Comparison of The Efficacy and Safety of Sertraline, Reboxetine, and Venlafaxine in Patients with Major Depressive Disorder: A Pooled Analysis of Four Randomized, Open-Label Trials

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ÖZET:

Major depresif bozukluk'ta sertralin, venlafaksin ve reboksetinin etkiliği ve güvenilirliğinin karşılaştırılması: dört randomize, açık çalışmanın verilerinin analizi

Amaç: Bu araştırma major depresif bozukluk (MDB) tedavisinde sıkça kullanılan sertralin, reboksetin, venlafaksin ve sertralin-reboksetin kombinasyonunun depresif belirtiler üzerine etkisi ile bu tedavilerin etkililik ve güvenlik açısından birbiriyle karşılaştırılmasını amaçlamıştır.
Yöntem: Daha önceki dört çalışmaya alınmış ve bu çalışmaları tamamlamış hastaların verileri bir arada değerlendirilmiştir. 206 hasta reboksetin, venlafaksin, sertralin ve sertralin-reboksetin kombinasyon gruplarına dahil edilmiş olup 37 hasta çalışmaları tamamlayamamıştır. Kalan 169 hastanın 43'er tanesi reboksetin ve venlafaksin, 42'si sertralin, 41'i sertralin- reboksetin kombinasyon grubunda yer almaktaydı.
Bulgular: MDB klinik özellikleri ile sosyodemografik özellikler açısından gruplar arasında fark yoktu. Hamilton Depresyon Derecelendirme Ölçeği (HAM-D) değerlerindeki yüzdelik düşüş venlafaksin grubunda vizit 2 ve 3'te sertraline göre [sırasıyla p=0.001, ES: 0.1404 (büyük) ve p=0.002, ES: 0.1109 (orta)] ve sertralin-reboksetin kombinasyonuna göre vizit 2 ve 3'te [sırasıyla p=0.006, ES: 0.0910 (orta) ve p=0.004, ES: 0.1023 (orta)] daha yüksek olduğu saptanmıştır. Yine HAM-D değerlerindeki yüzdelik düşüş reboksetin grubunda sertraline göre vizit 2'de daha yüksek bulundu [p=0.02, ES: 0.0615 (orta)]. En sık rastlanan kalıntı belirtileri 1., 7., 10., 11., 13., ve 14. HAM-D maddeleriydi.
Sonuç: Farklı nörotransmiter mekanizmaları üzerinden etki etmekle beraber bu çalışmadaki antidepresanlar benzer etkililik göstermişlerdir. Bununla beraber her tedavi yöntemi farklı belirti ve belirti grupları üzerinde etkili bulunmuş, antidepresan etkililiğin ortaya çıkış zamanları açısından farklılık göstermişlerdir. Bir takım kısıtlılıklarına karşın, bu alandaki çalışmaların az olması da göz önüne alındığında, bu çalışmanın bir ön çalışma olarak literatüre katkı sağlayacağı kanısındayız.

Anahtar sözcükler: Unipolar depresyon, antidepresan, nörotransmiter, reboksetin, sertralin, venlafaksin

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ABSTRACT:

Comparison of the efficacy and safety of sertraline, reboxetine, and venlafaxine in patients with major depressive disorder: a pooled analysis of four randomized, open-label trials

Objective: This paper aims to compare the efficacy and safety of three widely used antidepressants, sertraline, reboxetine, a sertraline-reboxetine combination and venlafaxine, in the treatment of MDD and their effect on depressive symptoms in MDD patients.
Methods: A total of 206 patients were included in reboxetine, venlafaxine, sertraline, and sertraline-reboxetine combination groups; however 37 cases dropped out during the study period. The remaining 169 patients were distributed to groups as follows: reboxetine: 43, venlafaxine: 43, sertraline 42, sertraline-reboxetine combination group: 41. The data from patients, who were included and completed the previous four open-label studies, were pooled in the current study.
Results: Treatment groups did not differ in terms of depression-related and sociodemographic features. There were no significant differences among treatment groups in terms of efficacy, safety, and remission. The reductions in HDRS scores as percentages were higher in venlafaxine group compared to sertraline group at visit 2 and visit 3 [p=0.001, ES: 0.1404 (large) and p=0.002, ES: 0.1109 (medium), respectively] and to the sertraline-reboxetine combination group at visit 2 and visit 3 [p=0.006, ES: 0.0910 (medium) and p=0.004, ES: 0.1023 (medium), respectively]. In addition, percentage changes of HDRS scores were higher in the reboxetine group compared to sertraline group at visit 2 [p=0.023, ES: 0.0615 (medium)]. HDRS items 1, 7, 10, 11, 13, and 14 formed the total HDRS score of all patients in remission.
Conclusions: The antidepressants acting through different neurotransmitter systems display similar efficacy, though they are effective on different depressive symptoms or symptom clusters. Those treatment strategies also differed from each other in terms of onset of antidepressant efficacy. Despite its limitations, due to the lack of studies on this issue in the literature, the present stuydy is a valuable preliminary study.

Key words: Unipolar depression, antidepressant, neurotransmitters, reboxetine, sertraline, venlafaxine

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INTRODUCTION

Major Depressive Disorder (MDD) is a common mental disorder with severe socio-economic consequences and a high recurrence rate (1). Although the complex pathophysiology of MDD remains unknown, it has been suggested that, dysfunction in adrenergic and/or serotonergic systems, which modulate a wide range of neurological processes, may lead to MDD development (2). This notion has been supported by the fact that almost every compound, that has been used for the purpose of inhibiting noradrenaline and/or serotonin reuptake, has

been proven to be clinically effective as an antidepressant (3). Since all neuronal systems interact with each other, it is hard to target a specific system or body region without affecting the other systems. In addition to the effects and roles of antidepressant agents in central nervous system, they also act as antagonists of many different neuronal receptors such as muscarinic-cholinergic, adrenergic, and histaminergic receptors in the periphery (4-7). The associations between neuronal receptors in other body regions and antidepressant agents results in the development of side effects during antidepressant therapy. Therefore, the effect and side effect profiles differ depending on the class of antidepressant. Noradrenergic antidepressants are associated with side effects such as dry mouth, constipation, insomnia, flushing, and hypotension; whereas serotonergic antidepressants cause nausea and diarrhea. Moreover, noradrenergic antidepressants have been reported to have prominent effects on motivation and drive (8,9), which might be reflected in the improvement in loss of interest, anhedonia, lack of energy, or motor retardation. On the other hand serotonin reuptake inhibitors have been reported to improve anxiety and mood in depressed patients (10). Although, there are numerous approaches for the treatment of MDD, no gold standard treatment has been identified so far, and the choice of drugs still remains a challenge for physicians.

