

Comparison of Reboxetine and Sertraline in Terms of Efficacy and Safety in Major Depressive Disorder

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SUMMARY

Objective: To compare the efficacy, safety and tolerability of reboxetine and sertraline in major depressive disorder (MDD).

Method: The study subjects consisted of 41 patients who met the DSM-IV MDD diagnostic criteria. Patients were randomly assigned to receive either reboxetine or sertraline. During the study the patients were assessed 6 times (baseline visit=day 0, visit 1=day 8, visit 2=day 22, visit 3=day 36, visit 4=day 57 and visit 5=day 78) over 11 weeks. Antidepressant response was measured by the Hamilton Depression Rating Scale (HDRS), Clinical Global Impressions-Severity of Illness (CGI-SI) and Global Impressions-Global Improvement (CGI-GI).

Results: Comparing the two groups in terms of response and remission (HAM-D $\leq$ 10) measures, the results were in favour of the reboxetine group at visits 2, 3 and 4. At visit 5, the scores were similar and no statistically significant difference was found between the two groups. However, when remission was evaluated as HAM-D $\leq$ 7, a significant statistical difference was found in favour of the reboxetine group. Evaluating the side effects, dry mouth, sweating, palpitation, headache, hot flushing and sedation were more frequent in the reboxetine group. Only one patient, in the reboxetine group, dropped out due to a side effect (constipation).

Conclusion: Higher rates of full remission achievement, which is the main target of MDD treatment, in the reboxetine group compared with the sertraline group may be due to the suppression of anxiety symptoms by the noradrenergic feature of the drug. In order to understand the role of the noradrenergic system in treating MDD, larger patient samples are needed. Both reboxetine and sertraline were well tolerated and effective in treating MDD.

Key Words: Depression, reboxetine, sertraline

INTRODUCTION

Major Depressive Disorder (MDD) is a destructive disorder which results in physical and psychological disability. It is a common and chronic disorder which has high rates of relapse and recurrence (Kessler et al. 1994).

In recent years, among the neurotransmitters related to physiopathology of depression, serotonin and noradrenaline have been the subject of interest. Serotonin and noradrenaline are reported to be equally significant in physiopathology of depression (Kırlı 2000a, Tamam and Zeren 2002).

Tricyclic antidepressants (TCA) which have been in use for many years effect both serotonin and noradrenaline neurotransmitter systems. However they are not selective and there is a great problem of side effects. Selective Serotonin Reuptake Inhibitors (SSRI) are the first antidepressants which were developed in order to decrease side effects and safety problems and increase compliance (Anderson 2000, anderson 2001). Antidepressant efficacy of sertraline, one of the SSRI, has been shown in many clinical studies (Shelton 1994, Montgomery 1995, Fabre et al. 1995, Feiger et al. 1996, Arık et al. 1996, Lydiard et al. 1997, Ekselius et al. 1997).

Several studies, investigating effects of SSRI, have shown that not only SSRI but all antidepressants effect through serotonergic system As a conclusion, the role of noradrenaline in depression lost its significance (Delgado and Moreno 2000).

It has been reported in many studies that SSRI were not as effective as TCA in treatment of depression (Danish University Antidepressant Group 1986, 1990, Roose 1994, Anderson 2000, Faravelli et al. 2003). Considering prominent effects of TCA on noradrenergic system, researchs in different directions were employed (Schatzberg 2000, Scates and Doraiswamy 2000). According to contemporary information about depression, there is an impairment in noradrenergic system and this system interferes with various neurotransmitters which may have a role in symptomatology (Leonard 200, Anand and Charney 2000). Thus, the antidepressant effect of reboxetine which is a selective noradrenaline reuptake inhibitor (NRI) (Baldwin and Carabal 1999, Schatzberg 2000, Scates and Doraiswamy 2000, Baldwin et al. 2000) has significance for that reason (Berzowski et al. 1997, Ban 1998, Katona et al. 1999, Maio and Johnson 2000, Montgomery et al. 2003). Development of reboxetin lead to an increase in studies about the role of noradrenaline in depression (Montgomery 1997a).

