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An Open Clinical Trial of Reboxetine in the Treatment of Social Phobia

To the Editors:

Social phobia (SP) is an anxiety disorder characterized by the fear of situations where an individual fears humiliation or embarrassment when under the scrutiny of others.[1] Although some psychotherapeutic approaches have been reported to be effective and useful, they do not seem to be widely available and accessible for the majority of the patients.[2] It has been shown that both irreversible[3,4] and reversible[5,6] monoaminooxidase inhibitors are effective in SP although there are disappointing results especially for moclobemide.[7,8] Although the serotonergic system involvement has been relatively established because of good response to selective serotonin reuptake inhibitors,[9,10] the role of noradrenergic system is unclear. Despite relatively limited number of studies, tricyclic antidepressants having both serotonergic and noradrenergic activity have been found to be ineffective in the treatment of SP.[11] However, venlafaxine, a dual 5-HT/norepinephrine reuptake inhibitor, has showed a marked improvement on patients with SP.[12] Therefore, we suggest that it may be helpful to evaluate the efficacy of reboxetine, a unique selective noradrenaline reuptake inhibitor, in patients with SP.

Our study consisted of consecutive patients (aged 20-42 years) who gave their consent to voluntarily participate in the present study after procedures, and possible side effects were explained to them. Ethical permission was approved by the Local Ethics Committee of the Firat University School of Medicine. Exclusion criteria included the presence of a severe physical illness, the history of alcohol and substance abuse or dependence, the presence of dementia or mental retardation. Thus, a total of 23 patients (20 generalized and 3 specific phobic patients) were recruited to the study. After 2 weeks (4 weeks for fluoxetine) of washout period, reboxetine was orally started twice daily at a dosage of 4 mg/d and titrated to 8 mg/d at 2 weeks if tolerated. Before being treated with reboxetine, 8 patients were treated with moclobemide, 9 patients were treated with a selective serotonin reuptake inhibitor, and 9 had no pharmacologic treatment. The use of concomitant medications, except for benzodiazepines, was prohibited. Each patient underwent a detailed diagnostic evaluation by 1 trained senior psychiatrist using the Structured Clinical Interview for DSM-III-R outpatient form.[13] The patients with any kind of Axis I comorbidity were excluded. No patient had comorbid major depression or another Axis I disorder. In addition, all patients were evaluated by using the Hamilton Anxiety Rating Scale (HAM-A)[14] and the Liebowitz Social Anxiety Scale (LSAS)[15] at 0, 2, 4, and 8 weeks, and the Clinical Global Impression Scale-Improvement (CGI-I) at 2, 4, and 8 weeks. In addition, they were asked for adverse effects by an instrument designed by the authors. The instrument we used included open-ended questions. The efficacy was principally assessed by the change in mean total LSAS score from baseline to last assessment (50% or greater reduction in total LSAS score) and by having ratings of ''very much'' or ''much improved'' on the CGI-I. Statistical analysis was performed by using the SPSS/PC 9.05 version, 1998.

Of the 23 patients, 22 (13 males and 9 females) completed the 8-week trial of reboxetine. One patient discontinued prematurely because of blurred vision. The mean age and duration of the illness in the patient group were 27.9 ± 10.6 and 5.8 ± 3.2 years, respectively. At baseline, the mean HAM-A score was 27.9 ± 6.1. The mean LSAS-Fear and LSAS-Avoidance scores were 61.9 ± 6.8 and 64.1 ± 7.9, respectively. Reductions in the mean HAM-A and total LSAS scores from baseline to the last assessment were statistically significant (t = 16.4, $P < 0.001$ for HAM-A; t = 19.9, $P < 0.001$ for total LSAS). Statistical significance appeared at the evaluation of week 2 for HAM-A and LSAS-Fear scales and at the evaluation of week 4 for LSAS-Avoidance scale (Table 1). At 8 weeks, 14 of the patients (63.6%) were considered as responders, with 50% or greater reduction in LSAS total score and having ratings of ''very much'' (n = 5) or ''much improved'' (n = 9) on CGI-I. Reboxetine was well tolerated. There were 17 reports of experienced side effects from 13 patients. The most frequently reported side effects were weakness (n = 5), dry mouth (n = 4), and insomnia (n = 3).

This 8-week trial shows that reboxetine is an effective alternative in the treatment of SP and that its therapeutic action starts in the early stage. Both HAM-A and total LSAS scores significantly decreased during the 8-week treatment period. However, we should note that, as in any open-label trial, the results found may have been due to nonspecific effects and not due to the drug itself. The fact that selective and nonselective monoaminooxidase inhibitors considerably affecting 5-HT receptors are effective in the treatment of SP has led us to focus on the serotonergic system. The efficacy of selective serotonin reuptake inhibitors has been considerably shown.[9,10] On the other hand, the role of the noradrenergic system in SP remains unclear. Neuroendocrine investigations have been performed by using clonidine as a

TABLE 1. HAM-A, LSAS-Fear, and LSAS-Avoidance Scores During Treatment*

Weeks	HAM-A	LSAS-Fear	LSAS-Avoidance
0	27.9 ± 6.1	61.9 ± 6.8	64.1 ± 7.9
2	23.4 ± 6.8†	54.2 ± 7.2†	62.3 ± 7.4
4	19.3 ± 7.2‡	48.3 ± 7.8‡	50.8 ± 8.2‡
8	16.5 ± 6.3§	31.7 ± 8.1§	32.1 ± 8.7§

*Used paired *t* test (comparing with baseline at weeks 2, 4, and 8).
†$P < 0.05$.
‡$P < 0.01$.
§$P < 0.001$.

challenge to growth hormone response as a measure to assess noradrenergic function and have exhibited contradictory findings. Tancer and Uhde[16] reported that patients with SP and panic disorder showed blunted growth hormone response compared with controls, but this could not be replicated in their other study.[17] Actually, both reversible and irreversible monoaminooxidase inhibitors already inhibit the metabolism of norepinephrine and dopamine in addition to serotonin (5-HT). Although tricyclic antidepressants having serotonergic and noradrenergic enhancement impact have not had useful effects on SP, venlafaxine, a compound of dual 5-HT and norepinephrine reuptake inhibitor, has been found to be effective at the dosage of 150 mg/d at which the noradrenergic activity occurs.[12] In addition, in a case study, Goldstein[18] reported that a patient with SP was successfully treated with clonidine. In the present study, the response rate (66.7%) was comparable with the trials that used selective serotonin reuptake inhibitor. This considerable efficacy of reboxetine provides further support for the involvement of the noradrenergic system in SP. In summary, our results suggest that reboxetine is effective and well tolerated by patients with SP. The main limitations of the present study are limited sample size and uncontrolled design of clinical assessment and treatment. Controlled trials are required to confirm the efficacy of reboxetine for SP.

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