Though it is suggested that all kinds of antidepressant treatments have similar efficacy (11), clinical trials demonstrate different outcomes. Moreover, the effects of antidepressants with different pharmacological properties in specific populations, such as women, have recently become the target of research (12,13). Sertraline is a widely used, selective serotonin reuptake inhibitor (SSRI) agent that has antidepressant efficacy in MDD (14,15) as well as in other psychiatric conditions (16-19). Reboxetine is a selective noradrenaline reuptake inhibitor and is also known to be effective in the treatment of MDD (20,21,); however, comparative clinical trials conducted on reboxetine have revealed contradictory results. A multiple randomized, double-blind, parallel group study by Langworth et al. (2) demonstrated no significant difference between reboxetine and SSRIs. In two meta-analyses Papakostas et al. (22,23) reported no evidence of difference in response rates between reboxetine and SSRIs. Nevertheless, there are also many studies reporting clinically superior efficacy of reboxetine over both placebo and SSRIs (24,25). Venlafaxine is a selective serotonin and noradrenaline inhibitor (SNRI) and is often effective in depression unresponsive to SSRIs (26). Moreover, many studies have reported that the 'dual action' agent venlafaxine has a superior efficacy over the 'single action' SSRIs (27-29). In addition, superior remission rates in favour of venlafaxine compared to SSRIs have been reported recently with or without regard to the baseline severity of depression (30). However, some trials have reported no significant difference between the two types of antidepressants in terms of efficacy (23, 31-33).

Despite the currently used treatment strategies, 15-30% of major depressive patients still fail to respond to antidepressant mono-therapies (34). There are frequently preferred strategies such as augmentation of a serotonergic antidepressant with another agent from a different class of antidepressant or switching the treatment to a dual-acting antidepressant in order to achieve remission. It is reported that the combination of serotonergic and noradrenergic antidepressant is effective in the treatment of depression not responding to either class when used alone (34,35); however, the mechanism of action has not been clarified yet.

The objective of the present study is to compare the efficacy and safety of sertraline, reboxetine, venlafaxine, and a sertraline-reboxetine combination in the treatment of MDD and their effects on depressive symptoms in a group of MDD patients.

PATIENTS AND METHODS

Patient population

Subjects were recruited from the databases of four previous studies with the same study design. These studies compared reboxetine and venlafaxine (36), reboxetine and sertraline (24), venlafaxine and a combination of reboxetine and sertraline (37), and sertraline and a combination of reboxetine and sertraline (data on file). The data from the patients who completed the above mentioned studies were included in the current study.

According to the patient eligibility criteria of the 4 above mentioned 4 studies, patients aged 18–65 years who were diagnosed with MDD, determined on the basis of the

Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Text Revision (DSM-IV-TR) (38), were eligible for participation in the present study. The patients in these four studies had been required to have a score of at least 16 at baseline on the 17-item Hamilton Depression Rating Scale (HDRS) (39). Patients fulfilling the criteria for a DSM-IV Axis I disorder other than MDD or a DSM-IV Axis II disorder, patients having MDD with psychotic features or patients with a history of psychosis, and patients with significant suicide risk were excluded from the study. Patients who had not responded to venlafaxine, reboxetine or sertraline in previous episodes of depression, patients who had a history of treatment resistance (continuation of the depressive episode despite the use of two different antidepressants at adequate dose and duration), patients who had electroconvulsive therapy within the previous 6 months, patients whose HDRS had decreased by more than 30% between screening and baseline assessments, patients having a history of drug sensitivity (especially to psychotropic drugs) and patients with any clinically significant medical disorder or laboratory abnormality were not eligible for participation in the present study. Women were excluded if pregnant or if not using a reliable method of contraception throughout the study.

Study design

The data of the previous four studies were pooled. These four studies had been designed as open-label studies; thus researchers and patients were not blind to the study drugs. Subjects had been randomized in a 1:1 ratio to treatment groups for 10 weeks. Throughout the studies, the patients were assessed six times; on the day of the screening visit (-7th day), at baseline or at the first visit (day 0), and on the second visit (14th day), third visit (28th day), fourth visit (49th day), and fifth visit (70th day) after baseline. All patients underwent a detailed psychiatric evaluation at the screening visit, where inclusion and exclusion criteria, as well as MDD diagnosis, were assessed according to DSM-IV criteria. Physical examination and laboratory work including biochemical blood and urine analysis, complete blood count, and electrocardiography were carried out and vital signs were measured at the screening visit and at the end of study. Sociodemographic data were also collected at the screening visit. Relevant ethics committees approved the study protocols, and the studies were conducted in accordance with the latest version of the Declaration of Helsinki. All subjects gave written informed consent prior to participation.

Drug Administration

Patients who met the study inclusion criteria were assigned, at the first visit, to venlafaxine 75 mg daily, reboxetine 4 mg twice daily, sertraline 50 mg daily or reboxetine 4 twice daily + sertraline 50 mg daily for the combination group. At the second visit, the dose of venlafaxine was increased to 150 mg daily and reboxetine to 8 mg twice daily, while sertraline was kept at the same dosage.

Assessment Instrument

The Turkish version of HDRS (35) was applied at all assessment points (Item 1 covers depressed mood; item 2 covers feelings of guilt; item 3 covers suicide; items 4, 5 and 6 cover insomnia early, middle and late respectively; item 7 covers work and activities; item 8 covers retardation; item 9 covers agitation; item 10 covers psychic anxiety; item 11 covers somatic anxiety; item 12 covers somatic symptoms; item 13 covers general symptoms;, item 14 covers genital symptoms; item 15 covers hypochondriasis; item 16 covers loss of weight; item 17 covers insight). The side effects, that were spontaneously reported by patients and assessed by a checklist, were recorded at visit 2, 3, 4, and 5. The severity of the side effects and the need for an intervention were also assessed on these forms. One investigator was appointed for each study and all scales were fulfilled by that investigator. There was substantial agreement among four raters (Percentage of overall agreement Po =0.8833, kappa=0.766081). The Cronbach alfa coefficient is 0.75 for the Turkish version of HDRS (35). Response to an antidepressant was defined as ≥50% decrease in HDRS score in comparison to the baseline value, and remission was defined as having an HDRS score ≤7.