Comparative studies with selective drugs on serotonin and noradrenaline systems which seem to have important roles in physiopathology of MDD are very limited. There are some studies performed with fluoxetine (Dubini et al. 1997, Massana 1998, Andreoli et al. 2002) and paroxetine (Ferguson et al. 2003), but there is not any study which compare sertraline and reboxetine.

In this study we aimed to compare sertraline which inhibits serotonin reuptake and is proposed as first line treatment of depression (Gourion et al. 2004) with reboxetine which inhibits noradrenaline reuptake and to investigate the role of noradrenaline in treatment of depression.

MATERIALS AND METHOD

Subjects

The participants were randomly chosen from patients who applied to Uludağ University Medical School Psychiatry outpatient clinics between May 1st, 2003 and May 1st, 2004 and were diagnosed as MDD according to Diagnostic and Statistical Manual, 4th edition (DSM-IV, American Psychiatry Association 1994) and met inclusion criteria of the study. The participants were randomized into two treatment groups. Forty nine patients were included at the beginning, but only 20 patients from

reboxetine group and 21 patients from sertraline group (totally 41 patients, 33 females and 8 males) completed the study. Approval from ethic committee was obtained before beginning the study.

Inclusion Criteria: MDD patients (18-65 years of age), whose scores from Hamilton Depression Rating Scale-17 items (HDRS) were at least 16 and who gave written informed consent were included in the study. Patients selected, in the screening visit, were reevaluated in the first visit and the ones whose HDRS scores were still at least 16 or did not decrease more than 30% of the measurement in the screening visit and who still met the criteria of the study were included to subject group.

Exclusion Criteria: Patients who had psychotic symptoms, who did not response to reboxetine or sertraline treatment previously, who had positive history of pharmacotherapy resistant depression (continuity of current depressive attack despite the use two different antidepressants at appropriate doses and duration), who had electroconvulsive therapy within the last six months, who met the criteria any of bipolar affective disorder, cyclothymia, dysthymia, personality disorder or double depression according to DSM-IV measures, who had clinically significant physical or laboratory findings, diseases of gastrointestinal, hematological or cardiovascular systems, urinary retention or glaucoma were excluded from the study. Moreover, individuals who had chronic respiratory insufficiency within last six months, who had positive history for any significant clinical condition, convulsion or cranial trauma, who had any anomaly which could influence on absorption, distribution, metabolism and excretion of the agent, who had positive history for hypersensitivity especially against psychotropic drugs, who had risk for suicide, had depression due to endocrine causes or females with child bearing potential and who did not use any effective contraceptive method or who were pregnant or lactating were excluded as well

Procedure

This study was an open label, uncontrolled, single centre study. Neither the physicians nor the patients were blinded to treatment modality. During the study, the patients were evaluated for six times; screening visit (Day 0), visit 1 (Day 8), visit 2 (Day 22), visit 3 (Day 36), visit 4 (Day 57) and visit 5 (Day 78). In screening visit, all patients underwent detailed psychiatric evaluation and were

TABLE 1. Characteristics of patients excluded from both groups.

	Absence of effect	Lost in follow up	Unrelated with medical reasons	Side effects	Total
Reboxetine group	1 (V4)	1 (V2) 1 (V3)	1 (V3)	1 (V3)	5
Sertraline group	0	1 (V2) 1 (V4)	1 (V3)	0	3

V: Visit (the numbers of visits are written in paranthesis).

reviewed for compliance with DSM-IV criteria for MDD diagnosis. Their sociodemographic characteristics were recorded. A physical examination consisting routine blood and urine examinations, electrocardiogram, x-ray of the lungs and measurement of vital signs was employed for all patients at screening visit. HDRS and Clinical Global Impression-Severity Index (CGI-SI) were administered to all patients at the screening visit. No treatment was administered for a week and then the same scales were administered and vital signs were measured again at visit 1. Patients who met inclusion criteria received sertraline 50 mg/day once a day or reboxetine 4 mg/day doses twice daily (b.i.d.). The patients continued to take these drugs at the same doses for two weeks. At the second visit sertalaine dose was not changed, but reboxetine dose was increased to 8 mg/day (b.i.d.) level. The doses remained at that level for eight weeks. The patients received the drugs for 10 weeks and at the end of 11th week the study was completed. Physical examination with the same content was repeated at final visit.

