Reboxetine, a Selective Norepinephrine Reuptake Inhibitor, Is an Effective and Well-Tolerated Treatment for Panic Disorder

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Background: Tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) as well as benzodiazepines have been shown to be effective for the treatment of panic disorder. The introduction of SSRIs has enabled a greater understanding of the role of serotonin in the etiology of panic disorder; however, the role of norepinephrine has been more challenging to ascertain. The aim of this study was to determine the efficacy and tolerability of reboxetine, a novel selective norepinephrine reuptake inhibitor, in patients with panic disorder with and without agoraphobia.

Method: Eighty-two patients (aged 18–65 years) with DSM-III-R panic disorder, with or without agoraphobia, were randomly assigned to receive 6 to 8 mg/day of reboxetine (42 patients) or placebo (40 patients) for 8 weeks in this placebo-controlled, parallel-group, double-blind clinical trial.

Results: Of the 82 patients enrolled in the trial, 75 were considered in the analysis (37 patients in the reboxetine group and 38 patients in the placebo group). At last assessment, there was a significant reduction in the mean number of panic attacks (range, 9.3–1.2) and phobic symptoms (range, 8.1–3.2) in the reboxetine group compared with the placebo group (ranges, 8.5–5.8 and 7.7–5.2, respectively; $p < .05$). Improvement in Hamilton Rating Scale for Depression, Hopkins Symptom Checklist-90, and Sheehan Disability Scale scores were also greater in the reboxetine group compared with the placebo group. Adverse events reported more frequently with reboxetine than placebo included dry mouth (36% vs. 16%), constipation (27% vs. 22%), and insomnia (26% vs. 22%).

Conclusion: Reboxetine was effective and well tolerated in the treatment of panic disorder.

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Panic disorder is a common and often chronic psychiatric illness that affects 2% to 4% of the general population.[1,2] The frequency and severity of panic attacks can vary, with some individuals experiencing moderately frequent attacks (e.g., once per week) that occur regularly for months at a time and others experiencing short bursts of more frequent attacks (e.g., daily for a week).[3] Indeed, 15% of the general population may experience isolated panic attacks at some time, although not all will receive, or warrant, a diagnosis of panic disorder.[4] The prognosis for patients with panic disorder is worse when comorbid agoraphobia, depression, or personality disorder is present.[5] The prevalence of comorbid major depression has been reported to be as high as 50% to 65%,[3] including 20% to 30% of patients treated during follow-up.[5]

The essential features of panic attacks have been defined and involve a discrete period of unprovoked, intense anxiety that produces overwhelming subjective feelings of fear or discomfort that build rapidly to a peak.[3] The symptoms include autonomic overactivity, such as sweating, palpitations, flushing, and dizziness, and psychological symptoms, such as depersonalization, fear of dying, and fear of losing control. Hyperventilation and paresthesias are also commonly associated with panic attacks.[3] Moreover, anticipatory anxiety and agoraphobia are disabling and common complications of repeated episodes of panic.[6]

A variety of hypotheses involving dysfunction of neurotransmitter systems (including γ-aminobutyric acid [GABA], serotonin, and norepinephrine) and peptide systems (cholecystokinin, neuropeptide Y, and corticotropin-releasing factor) and changes in lactate and carbon dioxide levels ("false suffocation response") as well as cognitive and behavioral mechanisms have all been implicated in the pathophysiology of panic disorder.[7]

The dysfunction within the serotonergic system has been ascribed to both an excess and a deficit of serotonin in certain brain regions,[8] and the success of the selective serotonin reuptake inhibitors (SSRIs) in the treatment of panic disorder has resulted in the widespread acceptance of a dysfunction within this neurotransmitter system as a key etiologic factor.[9] There is also a considerable body of evidence to implicate norepinephrine in the pathophysiology of panic disorder. Indeed, the locus ceruleus, which contains the highest concentration of norepinephrine cell bodies in the brain, is known to be involved in mediating fear and anxiety responses.[8,10] However, clinical studies in patients with panic disorder using agents with some degree of selectivity for the noradrenergic system have provided conflicting results. Lofepramine, a norepinephrine selective tricyclic antidepressant (TCA), was shown to be at least as effective as clomipramine in reducing both the symptoms and the number of panic attacks experienced by patients.[11] However, significant differences from placebo have not, so far, been demonstrated for the TCAs desipramine or maprotiline.[12,13] These conflicting results from clinical trials of antidepressants with a noradrenergic component make any predictions of response in panic disorder with such agents difficult. The recent introduction of reboxetine, the first purely norepinephrine selective antidepressant, should increase our understanding of the role of norepinephrine in panic disorder.