In the evaluation of the effects of the antidepressants on different components of depression, HDRS subscales were defined as follows: Core symptoms of depression (HAM-D6) subscale (41): HDRS items 1, 2, 7, 8, 10 and

Table 1: Distribution of patients in MDD subgroups according to total HDRS score in visit 1

	Reboxetine (n)	Venlafaxine (n)	Sertraline (n)	Sertraline-reboxetine (n)
Severe depression (HDRS≥25)	10	9	6	4
Moderate depression (HDRS=20–24)	18	12	17	14
Mild depression (HDRS<20)	15	22	19	23
Psychomotor retardation (PMRS≥8)	30	27	23	27
Anxiety (ASS≥7)	26	27	19	29

PMRS: Psychomotor retardation subscale, ASS: Anxiety-somatization subscale.

Table 2: Reasons and timing of dropouts.

Reason of dropout	Reboxetine (n=50)	Venlafaxine (n=50)	Sertraline (n=54)	Sertraline-reboxetine (n=52)	Total (n=206)
Lack of efficacy	2 (V4)	0	1 (V4)	1 (V2), 1 (V3)	5
Lost to follow-up	2 (V2), 1 (V3)	2 (V2)	3 (V2), 2 (V4)	2 (V2)	12
Side effects	1 (V3)	1 (V4)	2 (V2)	3 (V2), 1(V3)	8
Others	1 (V3)	3 (V2), 1 (V4)	2 (V2), 2 (V3)	2 (V2), 1 (V3)	12
Total	7	7	12	11	37

Numbers in brackets indicates the timing of dropouts, V: Visit.

13; Core symptoms of depression (HAM-D7) subscale (42): HDRS items 1, 2, 3, 7, 8, 10 and 13; Psychomotor retardation subscale: HDRS items 1, 7, 8 and 14; Anxiety-somatization subscale: HDRS items 10, 11, 12, 13, 15 and 17; Insomnia subscale: HDRS items 4, 5 and 6.

The patient distribution in the subgroups used to compare the effects of the antidepressants in patients with MDD (according to the total HDRS score at visit 1), are presented in Table 1.

Statistical Analysis

Study data were summarized using descriptive statistics (percentages, frequency, mean standard deviation, median, and range). Normality of distribution of continuous variables was tested with the Kolmogorov-Smirnov and Shapiro-Wilk tests. The homogeneity of groups for baseline HDRS scores was evaluated. Percentage changes were given for time-dependent variables. Study groups and subgroups were compared with nonparametric the Kruskal-Wallis test and/or Mann-Whitney U test (for post hoc analysis with Bonferroni correction) for continuous variables and with Pearson's chi-square test for categorical variables. Wilcoxon test was used for in-group comparisons of each study group. Additionally, the effect size, which is known to have advantages over significance tests and gives information on the relative effect of a research treatment, was calculated by using the algorithm described by Morse (43). Siegel and Castellan's (44) fixed-marginal multirater kappa statistics were used to calculate the interrater reliability. The statistical significance level was defined as $p < .05$. The Statistical Package for the Social Sciences (SPSS) software (SPSS v 13.0, SPSS, Inc, Chicago, IL) was used for the statistical analysis.

RESULTS

Demographic and clinical characteristics

A total of 206 patients were included in the reboxetine, venlafaxine, sertraline, and sertraline-reboxetine combination groups; however 37 cases dropped out during the study periods (Table 2). Treatment groups did not differ between each other in terms of drop-out rates (p=0.554). Of the remaining 169 patients, 140 (82.8%) were women and 29 (17.2%) were men and the mean age of the patients was 40.5±10.9 (42; 19-65). There was no significant difference between treatment groups in terms of gender distribution and age, (p=0.777) and (p=0.559) respectively. Treatment groups also did not differ between each other in terms of depression-related and sociodemographic features as was demonstrated in Table 3.

Table 3: Depression-related and sociodemographic features of treatment groups

	Reboxetine (n=43)	Venlafaxine (n=43)	Sertraline (n=42) reboxetine (n=41)	Sertraline	Total (n=169)
Age (years)	40±10.9 (19–61)	42±11 (19–64)	41.3±11.6 (20–65)	38.5±10.1 (20-55)	40.4±10.9 (19–65)
Weight (kg)	69.8±12.8 (42–101)	68.5±12.9 (40–108)	67.4±12.8 (39–110)	69.6±11 (48-96)	68.8±12.3 (39–110)
Height (cm)	165.4±7.2 (148–184)	163.2±8 (143–186)	164±6.2 (150–176)	163.2±7.4 (152-181)	164±7.2 (143–186)
Gender					
Male	8 (18.6%)	8 (18.6%)	5 (11.9%)	8 (19.5%)	29 (17.2%)
Female	35 (81.4%)	35 (81.4%)	37 (88.1%)	33 (80.5%)	140 (82.8%)
Education					
Elementary school	15 (34.9%)	18 (41.9%)	14 (33.3%)	17 (41.5%)	64 (37.9%)
High school	10 (23.3%)	14 (32.6%)	10 (23.8%)	14 (34.1%)	48 (28.4%)
University	18 (41.9%)	11 (25.6%)	18 (42.9%)	10 (24.4%)	57 (33.7%)
Time since the first episode (years)	3.4±5.4 (0.08–27)	4.4±5.7 (0.1–22)	4.1±6.3 (0.1–20)	4.8±6.1 (0.08-26)	4.2±5.8 (0.08–27)
Number of episodes	2±1.3 (1–5)	2.2±2.1 (1–11)	1.6±0.9 (1–4)	1.9±1 (1-5)	1.9±1.4 (1–11)

Efficacy

There was no significant difference between the treatment groups in terms of initial mean scores of HDRS at visit 1 (21.8; 20.8; 20.3; and 19.8 for reboxetine; venlafaxine; sertraline and sertraline-reboxetine combination groups, respectively). The significant decrease in the mean scores of HDRS started at visit 2 in all treatment groups (p=<0.001). The reduction in percentage changes of HDRS scores from baseline was significantly higher in the venlafaxine group compared to the sertraline group at visit 2 and visit 3 [p=0.001, ES: 0.1404 (large) and p=0.002, ES: 0.1109 (medium), respectively]. Moreover, venlafaxine treatment led to a significant reduction in percentage changes in HDRS scores from baseline, at visit 2 and visit 3 compared to the sertraline-reboxetine combination group [p=0.006, ES: 0.0910 (medium) and p=0.004, ES: 0.1023 (medium), respectively]. In addition, assessment of the reboxetine and sertraline groups in terms of reduction in percentage changes of HDRS scores from baseline, revealed a significant decrease in the reboxetine group at visit 2 [p=0.023, ES: 0.0615 (medium)].