Data Handling Instruments

In order to measure antidepressant efficacy 17 items HDRS, CGI-SI and Clinical Global Impression-Global Improvement (CGI-GI) scales were used. HDRS and CGI-SI scales were administered at screening visit and visits 1, 2, 3, 4 and 5 in order to evaluate the efficacy of the treatments. Moreover, CGI-GI scale was administered at all visits other than screening visit and visit 1. Presence of response was defined as the decrease in HDRS score $\geq 50\%$ when compared with the beginning and remission was defined as HDRS scores ≤ 7 or ≤ 10 at the end of the study. In order to determine which items were responsible from the differences

in HDRS scores between two treatment groups, the items of HDRS were combined to form clusters. These clusters were as following; Anxiety-somatization cluster: The summation of HDRS items no. 10 (Psychic anxiety), 11 (Somatic anxiety), 12 (Somatic symptoms-Gastrointestinal), 13 (Somatic symptoms-General), 15 (Hypochondriasis) and 17 (self perception); Sleep cluster: The summation of HDRS items no. 4 (unable to sleep), 5 (awakening at midnight) and 6 (awakening early in the morning).

Hamilton Depression Rating Scale: It has been developed by Hamilton and colleagues in order to determine the severity of depression in patients from all age groups (1960). Turkish validity and reliability study was performed by Akdemir and colleagues (1996).

Clinical Global Impression Scale: It has been developed by Guy and colleagues in order to evaluate the course of psychiatric disorders in patients from all age groups (1976). It is a three dimensional scale and completed during semi-structured interview in which the physician evaluates therapeutic responses of patients with psychiatric disorders:

I. CGI-SI: This scale had seven values. The patients were evaluated between 1-7 points according to the severity of current psychiatric disease. 1=Normal, not at all ill, 2=Borderline mentally ill, 3=Midly ill, 4=Moderately ill, 5=Markedly ill, 6=Severely ill, 7=Among the most extremely ill subjects.

II. CGI-GI: This scale had seven values. The patients were evaluated between 1-7 points according to the change in psychiatric disease since the beginning of the study. 1=Very much improved,

TABLE 2. Sociodemographic characteristics and their relationships with “Major Depressive Disorder” of Reboxetine and Sertraline groups.

	Reboxetine Group (n=20)	Sertraline Group (n=21)
Gender		
Female	15 (75%)	18 (85.7%)
Male	5 (25%)	3 (14.3%)
Age	41,3 ± 9,1 (23- 54)	40 ± 13,7 (23- 65)
Height (cm)	164,8±8,5 (148-183)	164,6±6,2 (152-175)
Weight (kg)	69,1 ± 11,6 (53-94)	67,1±15,1 (39- 110)
Duration of current attack (months)	5,6 ± 3,34 (2-12)	4,4 ± 2,7 (1- 9)
Time over first depressive attack	1,3 ± 1,6 (0,16-6)	2,2± 4,7 (0,1-19)
Number of attacks		
One	15 (75%)	16 (72.2%)
Two	3 (15%)	5 (23.8%)
Three	2 (10%)	-
Educational level		
Literal	-	1 (4.8%)
Primary school	7 (35%)	5 (23.8%)
Secondary school	1 (5%)	-
High school	4 (20%)	5 (23.8%)
College	8 (40%)	10 (47.6%)
Triggering factor in last attack		
Present	15 (75%)	15 (71.4%)
Absent	5 (25%)	6 (28.6%)
Family history for depression		
Present	4 (20%)	3 (14.3%)
Absent	16 (80%)	18 (85.7%)
Hospitalization for the study		
Yes	3 (15%)	2 (9.5%)
No	17 (85%)	19 (90.5%)
Hospitalization history due to depression		
Yes	2 (10%)	-
No	18 (90%)	21 (100%)
Type of depression		
*296.22	13 (65%)	13 (61.9%)
*296.23	2 (10%)	3 (14.3%)
*296.32	3 (15%)	3 (14.3%)
*296.33	2 (10%)	2 (9.5%)
Type of attack		
Melancholic	18 (90%)	16 (76.2%)
Atypical	2 (10%)	5 (23.8%)

*DSM-IV 296.22: Major Depressive Disorder, single attack, moderate severity; *DSM-IV 296.23: Major Depressive Disorder, single attack, severe, psychotic symptoms are absent; *DSM-IV 296.32: Major Depressive Disorder, repetitive, moderate severity (present attack); *DSM-IV 296.23: Major Depressive Disorder, repetitive, severe (present attack), psychotic symptoms are absent.