Reboxetine is a new selective norepinephrine reuptake inhibitor (selective NRI) with proven efficacy in major depression[14] and a favorable side effect profile different from that of existing agents.[15] The aim of the present study was to determine the efficacy and tolerability of reboxetine in patients with panic disorder with and without agoraphobia for a period of 8 weeks.

METHOD

The study was a multicenter, randomized, placebo-controlled, parallel-group, double-blind clinical trial conducted in Brazil and Italy. The study was performed in accordance with the Declaration of Helsinki (1964) and its subsequent amendment (1975). Written, informed consent was obtained from all patients. Male and female patients aged between 18 and 65 years meeting the criteria for the diagnosis of panic disorder (DSM-III-R)[16] with or without agoraphobia and who had experienced at least 4 panic attacks in the month preceding their admission to the study were included.

Patients were excluded from the study if they had a clinical history of any drug hypersensitivity, a history of brain injury or convulsive disorders, or a recent history of clinically relevant cardiorespiratory, endocrine, neurologic, or toxic-metabolic disorders. Patients with evidence of a concomitant major depressive episode[16] and those who had participated in clinical trials with an investigational drug within the 4 weeks preceding the study were also excluded.

Following an initial washout period of 7 days, during which time all drugs were discontinued (with the exception of the lowest dose of benzodiazepines required to prevent withdrawal symptoms),[17] patients were randomly assigned to receive either reboxetine (N = 42) or placebo (N = 40) for 8 weeks. Patients received reboxetine, 2 mg/day, on the first 2 days of treatment, increasing to 4 mg/day on days 3 and 4, and 6 mg/day on day 5. In the absence of significant clinical improvement (based on the clinicians' assessment), the dose was increased to 8 mg/day from day 14 to day 56.

A last-observation-carried-forward analysis (last assessment) was conducted and included all patients who received at least 3 weeks of treatment. The primary parameters of efficacy considered were the mean number of major panic attacks (spontaneous and situational) per week (as measured by the Sheehan Panic Attack and Anxiety Scale [SPAAS]),[18] the global scores of the severity of the phobic symptomatology (Phobia Scale[19]), and the score on the Clinical Global Impressions scale (CGI).[20] Efficacy measurements were determined by comparing baseline and last assessment scores. At weekly intervals, the number of patients with no major panic attacks was identified as an index of complete response to treatment. Secondary parameters considered were the mean number of minor panic attacks (spontaneous and situational) per week (as measured by the SPAAS), anticipatory anxiety, 6 factor scores derived from the Hamilton Rating Scale for Depression (HAM-D),[21] the scores of the Hopkins Symptom Checklist-90 (SCL-90),[22] and factors from and the impact of the disorder with regard to work, social, and family life as measured by the Sheehan Disability Scale.[23]

Tolerability was assessed by the reporting of adverse events using the Dosage Record and Treatment Emergent Symptom Scale (DOTES)[24] at weekly intervals. Standard laboratory tests were performed at screening and weeks 3 and 8, and an electrocardiogram was obtained and vital signs measured at screening and at weeks 1, 3, and 8.

Statistical Analysis

Comparisons between the reboxetine and placebo groups were performed using the chi-square test, analysis of variance (ANOVA), and the Student t test (2-tailed). Significance was determined at the 5% level.