There was no significant difference between moderately (HDRS=21-24) and severely depressed (HDRS≥25) patients in terms of reduction in percentage changes of the mean HDRS scores (p>0.05). However, for patients with mild depression (HDRS<20), reduction in percentage changes in the mean scores of HDRS from baseline at visit 2 was significantly higher in the venlafaxine group than in the sertraline group [p=0.002, ES: 0.2288 (large)] and the reboxetine group [p=0.009, ES: 0.1859 (large)]. The reductions in percentage changes of the mean HDRS scores of all treatment groups during the study are presented in Figure 1 and the significant percentage changes in the mean scores of HDRS items between treatment groups are given in Table 4. The percentage changes in the mean scores of HDRS of patients with psychomotor retardation and anxiety are presented in Figures 2a and 2b.

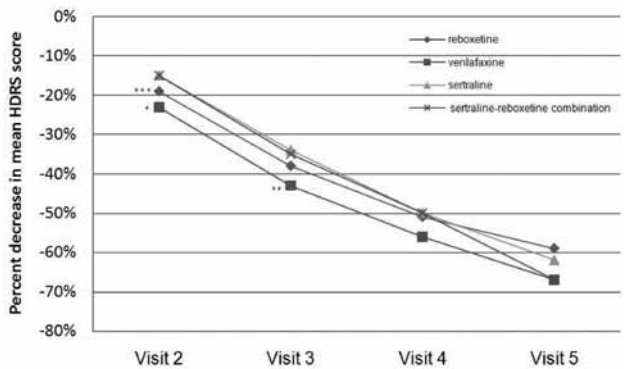

Figure 1: The percentage change in the mean HDRS score of treatment groups during the study.

*venlafaxine vs. sertraline, p=0.001; venlafaxine vs. sertraline-reboxetine combination, p=0.006.
**venlafaxine vs. sertraline, p=0.002; venlafaxine vs. sertraline-reboxetine combination, p=0.004.
***reboxetine vs. sertraline, p=0.023.

Response and remission

The response and remission rates in all antidepressant groups are presented as percentages in Figures 3a and 3b. The only significant difference observed was between the venlafaxine and the reboxetine groups at visit 5 in terms

Table 4: The significant percentage changes in the mean score of HDRS items and subscales.

	Reboxetine (n=43)	Venlafaxine (n=43)	Sertraline (n=42)	Sertraline-reboxetine (n=41)	p value	Effect Size
visit 2 vs. visit 1						
Item 3	-32%	-43%	-27%	-11%	0.005	0.1009 (medium)
Item 4	-8%	-52%	-11%	-16%	0.001	0.1323 (medium)
Item 14	-15%	-4%	-4%	-1%	0.009	0.0724 (medium)
Anxiety-somatization subscale	-16%	-19%	-6%	-13%	0.037	0.0507 (medium)
Insomnia subscale	-8%	-41%	-14%	-27%	0.044	0.0533 (small)
visit 3 vs. visit 1						
Item 1	-43%	-34%	-45%	-36%	0.019	0.0591 (small)
Item 4	-38%	-72%	-16%	-40%	0.000	0.1669 (large)
Item 5	-38%	-52%	-74%	-57%	0.030	0.0683 (medium)
Item 6	-40%	-82%	-41%	-53%	0.011	0.1033 (medium)
Item 10	-28%	-43%	-19%	-38%	0.009	0.0688 (medium)
Item 13	-34%	-36%	-8%	-12%	0.000	0.1118 (medium)
Item 16	-75%	-88%	-45%	-25%	0.039	0.2464 (large)
Anxiety-somatization subscale	-37%	-40%	-20%	-28%	0.001	0.0988 (medium)
Insomnia subscale	-31%	-63%	-40%	-59%	0.003	0.0914 (medium)
visit 4 vs. visit 1						
Item 1	-59%	-56%	-63%	-49%	0.038	0.0503 (small)
Item 2	-49%	-52%	-71%	-47%	0.044	0.0536 (small)
Item 4	-58%	-77%	-28%	-53%	0.001	0.1323 (medium)
Item 5	-51%	-50%	-89%	-71%	0.001	0.1236 (medium)
Item 6	-84%	-95%	-41%	-68%	0.000	0.2162 (large)
Item 14	-33%	-26%	-12%	-10%	0.043	0.0512 (small)
Item 16	-94%	-100%	-82%	-25%	0.006	0.3660 (large)
Insomnia subscale	-59%	-71%	-48%	-72%	0.008	0.0783 (medium)
visit 5 vs. visit 1						
Item 2	-55%	-70%	-81%	-64%	0.028	0.0604 (medium)
Item 3	-59%	-76%	-85%	-89%	0.002	0.1201 (medium)
Item 4	-65%	-77%	-43%	-57%	0.025	0.0714 (medium)
Item 5	-63%	-58%	-97%	-88%	0.000	0.1502 (large)
Item 6	-85%	-100%	-63%	-85%	0.003	0.1313 (medium)
Item 7	-55%	-74%	-61%	-76%	0.003	0.0823 (medium)
Item 10	-47%	-62%	-44%	-66%	0.008	0.0701 (medium)
Item 16	-100%	-100%	-82%	-50%	0.034	0.2559 (large)
Insomnia subscale	-63%	-71%	-65%	-82%	0.040	0.0545 (small)