2= Much improved, 3=Minimally improved, 4=No change, 5=Minimally worse, 6=Much worse, 7=Very much worse.

III. Clinical Global Impression-Efficacy: This scale which was evaluated over four points was

not used in this study.

Safety measurement: In order to evaluate the safety of the treatment administered physical examination, vital sign measurements and laboratory evaluations were performed. Moreover, side ef-

TABLE 3. Evaluation of changes in HDRS, CGI-SI and CGI-GI values in reboxetine and sertraline groups.

Scales		Screening Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
HDRS	Reboxetine	22.4±3.84	22.15±3.66	16.05±3.81	11.50±5.59	7.85±4.10	6.55±5.23
	Sertraline	21.33±3.11	20.71±2.90	18.28±2.90	14.76±2.18	11.33±2.26	7.76±2.89
CGI-SI	Reboxetine	4.90±0.55	4.90±0.55	4.25±0.63	3.45±0.99	2.80±1.05	2.20±1.32
	Sertraline	4.47±0.67	4.47±0.67	4.19±0.40	3.80±0.40	2.85±0.79	1.95±1.02
CGI-GI	Reboxetine	a	a	3.40±0.59	2.50±0.68	2.05±0.68	1.55±0.88
	Sertraline	a	a	3.14±0.47	2.66±0.57	1.76±0.76	1.28±0.56

a: CGI-GI was marked as “unevaluable” in screening visit and visit 1, there were not points for them. $p \leq 0.01$, $p \leq 0.001$

fects report forms which depended on self expressions of patients were filled up at visits 2, 3, 4 and 5. The severity of side effects and the need for additional interventions were assessed with these forms. All scales and forms were administered by the same investigator.

Statistical analysis

Data of 41 patients who completed the study were entered to the computer and processed with SPSS for Windows Version 10.0. Categorical data were presented as frequency (n, %) and continuous data were presented as mean $\pm$ standard deviation. Comparisons between different treatment modalities were performed with t-test in independent groups and Mann-Whitney U test, if needed. Comparisons of categorical data were realized with Pearson's chi-square test, Fisher's Exact chi-square test and Kolmogorov-Smirnov test. The changes in mean values of drug groups by time were evaluated with matched t-test and when normalization proposal was not met Wilcoxon test. Cluster of anxiety-somatization items of HDRS was evaluated with single directional variance analysis in repeated measurements following correction of Greenhouse-Geisser. The level of significance was

accepted as 0.05 in all analyses.

FINDINGS

Patients who were excluded from the study were presented in details at Table 1. Totally 8 patients (5 from reboxetine and 3 from sertraline groups) could not complete the study. Thus, 20 patients who received reboxetine and 21 patients who received sertraline (totally 41 patients) were included in the study.

Sociodemographic characteristics and MDD related specifications of the groups were presented in Table 2.

Sociodemographic characteristics, type of depression, years passed since first attack, attack characteristics and duration were similar in both groups. Body temperature, pulse, weight and blood pressure measurements did not significantly change in or between both groups at the beginning and end of the study. Mean HDRS and CGI-SI scores were similar in both groups at the beginning of the study (Table 3).

Mean scores of HDRS, CGI-SI and CGI-GI

TABLE 4. Evaluation of values for Anxiety-Somatization and Sleep items in reboxetine and sertraline groups.

Scales		Screening Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
A-S	Reboxetine	7.10±1.37	6.80±1.61	4.75±1.44	3.50±1.27	2.45±0.99	2.30±1.26
	Sertraline	5.95±1.36	5.67±1.24	5.52±1.47	5.28±1.23	4.23±0.99	3.38±1.02
Sleep	Reboxetine	2.65±1.38	2.60±0.99	2.25±1.37	1.60±1.35	0.95±1.10	0.65±0.87
	Sertraline	3.0±1.14	3.0±0.95	2.66±1.23	1.85±0.96	1.81±0.68	1.05±0.67

A-S: Cluster of anxiety-somatization items; Sleep: Cluster of sleep items. $p \leq 0.01$, $p \leq 0.001$

TABLE 5. Distribution of side effects which were more frequent than 10% in reboxetine and sertraline groups.