RESULTS

A total of 82 patients from 2 centers (40 patients from one center and 42 patients from the other) were recruited for the study and were randomly assigned to receive reboxetine (N = 42) or placebo (N = 40). Of the 82 patients who entered the study, 75 received at least 3 weeks of treatment

Table 1. Baseline Demographics of the Study Population

Characteristic	Reboxetine Group (N = 37)	Placebo Group (N = 38)
Patients, male/female, N	12/25	13/25
Age, mean ± SD, y	36.5 ± 10.4	35.1 ± 10.9
Duration of present episode, mean ± SD, mo	26.2 ± 30.5	17.7 ± 21.9
Presence of precipitating events, N		
Definite	3	3
Absent/probable	34	35
Type of course, N		
Chronic disease	11	9
Exacerbation of chronic disease	2	5
First episode in patient with negative history	15	17
No. of major panic attacks in the last month, mean ± SD	28.3 ± 16.2	25.9 ± 15.2
No. of minor panic attacks in the last month, mean ± SD	31.8 ± 21.6	38 ± 21.3
No. of agoraphobia-related items, mean	6.1	5.4
Severity of disease (Phobia Scale)	5.2	5

and were considered in the efficacy analysis (37 in the reboxetine group and 38 in the placebo group). The 7 patients who discontinued treatment prior to week 3 were excluded from the efficacy analysis and included 5 patients in the reboxetine group (3 patients were lost to follow-up, 1 patient discontinued due to an adverse event, and 1 patient was excluded due to protocol violation). No major differences between the treatment groups were observed (Table 1). Of the remaining 75 patients, 6 in the reboxetine group discontinued treatment (poor efficacy [N = 4], refusal to continue [N = 1], and protocol violation [N = 1]) compared with 19 in the placebo group (12 patients withdrew because of poor efficacy and 7, for other reasons including protocol violation [N = 3], adverse event [N = 2], refusal to continue [N = 1], and an intercurrent medical problem [N = 1]).

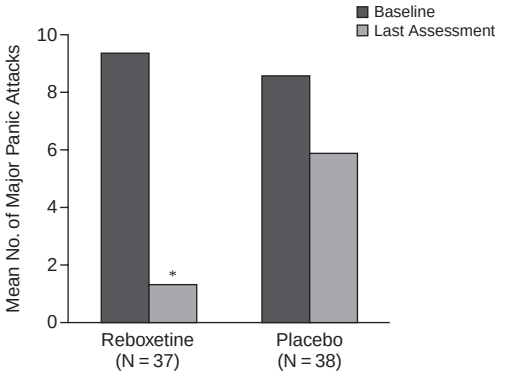
Efficacy

At baseline, there was no statistical difference in the mean ± SD number of major panic attacks experienced by patients randomly assigned to receive reboxetine (9.3 ± 6.2) or placebo (8.5 ± 5.9). At last assessment, patients treated with reboxetine experienced significantly fewer major panic attacks per week compared with those who received placebo (1.2 ± 1.7 vs. 5.8 ± 6.8, respectively; p = .0002; Figure 1). The mean number of major panic attacks was also significantly reduced at weeks 2, 3, 6, and 8 (p ≤ .05) in the reboxetine group compared with the placebo group. In total, 19 patients in the reboxetine group reported no major panic attacks at week 8 compared with 9 patients in the placebo group. Phobic symptomatology scores (which include agoraphobia scores) improved progressively from baseline in both groups. At last assessment, the mean overall scores were significantly lower (p ≤ .05) for patients in the reboxetine group (8.1 at baseline vs. 3.2 at last assessment) compared with those in the placebo group (7.7 at baseline vs. 5.2 at last assessment). Mean scores were also significantly lower in the reboxetine group (2.9) compared with the placebo group (4.2) at week 5 (p ≤ .05).

Consistent with the reduction of both major panic attacks and improvement in phobic symptomatology, significantly greater improvements in mean CGI scores for severity of illness were observed for patients in the reboxetine group (5.2 at baseline vs. 2.5 at last assessment) compared with those in the placebo group (5.0 at baseline vs. 3.8 at last assessment; p = .0002; Figure 2).