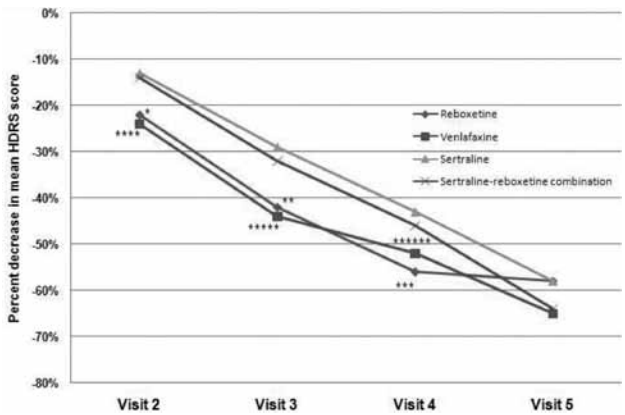

Figure 2a: The percentage change in the mean HDRS score of patients with psychomotor retardation during the study.

**reboxetine vs. sertraline, p=0.014, ES: 0.1154 (medium); reboxetine vs. sertraline-reboxetine combination, p=0.036, ES: 0.0783 (medium).
**reboxetine vs. sertraline, p=0.029, ES: 0.0922 (medium).
***reboxetine vs. sertraline, p=0.014, ES: 0.1171 (medium).
****venlafaxine vs. sertraline, p=0.001, ES: 0.2119 (large); venlafaxine vs. sertraline-reboxetine combination, p=0.010, ES: 0.1263 (medium).
*****venlafaxine vs. sertraline, p=0.001, ES: 0.2222 (large); venlafaxine vs. sertraline-reboxetine combination, p=0.007, ES: 0.1393 (medium).
******venlafaxine vs. sertraline, p=0.025, ES: 0.1032 (medium).

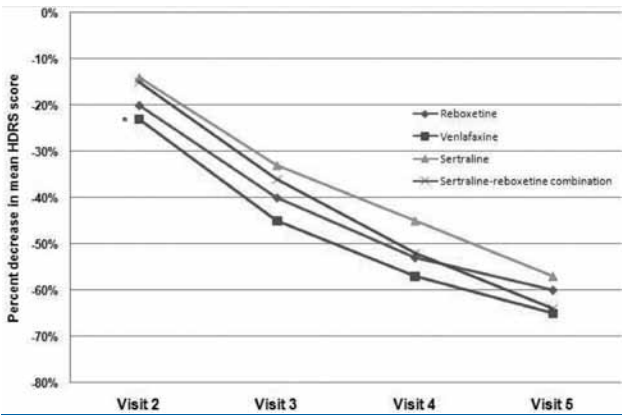

Figure 2b: The percentage change in the mean HDRS score of patients with anxiety during the study.

*venlafaxine vs. sertraline, p=0.019, ES: 0.1221 (medium); venlafaxine vs. sertraline-reboxetine combination, p=0.039, ES: 0.0777 (medium).

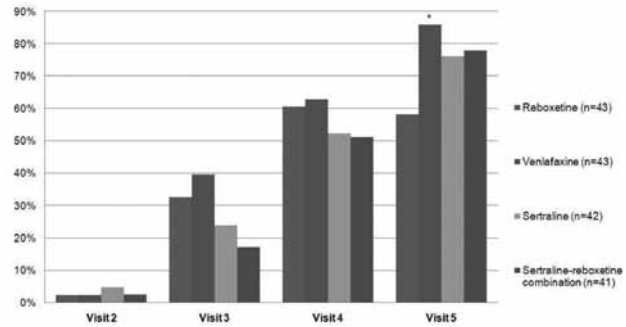

Figure 3a: The response rates as percentage in all antidepressant groups.

*venlafaxine vs. reboxetine, p=0.004, ES: 0.3110 (medium).

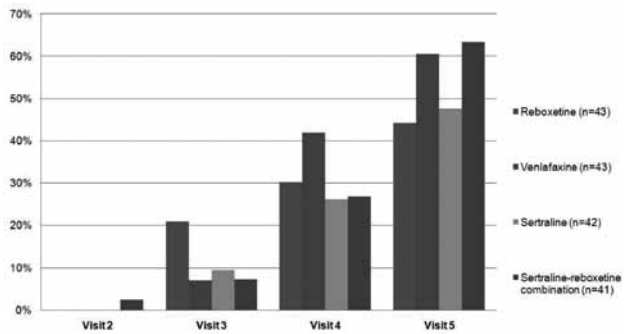

Figure 3b: The remission rates as percentage in all antidepressant groups.

of response rates.

The mean HDRS score of patients in remission at visit 5 was 4.0±1.8 (4.0; 0-7). The mean HDRS score of 19 remitting patients in the reboxetine group at visit 5 was 3.7±2.0 (3; 1-7); the mean HDRS score of 26 remitting patients in the venlafaxine group at visit 5 was 4.0±1.6 (4; 1-7); the mean HDRS score of 20 remitting patients in the sertraline group at visit 5 was 4.5±2.1 (5.5; 1-7) and the mean HDRS score of 26 remitting patients in the sertraline-reboxetine combination group at visit 5 was 3.8±1.7 (4; 0-7). In terms of the mean HDRS scores at visit 5, there was no significant difference among patients in remission regardless of antidepressant group (p=0.202).HDRS items 1, 7, 10, 11, 13, and 14 formed the total HDRS score of all patients in remission. The mean total HDRS score was formed primarily of item 1 (19%) and item 7 (26%) in the reboxetine group; item 1 (22%) and item 11 (22%) in the venlafaxine group; item 10 (21%) and item 14 (27%) in the sertraline group; and item 11 (21%) and item 13 (22%) in the sertraline-reboxetine combination group. The mean score of item 7 in the reboxetine group was significantly higher than that of both the venlafaxine [0.89 vs. 0.19, p=<0.001, ES: 0.3176 (large)] and the sertraline-reboxetine combination groups [0.89 vs. 0.23, p=<0.001, ES: 0.2783 (large)]. The mean score of item 11 was significantly higher in both the venlafaxine and the sertraline-reboxetine combination