Side effect	Reboxetine	Sertraline	p value
Dry mouth	13 (65%)	1 (4.8%)	<0.001
Sweating	7 (35%)	-	=0.003
Palpitation	6 (30%)	-	=0.009
Headache	6 (30%)	1 (4.8%)	=0.045
Flushing	4 (20%)	-	=0.048
Sleeplessness	4 (20%)	1 (4.8%)	>0.05
Constipation	3 (15%)	-	>0.05
Nausea	1 (5%)	5 (23.8%)	>0.05
Increase in dullness	5 (25%)	5 (23.8%)	>0.05
Sedation	4 (20%)	-	=0.048

scales at each visit were presented in Table 3. Statistical significance levels of the changes in scores between visits were presented as well. Decreases in HDRS and CGI-SI scores between screening visit and visit 2 and subsequent visits and in CGI-GI

scores between visit 2 and visit 3 and subsequent visits were found to be statistically significant in both treatment groups ($p \leq 0.01$).

Comparisons between reboxetine and sertraline groups according to the changes in HDRS, CGI-SI and CGI-GI scales in time were performed by calculating the percentages of decreases at each visit with respect to screening visit. Decreases expressed as percentages in HDRS scores at visits 2, 3 and 4 with respect to screening visit were significantly higher in reboxetine group (26.2, -49, -63.98 respectively) than sertraline group (-15.38, -31.57, -47.36 respectively) ($p \leq 0.001$) (Figure 1). Decreases expressed as percentages in CGI-SI scores at visits 2 and 3 with respect to screening visit were significantly higher in reboxetine group (-18.33, -22.5 respectively) than sertraline group (0, -20 respectively). In CGI-GI scale, changes in time were not found to be different in reboxetine and sertraline groups.

Values for clusters of anxiety-somatization and sleep items of HDRS and statistical significance of changes in each visit with respect to screening visit were presented in Table 4. Values for anxiety-somatization cluster decreased significantly at visits

FIGURE 1. Distribution of changes in HDRS values in percentages when compared with screening visit in reboxetine and sertraline groups.