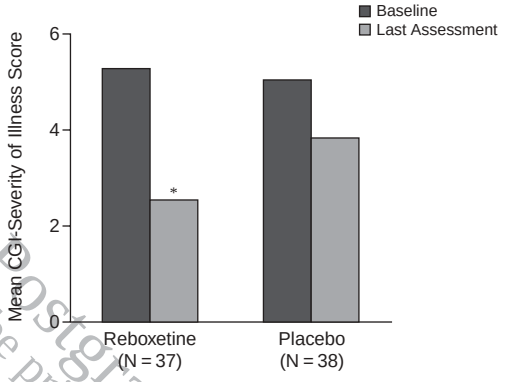
Similar results were observed when the number of limited-symptom panic attacks was considered. Patients in the reboxetine group experienced fewer limited-symptom attacks at weeks 2, 3, 5, 7, and 8 (p ≤ .05) compared with

Figure 1. Mean Number of Major Panic Attacks (spontaneous and situational) at Last Assessment for Patients Receiving Reboxetine or Placebo



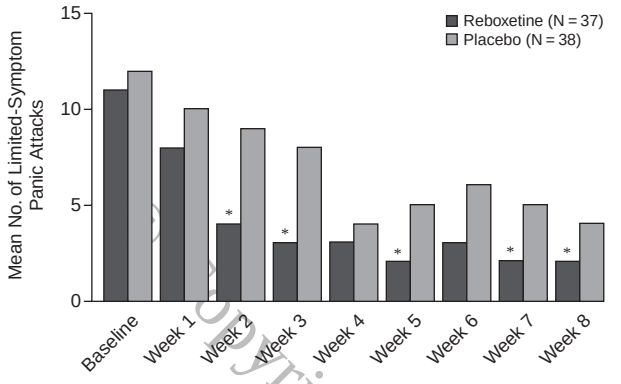
*p = .0002, reboxetine vs. placebo.

Figure 2. CGI-Severity of Illness Scores for Patients Receiving Reboxetine or Placebo[a]



[a]Abbreviation: CGI = Clinical Global Impressions scale.
*p = .0002, reboxetine vs. placebo.

Figure 3. Mean Number of Limited-Symptom Panic Attacks (spontaneous and situational) in Patients Receiving Reboxetine or Placebo



*p ≤ .05, reboxetine vs. placebo.

those in the placebo group (Figure 3). An improvement was also observed regarding the amount of time anticipatory anxiety was experienced. Patients in both the reboxetine and placebo groups showed a progressive reduction in anticipatory anxiety up to week 4. At weeks 5 (21% vs. 34%), 7 (19% vs. 33%), and 8 (15% vs. 27%), there was a marked reduction in the percentage of time anticipatory anxiety was experienced by patients in the reboxetine group compared with those in the placebo group ($p < .05$).

Analysis of HAM-D scores for 6 factors at baseline and last assessment showed significant improvement for anxiety and somatization factors, body weight, cognitive disorders, and psychomotor retardation ($p < .05$) in patients receiving reboxetine compared with those in the placebo group. No significant differences were observed between the 2 groups for the remaining 2 factors, diurnal variation and sleep disturbance. Significant improvements ($p < .05$) in SCL-90 scores for somatization, depression, anxiety, and phobic anxiety factors were observed for patients receiving reboxetine compared with those in the placebo group.

An evaluation of the disruption caused by the disorder on work, social, and family functioning was also assessed using the Sheehan Disability Scale. Patients receiving reboxetine showed significant ($p < .05$) improvements in all the domains (interference of disorder on occupational functioning, social adjustment, and family adjustment) compared with patients in the placebo group.

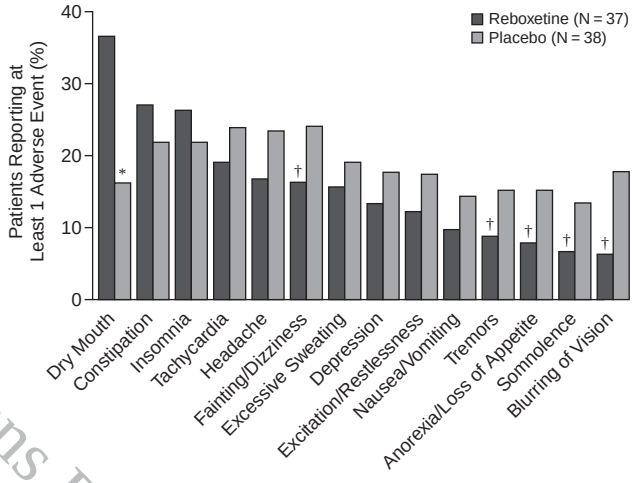
Safety and Tolerability Analysis

The majority of adverse events occurred during the first 3 weeks of treatment, progressively decreasing during the subsequent treatment period. The number of patients reporting adverse events during the 8-week study did not differ significantly between the reboxetine and placebo groups (Table 2). Adverse events experienced by

