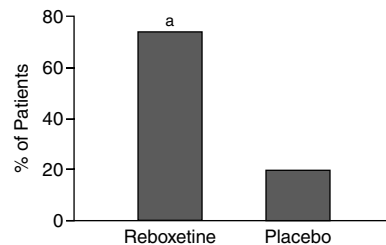
*Data on file, Pharmacia & Upjohn.

Global Improvement components of the Clinical Global Impressions (CGI) scale¹¹ were also often used as measures of therapeutic efficacy. Adverse events were monitored, ECG and vital signs were recorded, and standard laboratory tests performed to assess the tolerability of reboxetine.

CLINICALLY EFFECTIVE DOSE OF REBOXETINE

Increasing doses of reboxetine were administered for 4 weeks to 5 different groups of hospitalized patients with MDD, with maximum daily doses of 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg. Clinically significant improvement in patient symptoms, as measured by a minimum 50% reduction in the HAM-D total score, was observed up to a dose of 10 mg/day. Dose levels of 8 to 10 mg/day provided the largest safety margin, being associated with maximal response rate and minimal significant adverse event rate (Figure 1). Thus, subsequent clinical trials were conducted with reboxetine (8–10 mg/day in the adult), with the exception of trials in the elderly, in which, for pharmacokinetic reasons,¹² lower doses (4–6 mg/day) were mostly used.

Figure 2. Significantly Greater Proportion of Reboxetine-Treated Patients Compared With Patients in the Placebo Group Responded to Treatment*



*Data on file, Pharmacia & Upjohn. Response was defined as $\geq 50\%$ reduction of HAM-D total score at last assessment compared with baseline.

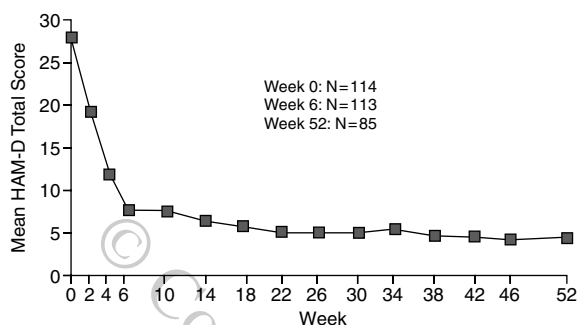
^a $p < .001$.

REBOXETINE IN THE SHORT-TERM TREATMENT OF MAJOR DEPRESSIVE DISORDER

The efficacy and tolerability of reboxetine (N = 28) versus placebo (N = 28) were determined in a 6-week study in hospitalized patients with MDD. After a placebo washout period of 7 days, patients were randomly assigned to receive either reboxetine or placebo. Clinical improvement, as shown by a $\geq 50\%$ decrease in HAM-D total scores from baseline to last assessment, was evident in 74.1% of patients treated with reboxetine compared with only 20% of patients in the placebo group ($p < .001$) (Figure 2). Mean total HAM-D scores decreased over time with a significantly greater improvement seen after just 10 days of treatment with reboxetine compared with placebo ($p < .01$). The therapeutic effects of reboxetine were also significantly greater than those of placebo by day 14 as assessed by the CGI-Severity of Illness ($p < .001$).

Reboxetine was well tolerated over the 6-week study period, with the majority of newly reported adverse events assessed as either mild or moderate in severity (94% for reboxetine; 98% for placebo). The most commonly occurring adverse events (in $> 15\%$ of patients) observed in

Figure 3. Improvement in HAM-D Total Score, Seen Over 6 Weeks, Was Maintained Over 1 Year in the Long-Term Open Study



*Data on file, Pharmacia & Upjohn.

patients in the reboxetine group were increased sweating, blurred vision, insomnia, and dry mouth. Headache and dry mouth were the 2 adverse events that occurred in > 15% of patients in the placebo group. One patient in each treatment group dropped out of the study due to adverse events. Fewer patients in the reboxetine group (N = 3) than in the placebo group (N = 15) withdrew from the study due to lack of efficacy. However, the vast majority of the patients (96% in each group) received treatment for up to 3 weeks. No clinically relevant changes in vital signs or results of laboratory tests were reported.

REBOXETINE IN THE LONG-TERM TREATMENT OF MAJOR DEPRESSIVE DISORDER

Three studies have assessed the efficacy and tolerability of reboxetine over a 12-month period (Table 1). Favorable results for reboxetine were observed in 2 open studies in adult and elderly populations (interim analysis only available) where patients were diagnosed with either MDD or dysthymia. After an initial 6-week run-in phase, patients classified as responders to treatment ($\geq 50\%$ decrease in HAM-D total score compared with baseline) continued to be treated with reboxetine for up to a year. The acute response to treatment, shown by the fall in mean HAM-D total scores, was sustained over the 12-month study (Figure 3). In the adult population, 73% of patients with a diagnosis of MDD and 79% with dysthymia were classed as responders and allowed to enter the long-term phase of the study. Among the patients treated with reboxetine during long-term therapy, 72% of patients with MDD and 88% of patients with dysthymia were classed as in remission at last assessment. Overall, only 14% of patients relapsed during long-term treatment.

Interim analysis of results in the elderly population showed a similar trend. Thirty-two of the 44 patients completed the 12-month study, and over 90% of patients were considered "much" or "very much" improved after 6 weeks of treatment; this level of improvement was maintained over the 12-month period.

The results of these open studies were confirmed in a large, long-term placebo-controlled study in a population of patients with a diagnosis of MDD. After an open 6-week run-in phase, patients responding to reboxetine ($\geq 50\%$ decrease in HAM-D total score) were randomly assigned to receive either reboxetine or placebo for up to 12 months. At the last assessment, significantly more patients in the reboxetine group (over 75%) were in remission (HAM-D total score ≤ 10) compared with patients in the placebo group (45%) ($p \leq .001$), and fewer patients in the reboxetine group relapsed compared with placebo patients (HAM-D total score increased by $> 50\%$ at week 6 and was ≥ 18) during the study.

The safety profile of reboxetine in the 3 studies of 12 months' duration was similar to that observed in the short-term study. The majority of adverse events reported were mild to moderate in severity, and there were no clinically significant changes in vital signs or laboratory parameters reported. Interestingly, in the placebo-controlled study, there was no difference between either reboxetine-treated patients or those in the placebo group in terms of the overall incidence of adverse events, and less than 5% of patients in either treatment group withdrew from the study because of adverse events.

CONCLUSIONS

Reboxetine, the first selective NRI, is an effective and well-tolerated therapy for both short- and long-term treatment of major depressive disorders and dysthymia. The effective doses of reboxetine in adults were 8 to 10 mg/day. Reboxetine was significantly superior to placebo in efficacy in hospitalized patients during acute treatment, with therapeutic benefit observed as early as day 10 of treatment. The efficacy of reboxetine was maintained over a 12-month study period in both adult and elderly populations.

Adverse events reported with reboxetine were mild to moderate in severity, and a similar adverse event profile was observed over both short- and long-term treatment.

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