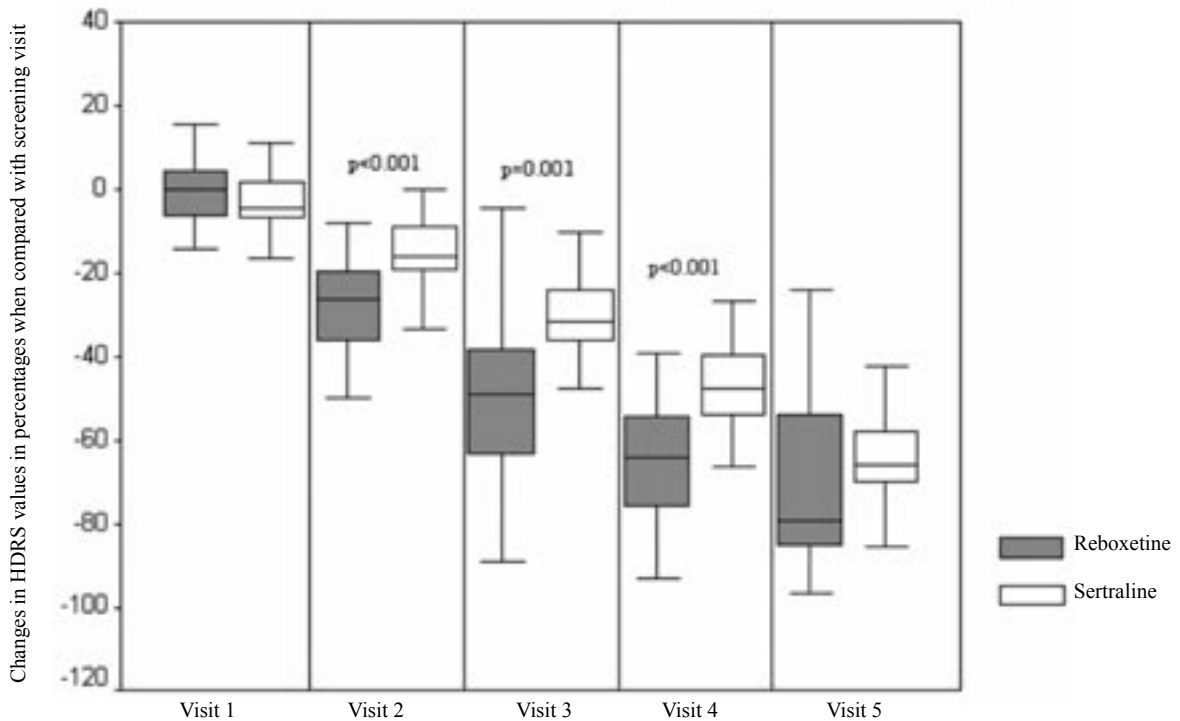
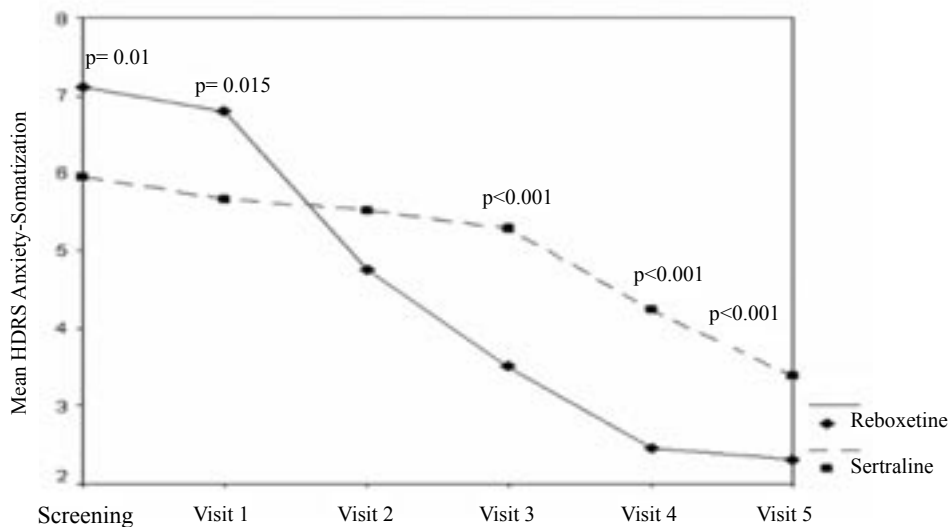


FIGURE 2. Mean values for cluster of HDRS Anxiety-Somatization items in reboxetine and sertraline groups according to visits.



2, 3, 4 and 5 with respect to screening visit in reboxetine group ($p<0.001$), but only at visits 4 and 5 in sertraline group ($p<0.001$). There were statistically significant decreases in values for sleep cluster at visits 3, 4 and 5 in both groups ($p\leq 0.01$).

Values for anxiety-somatization cluster at visit 1 with respect to screening visit were significantly higher in reboxetine group than sertraline group ($p<0.05$). The values at visit 2 were lower in reboxetine group also, but the difference was not statistically significant. The decreases in reboxetine group at visits 3, 4 and 5 were significantly higher than sertraline group ($p<0.001$) (Figure 2).

When items of anxiety-somatization cluster were compared separately between two groups, values of item 10 at screening visit and items 10 and 13 at visit 1 were significantly higher in reboxetine group ($p<0.05$); values of item 12 at visit 2 and items 10, 11, 12 and 13 at visits 3 and 4 and items 10 and 13 at visit 5 were significantly lower in the same group ($p<0.05$).

There was not any statistically significant difference between treatment modalities for the changes in values of sleep cluster with respect to screening visit.

When remission ratios were evaluated, it was shown that there were statistically significant differences in favor of reboxetine group at visits 3 (45% vs 0%) and 4 (80% vs 28.6%) when remis-

sion was accepted as HDRS scores ≤ 10 ($p\leq 0.001$). This difference disappeared at visit 5 and remission levels were similar at both groups (75% vs 81%). When remission was accepted as HDRS scores ≤ 7 , there were statistically significant differences in favor of reboxetine group at visits 3 (35% vs 0%), 4 (50% vs 4.8%) and 5 (70% vs 38.1) ($p<0.05$) (Figure 3).