Table 2. Patients Experiencing Adverse Events at Each Week

	Reboxetine Group		Placebo Group	
Week	N/Total N	%	N/Total N	%
1	24/38	63	24/37	65
2	27/38	71	26/37	70
3	30/37	81	27/37	73
4	25/34	74	20/27	74
5	19/33	58	18/25	72
6	16/28	57	14/22	64
7	14/24	58	12/18	67
8	14/24	58	12/18	67

Figure 4. Adverse Events Reported by ≥ 10% of Patients With at Least 1 Adverse Event



*p ≤ .05, significantly in favor of placebo.
†p ≤ .05, significantly in favor of reboxetine.

≥ 10% patients reporting at least 1 adverse event are shown in Figure 4. The percentage of patients with at least 1 episode of dry mouth was significantly higher for patients receiving reboxetine than for patients receiving placebo. However, the percentage of patients with at least 1 episode of blurred vision, diarrhea, fainting and dizziness, anorexia, somnolence, and tremors was significantly lower ($p \leq .05$) in the reboxetine group compared with the placebo group. The frequency of severe adverse events was similar in the reboxetine (67 events, 57.8% of total events) and placebo groups (49 events, 42.2% of total events).

Clinically significant abnormalities in laboratory test results were similar to baseline for all parameters. There were no clinically significant changes in laboratory test results or vital signs.

DISCUSSION

The pathophysiology of panic disorder has not been fully elucidated. However, dysfunction of the GABA, serotonin, and norepinephrine systems has been impli-

cated.[8] There is accumulating preclinical evidence to suggest a relationship between noradrenergic brain systems and behaviors associated with stress and anxiety. The present study is the first clinical report of a pharmacotherapeutic agent which acts specifically on the noradrenergic system—reboxetine—that is able to successfully alleviate the symptoms of panic disorder.

In this study, the selective NRI reboxetine significantly improved the clinical profile of patients with panic disorder after 8 weeks of treatment. Reboxetine reduced the number of major panic attacks by 87% compared with 32% for placebo and progressively improved phobic symptoms associated with panic disorder. Likewise, symptoms of anticipatory anxiety also responded progressively with reboxetine therapy. Thus, it would appear from this study that the specific norepinephrine reuptake inhibitor reboxetine is effective in panic disorder. These results are in contrast to earlier studies with other, less specific noradrenergic agents such as maprotiline,[13] in which no clear benefit over placebo was observed. The results reported here are comparable to those from other recent studies with benzodiazepines and antidepressants in which efficacy in panic disorder has been established.

Since the 1980s, benzodiazepines have been used for the treatment of panic disorder. Alprazolam has been shown to be an effective short- and long-term treatment for panic disorder,[25–29] and there is indirect evidence to suggest that this agent modulates the noradrenergic system.[30] One of the largest clinical studies[31] compared alprazolam with placebo in 526 patients. Alprazolam produced a 69% reduction in the number of panic attacks compared with a 30% reduction in the placebo group. The results with reboxetine compare favorably with those for alprazolam, not only in terms of a lower incidence of panic attacks but also in other domains associated with panic disorder.

TCAs, monoamine oxidase inhibitors (MAOIs), and SSRIs have also been widely used for the treatment of panic disorder. Of the TCAs, imipramine is probably the most widely investigated and has been shown to be effective in the treatment of panic disorder.[32–34] In a clinical trial comparing imipramine with alprazolam and placebo,[25] both active drugs were shown to be more efficacious than placebo. Twenty percent more patients receiving alprazolam or imipramine were free from panic attacks compared with those receiving placebo. In a clinical trial comparing imipramine with clomipramine,[35] both drugs were shown to be efficacious, with a similar proportion of patients panic-free at the end of 10 weeks of treatment (67% and 77%, respectively). However, 35% fewer patients receiving imipramine were free from panic attacks compared with those receiving clomipramine at the end of 2 weeks of treatment.[35] In the present study, 28% more patients receiving reboxetine were free from panic attacks compared with those in the placebo group.