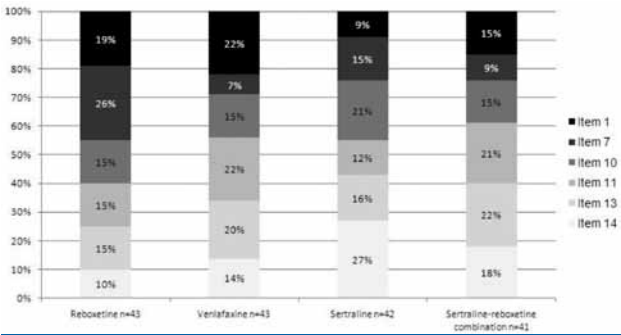

Figure 4: Percentage contribution of items forming total HDRS score for patients in remission at visit 5 according to treatment groups.

groups compared to the sertraline group [0.85 vs. 0.45, for both, p=0.005, ES: 0.1755 (large)]. Moreover, the difference in the mean score of item 14 among treatment groups [p=0.03, ES: 0.0994 (medium)] was related to a higher mean score of item 14 in the sertraline group than the venlafaxine group [1.05 vs. 0.5, p=0.013, ES: 0.1384 (medium)] and the reboxetine group [1.05 vs. 0.47, p=0.026, ES: 0.1483 (large)]. The mean scores of the other items were similar among treatment groups (p>0.05). The percentage contribution of items forming the total HDRS score for patients in remission at visit 5 according to treatment groups is presented in Figure 4.

Safety

The side effects, with a frequency over 10%, observed in the patients during the studies are listed in Table 5. The mean body weights of patients (kg) at the end of the study in the reboxetine, venlafaxine, sertraline and sertraline-reboxetine combination groups were 69.2±12 (67.5; 43-100), 68.1±13 (68; 42-110), 67.4±12.4 (66.5; 42-108) and 69±11 (68; 50-97), respectively. There was no statistically significant difference between treatment groups, in terms of percentage changes in body weight of the patients at the end of the study, compared to body weight at baseline (p=0.202).

DISCUSSION

In the present comparative study three antidepressants acting through different mechanisms of action, were found to be equally efficacious and safe in the treatment of MDD either in monotherapy (venlafaxine, reboxetine or sertraline) or in combination (sertraline-reboxetine). Although the overall efficacies for these drugs were similar, each of them was effective on different depressive symptoms or symptom clusters. The present study demonstrated that clinical response occurred earlier with venlafaxine and reboxetine compared to sertralineand with venlafaxine compared to the sertraline-reboxetine combination.

Efficacy

The significant decrease in the mean scores of HDRS at

Table 5: Side effects reported by patients in each treatment group [% (n)].

	Reboxetine (n=43)	Venlafaxine (n=43)	Sertraline (n=42)	Sertraline-reboxetine (n=41)	p value	Effect Size
Insomnia	49% (21) (medium)	2% (1)	10% (4)	17% (7)	<0.001	0.4514
Dry mouth	79% (34)	35% (15)	10% (4)	37% (15)	<0.001	0.5113 (large)
Constipation	44%(19)	16% (7)	0%	12% (5)	<0.001	0.4196 (medium)
Sweating	35% (15)	12% (5)	0%	34% (14)	<0.001	0.3710 (medium)
Tachycardia	21% (9)	0%	0%	5% (2)	<0.001	0.3507 (medium)
Vertigo	16% (7)	16% (7)	5% (2)	5% (2)	0.12	-
Nausea	23% (10)	49% (21)	29% (12)	22% (9)	0.03	0.2348 (small)
Headache	21% (9)	5% (2)	12% (5)	12% (5)	0.15	-
Flushing	16% (7)	0%	0%	5% (2)	0.002	0.2982 (small)
Discomfort	12% (5)	5% (2)	21% (9)	12% (5)	0.14	-
Dizziness	2% (1)	26% (11)	5% (2)	5% (2)	0.003	0.2875 (small)
Hot flushes	12% (5)	0%	0%	10% (4)	0.02	0.2404 (small)

visit 2 in all treatment groups indicates that antidepressant efficacy commences at the 2nd week of antidepressant treatment. The greater percentage change in HDRS scores in the reboxetine and venlafaxine groups compared to the sertraline group by visit 2, and the maintenance of this effect in the venlafaxine group over the sertraline group at visit 3, can be interpreted as earlier efficacy of reboxetine and venlafaxine over sertraline. In line with the present finding, earlier and superior efficacy of venlafaxine over single-action agents has been reported previously (26,27,45). It also has been observed that venlafaxine has a superior efficacy over the sertraline-reboxetine combination at visit 2 and 3. Although stimulation of the noradrenergic system is also essential for an earlier antidepressant efficacy, lack of such effect with the sertraline-reboxetine combination, in spite of the presence of reboxetine, is noteworthy. Thus, it is not clear how this synergism and augmentation differs from the dual-action mechanism of venlafaxine that inhibits re-uptake of both serotonin and noradrenaline. This finding suggests that other mechanisms may explain the efficacy and interactions of different antidepressants. It is challenging that the items and subscales that are responsible for the difference in the percentage changes at visit 2 and visit 3 in the individual analysis of HDRS scores were different in sertraline and sertraline-reboxetine combination groups.