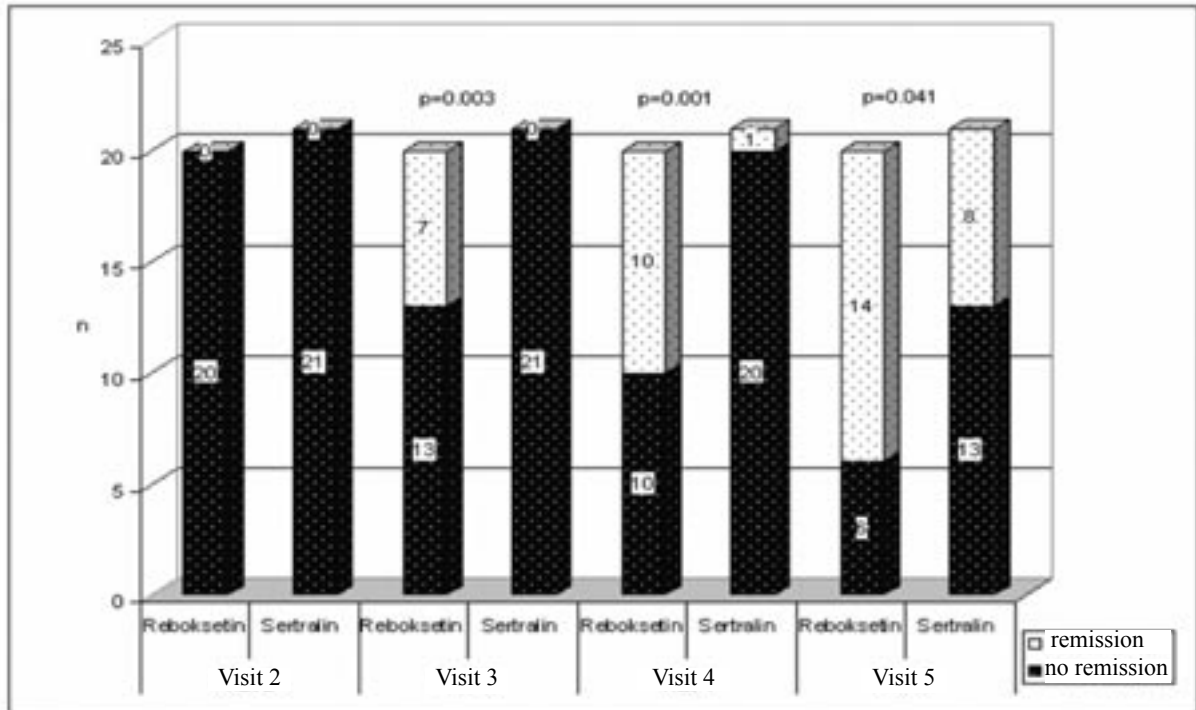
When we accepted decreases in HDRS scores $\geq 50\%$ with respect to screening visit as the presence of response, it was shown that there were statistically significant differences in favor of reboxetine group at visits 3 (50% vs 0%) and 4 (90% vs 42.9%) ($p\leq 0.001$). Both groups showed similar response rates at visit 5 (80% and 81% respectively).

When both groups were compared for side effects, it was shown that dry mouth, sweating, palpitation, head ache, flushing and sedation were more frequent in reboxetine group ($p<0.05$) (Table 5). One patient from reboxetine group was dropped out from the study at visit 3 due to side effect (constipation).

DISCUSSION

In this study two antidepressants which have selective effects on noradrenalin and serotonin were compared and it was shown that clinical response and remission were earlier with reboxetine and there was a significant difference in favor of

FIGURE 3. Distribution of patients who showed remission (remission: HDRS $\leq$ 7) according to visits in reboxetine and sertraline groups.



reboxetine when remission criterion was accepted as HDRS $\leq$ 7.