Other TCAs such as lofepramine and clomipramine have been shown to have efficacy in panic disorder,[11,36] with results similar to the findings in the present study with reboxetine. However, studies with the TCA desipramine have been controversial. In a placebo-controlled study with 56 patients,[12] no difference between desipramine and placebo was demonstrated in terms of reducing the frequency of panic attacks. However, significant improvements in Hamilton Rating Scale for Anxiety scores and global phobia scores were observed in desipramine-treated patients compared with those in the placebo group.[12] Interestingly, patients in the desipramine group did not show significant improvement in CGI scores compared with those in the placebo group.[12] In a smaller uncontrolled study with desipramine (15 patients),[37] a reduction in panic attack frequency was observed, although this did not reach statistical significance. In this small study,[37] CGI scores improved significantly, in contrast to the findings from the larger study by Lydiard and coworkers.[12] It has been suggested that the discrepancy in the results obtained from these studies may be due to a poor understanding of the components of panic disorder responsive to treatment with desipramine.[12,37]

Recent studies have suggested that the reversible MAOI moclobemide may also be useful in the treatment of panic disorder with comparable efficacy to that of the SSRI fluoxetine[38] and that of clomipramine.[39] Of the SSRIs, paroxetine,[40] sertraline,[41] citalopram,[42] and fluoxetine[41] have all been shown to be efficacious in treating panic disorder. The percentage of patients experiencing 0 or 1 panic attack in these studies was 36% (vs. 16% for placebo), 57% (vs. 41% for placebo), 65% (vs. 48% for placebo [data estimated from a graph]), and 44% for patients receiving paroxetine, sertraline, citalopram, and fluoxetine, respectively.[40–43] These results compare favorably with the present study, in which 63% of patients receiving reboxetine were free from panic attacks. Finally, a number of case reports and small-scale studies have suggested that the novel dual-action antidepressant venlafaxine may be effective in the treatment of panic disorder, although larger, well-controlled trials are needed to confirm these results.[44–46]

The low incidence and severity of adverse events observed with reboxetine treatment in the present study were comparable to those observed with reboxetine in major depressive disorder.[15] The low dropout rate observed with reboxetine therapy (4 of 37 patients) further suggests that reboxetine is a well-tolerated treatment for panic disorder.

Over the years, there has been the general perception that noradrenergic agents may be less effective than serotonergic agents in panic disorder. This perception is supported by the results with maprotiline, for which no efficacy in panic disorder was demonstrated.[13] This observation contrasts with the findings of the present study, in

which the highly selective norepinephrine reuptake inhibitor reboxetine reduced both the number and severity of panic attacks. It has been suggested that there may be an imbalance between norepinephrine and serotonin systems leading to heterogeneity in panic disorder. Thus one group of patients may experience panic as a result of dysfunction of the norepinephrine system and others, as a result of dysfunction of the serotonin system.[13] Alternatively, dysfunction at the level of a downstream pathway common to both the serotonin and norepinephrine systems may be responsible such that agents acting on either system specifically could be effective. Moreover, crosstalk between the serotonin and norepinephrine systems adds complexity when attempting to distinguish precise etiologic factors in the development of panic and other mood disorders. Thus, the use of the specific norepinephrine reuptake inhibitor reboxetine may facilitate a clearer understanding of the role of norepinephrine in the pathophysiology and treatment of panic disorder.

CONCLUSION

Despite the small number of patients included in the present study, the results have shown reboxetine, the first selective norepinephrine reuptake inhibitor, to be an effective treatment for panic disorder in adults. The favorable tolerability profile of reboxetine will prove to be a valuable alternative therapy for treatment of this debilitating illness.

Drug names: alprazolam (Xanax and others), citalopram (Celexa), desipramine (Norpramin and others), fluoxetine (Prozac and others), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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