In the present study we found that HDRS item 4 and the insomnia subscale were significantly improved with venlafaxine compared to sertraline at visit 2. Moreover, there was a superiority of venlafaxine over sertraline-reboxetine combination in terms of HDRS item 4 but not in the insomnia subscale. These findings suggest that dual-acting drugs may have beneficial effects on sleep quality over single acting drugs. Also, the significant reduction in the percentage changes of the anxiety-somatization subscale at visit 2 that was found in favour of venlafaxine compared to sertraline may be explained by the relatively earlier anxiolytic and sleep management effects of venlafaxine. The reduction in percentage changes in HDRS items 4, 6, 10, 13, 16 and the subscales of anxiety-somatization and insomnia indicate the superiority of venlafaxine over sertraline at visit 3. In addition, the superiority of venlafaxine over sertraline-reboxetine combination was indicated by the reduction in percentage changes of HDRS items 4, 6, 13, and the anxiety-somatization subscale. Moreover, reduction in percentage change of HDRS item 4 was significant in the sertraline-reboxetine combination compared to sertraline. These findings suggest that the reported differences between treatment groups at visit 3 originate from HDRS items associated with sleep and anxiety. Also we found that the reduction in percentage change of HDRS item 4 beginning at visit 2 and HDRS item 6 beginning at visit 3 was highest in the venlafaxine group throughout the study. We consistently observed that reduction in the percentage change of HDRS items 4 and 6 was higher in treatment modalities effective on the noradrenergic system. On the other hand reduction in the percentage change of HDRS item 5 was higher with sertraline. It is remarkable that the sertraline-reboxetine combination group led to a decrease in HDRS items 4 and 6 as seen with venlafaxine and reboxetine, and a decrease in HDRS item 5 as seen with the serotonergic agent sertraline. Therefore, the sertraline-reboxetine combination reached and even exceeded the efficacy of venlafaxine by visit 3 in terms of the reduction in percentage change of the insomnia subscale. The low percentage change of reboxetine in the insomnia subscale at visit 2 and 3, which caused predominantly insomnia as a side effect in the early stages of treatment, was remarkable. It is known that venlafaxine improves sleep disturbances in MDD patients, probably due to its dual-action (46). Additionally, since there is some neurobiological evidence supporting the involvement of both serotonin and norepinephrine in the pathogenesis and treatment of anxiety disorders, it is conceivable that antidepressants that modulate the activity of both neurotransmitters, eg. venlafaxine, may be associated with therapeutic advantages over more selective agents (47). These reports are consistent with our findings.

Sexual dysfunction is considered as a potential side effect of antidepressant treatment and has been reported frequently with SSRIs and SNRIs during MDD treatment in both comparative and placebo controlled studies (48-51). The deterioration in scores of HDRS item 14, which evaluated the genital symptoms, by the 2nd week of treatment in the sertraline group and the significant difference in the percentage change compared to the reboxetine group were remarkable findings. The highest reduction in percentage change of HDRS item 14 was also observed in the reboxetine group at visit 4.

Though it is insignificant, the lowest reduction in percentage change of the anxiety-somatization subscale

which was observed in the sertraline group at visit 5 is noteworthy. This finding was significant at visit 2 and 3. The only significant reduction in percentage change of the anxiety-somatization subscale was observed in favour of venlafaxine compared to sertraline at visit 2. At the next visit venlafaxine and reboxetine were superior to sertraline and the sertraline-reboxetine combination. On the other hand, we observed a slight reduction in percentage changes of HDRS items 10 and 13 with the sertraline group at visit 3. The superiority of venlafaxine over sertraline at visit 2 and the superiority of both venlafaxine and reboxetine over sertraline at visit 3 contrasts with experimental evidence suggesting the key role of the serotonergic system in the pathophysiology of anxiety symptoms (52-54) and the efficacy of serotonergic agents on anxiety symptoms (55,56). The percentage change in favour of venlafaxine and reboxetine, which was presented in Figure 1, is largely due to the insomnia and/or anxiety-somatization subscales of HDRS. Thus, we believe that our findings can suggest the direction for further studies.

The percentage change in HDRS item 2 was higher in the sertraline group compared to the venlafaxine, reboxetine, and sertraline-reboxetine combination groups at visit 4. Additionally, the percentage change in HDRS items 2 and 3 was significantly higher in the sertraline group at visit 5. The difference in the percentage change by visit 4 and 5 might have been compensated by sertraline. Antidepressants that act through the noradrenergic system are known to improve symptoms such as loss of interest, anhedonia, lack of energy, or motor retardation (8,9). The percentage change in item 7 that represents all these symptoms to some extent was significantly higher for venlafaxine and the sertraline-reboxetine combination than for sertraline and reboxetine at visit 5. Similarly, the superior efficacy of noradrenaline reuptake inhibitors on the psychomotor retardation subscale (Figure 2a) has been reported in many studies (57-60). It can be speculated that the effects of noradrenergic antidepressants on motivation and drive are not independent from the serotonergic system. It is agreed that the interaction between the serotonergic and noradrenergic systems may play an important role in the pathogenesis of depression and anxiety (61). On the other hand, the dominant effect of sertraline on HDRS item 1 and/or 2 at visit 3, 4, and 5 can be considered as the positive effect of the serotonergic effect on mood.

Although the difference was not statistically

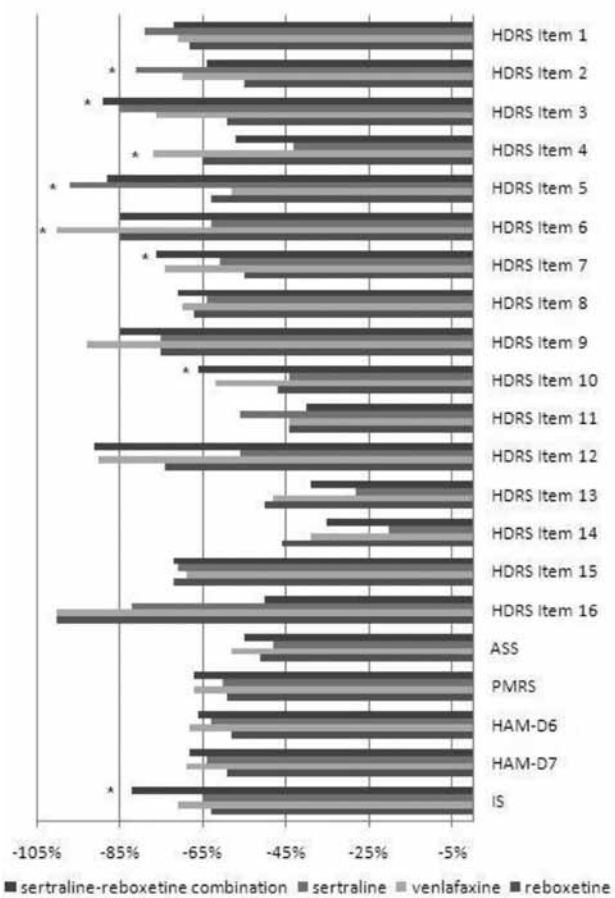

Figure 5: Percentage changes in HDRS items and subscales between Visit 1 and Visit 5.
IS: Insomnia subscale, HAM-D6 (Bech-6 item): Core symptoms of depression subscale, HAM-D7: Core symptoms of depression subscale, PMRS: Psychomotor retardation subscale, ASS: Anxiety-somatization subscale.