We did not meet any other study in which efficacies of reboxetine and sertraline were compared. In two other studies which were performed with an other SSRI, fluoxetine, efficacies were found to be close to each other. But, Massana and colleagues (1998) reported that reboxetine was more effective in severe depression subgroup. Response rates of reboxetine (80%) and sertraline (81%) were consistent with the study of Massana and colleagues (78% for reboxetine and 74% with fluoxetine, but different from the findings of Andreoli and colleagues (2002) (55.6% for reboxetine and 56.3% for fluoxetine). It should be taken into account that sampling sizes of both studies were considerably larger than ours. Moreover, our findings were consistent with some other studies; Versiani and colleagues reported response rates for reboxetine as 76% and 74% in two separate studies (1999, 2000) and Sechter and colleagues (1999) reported response rates as 74% for sertraline.

Remission criterion HDRS $\leq$ 10, remission criterion HDRS $\leq$ 7 and response rates at visit 3 were found as 0% in sertraline group and 45%, 35% and 50% respectively in reboxetine group. These

findings were consistent with general information about SSRI which stated that their effects began 3-8 weeks later (Kırlı 2000b) and the study of Suri and colleagues (2000) which reported response rate and remission criterion HDRS $\leq$ 7 for sertraline as 0% at 4th week. The level of remission achieved by sertraline at the end of the study was similar with the findings of Stahl (2000) (37%, 12 weeks duration, remission criterion HDRS $\leq$ 8) and Schweizer and colleagues (2001) (32%, 11 weeks duration, remission criterion HDRS $\leq$ 8).

Recently, it was emphasized that response rates were not adequate and residual symptoms might remain in MDD. Partial remission was found to be possibly related with high relapse rates, severe dysfunction and suicide risk (Bakish 2001). remission was a concept which was found in efficacy comparison studies where residual symptoms were absent (Ferrier 2001). When remission criterion was accepted as HDRS $\leq$ 10, both drugs were similar, but if HDRS $\leq$ 7 level was accepted as remission criterion as many other studies, there was a significant difference in favor of reboxetine (70% vs 38.1%). In the study of Yazıcı and colleagues (1993) which compared maprotiline and klomipramine (effective selectively on noradrenergic and

serotonergic systems), there was not any difference between two drugs in means of efficacy.

In order to determine the source of superiority of reboxetine, items and clusters of items of HDRS were analyzed and it was shown that the effect of reboxetine on anxiety-somatization cluster was more prominent than sertraline. It was considered that anxiety was responsible from the severity of MDD and cluster of anxiety items was found to be related with the severity of depression (Gibbons et al. 1993). In order to achieve remission, removal of anxiety symptoms was reported to have great importance (Fawcett 1997). Concurrence of anxiety besides MDD was reported to lead sudden changes in affective condition, increase in suicide and relapse rates and negative therapeutic results (Roy-Byrne 1996). Positive effects of reboxetine on anxiety-somatization cluster supported the data about drugs which altered noradrenaline transport were as effective as drugs which altered serotonine transport in treatment of anxiety (Silverstone 2004, Akkaya et al. 2004a and 2004b, Dunner et al. 2003).

In the comparison of side effects dry mouth, sweating, palpitation, head ache, flushing and sedation were more prominent in reboxetine group, but urinary retention which was reported in some other studies (Kasper and Wolf 2002, Demyttenaere K et al. 2001, Szabadi 1998) was not present in

reboxetine group. Relatively higher rates of side effects in reboxetine group might be due to noradrenergic effects. This higher rate of side effects was interpreted as compliance of reboxetine might be lower than sertraline.

As this study is open labeled, it has some limitations. The ratio for investigator faults may be higher due to lack of double blind fashion. Comparisons which have not statistical significance, but have a tendency towards this direction may have greater consistency and data evaluation with different statistical methods can be possible by increasing sample size.

As a conclusion, main objective of treatment is to achieve complete functioning. To be closer to that objective means lower relapse rates. Higher remission rates which were obtained with reboxetine in this study showed its superiority to sertraline. This superiority was due to positive changes in anxiety-somatization cluster of HDRS and revealed anxiety removing effect of noradrenaline transport system and was interpreted as reboxetine was a good therapeutic choice for MDD. Further controlled studies with greater patient population which compare the effects of agents which work on noradrenergic system with others which work on serotonine system, may lead to determination of the place of noradrenergic antidepressants in treatment chart of MDD.

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