*represents statistical significance
HDRS Item 2: sertraline vs. reboxetine, p=0.003, ES: 0.1213 (medium).
HDRS Item 3: sertraline vs. reboxetine, p=0.005, ES: 0.1287 (medium); reboxetine vs. sertraline-reboxetine combination, p=0.001, ES: 0.1742 (large); venlafaxine vs. sertraline-reboxetine combination, p=0.024, ES: 0.078 (medium).
HDRS Item 4: venlafaxine vs. sertraline, p=0.004, ES: 0.1225 (medium); reboxetine vs. sertraline, p=0.050, ES: 0.0534 (small).
HDRS Item 5: sertraline vs. reboxetine, p=0.000, ES: 0.1789 (large); sertraline vs. venlafaxine, p=0.000, ES: 0.2234 (large); reboxetine vs. sertraline-reboxetine combination, p=0.024, ES: 0.0784 (medium); venlafaxine vs. sertraline-reboxetine combination, p=0.013, ES: 0.1080 (medium).
HDRS Item 6: venlafaxine vs. reboxetine, p=0.050, ES: 0.0738 (medium); venlafaxine vs. sertraline, p=0.001, ES: 0.2027 (large); reboxetine vs. sertraline, p=0.033, ES: 0.1834 (large); venlafaxine vs. sertraline-reboxetine combination, p=0.030, ES: 0.1155 (medium).
HDRS Item 7: venlafaxine vs. reboxetine, p=0.003, ES: 0.1050 (medium); venlafaxine vs. sertraline, p=0.027, ES: 0.0578 (small); reboxetine vs. sertraline-reboxetine combination, p=0.003, ES: 0.1051 (medium); sertraline vs. sertraline-reboxetine combination, p=0.038, ES: 0.0527 (small).
HDRS Item 10: venlafaxine vs. sertraline, p=0.019, ES: 0.0654 (medium); reboxetine vs. sertraline-reboxetine combination, p=0.019, ES: 0.0660 (medium); sertraline vs. sertraline-reboxetine combination, p=0.003, ES: 0.1056 (medium).
IS: sertraline vs. sertraline-reboxetine combination, p=0.004, ES: 0.1125 (medium).

significant, the higher percentage change in all subscales for venlafaxine and the sertraline-reboxetine combination compared to reboxetine and sertraline in visit 5 was noticable. Percentage changes in HDRS items and subscales between visit 1 and visit 5 are presented in Figure 5.

MDD patients with different severity exhibited no difference in terms of treatment efficacy of antidepressant drugs;, however, the earlier therapeutic efficacy observed in the venlafaxine group compared to the reboxetine and sertraline groups in patients with mild-depression was striking (considering the difference in percentage change at visit 2). The difference disappeared at further visits. On the contrary, there are some reports pointing out that venlafaxine is an effective option in the treatment of severe depression (62-64).

Response and Remission

When the whole group was taken into consideration, a significant difference between the response rates of the venlafaxine and reboxetine groups was solely observed at visit 5. The lack of significance between the remission rates of these groups that are prioritized in improvement was interesting and the higher remission rates observed in the venlafaxine and sertraline-reboxetine combination groups were noteworthy.

Residual Symptoms

It was observed that, the HDRS items comprising the anxiety-somatization and psychomotor retardation subscales primarily formed the total HDRS scores of patients in remission at visit 5. This finding suggests the symptoms that should be targeted in the treatment of residual symptoms in depression. Moreover, the absence of item 7 that reflects psychomotor retardation in the venlafaxine and sertraline-reboxetine combination group, and item 1 in the sertraline group in the items predominantly determining total HDRS score, was considered noteworthy. The presence of HDRS item 11 was observed among frequently encountered items in both the venlafaxine and sertraline-reboxetine combination groups. HDRS item 14 was among the most frequently encountered residual symptoms in the sertraline group. The sertraline-reboxetine combination group ranked second at a rate of 18%. These results reflect the association between SSRIs and sexual dysfunction. Our findings are contrary to Nelson et al. (65) who reported that residual symptoms appear to be similar following treatment with different selective agents.

Safety

Side effects are known to be one of the major causes of drug cessation. Although side effect profiles are predictable in most cases, infrequent ones were reported with both reboxetine (66,67) and sertraline (68,69). Relatively higher rates of side effects were observed in the reboxetine group. Side effects such as insomnia, dry mouth, constipation, sweating, tachycardia, and flushing are considered to be related to the stimulation of the noradrenergic system. This situation renders reboxetine as a less tolerable agent, due to its side effects. Nevertheless only one patient in the reboxetine group and one patient in the venlafaxine group, two patients in the sertraline group and four patients in the sertraline-reboxetine combination group discontinued the study due to side effects. It is interesting that sertraline-reboxetine combination did not cause side-effects to the same extent as reboxetine. This situation can be speculated to be due to the balance of noradrenergic and serotonergic stimulation.

Limitations

The pooled analysis of four open labelled studies without placebo-controlled groups constitutes a disadvantage for the present study. Furthermore, it is hard to draw a definite conclusion due to the limited numbers of patients in the treatment groups. It may be possible to transform the insignificant differences to statistically significant results by increasing the patient population. Even though there are papers (70,71) reporting that a daily dose of 50 mg./day of sertraline is effective in the treatment of MDD, the dose of sertraline administered in the current study might be considered to be low compared to the dosages of venlafaxine and reboxetine.

CONCLUSION

Efficacies of serotonergic and/or noradrenergic agents balance each other during the treatment period, regardless

of the neurotransmitter pathway and the mechanism of action. This finding supports the opinion that all antidepressants show their efficacy through a final common pathway. The present study reveals the importance of properly identifying target symptoms or symptom groups in antidepressant choice. As demonstrated in the present study, agents acting through the noradrenergic system, particularly dual-acting agents, may be the proper choice in cases when an earlier improvement is required in terms of psychomotor retardation, insomnia, and anxiety symptoms. In the present study it was observed that the sertraline-reboxetine combination did not show an early effect as did venlafaxine. However, further visits demonstrated that the sertraline-reboxetine combination appeared to be the treatment choice most similar to venlafaxine. It was also observed that the sertraline-reboxetine combination acted as two separate agents with different efficacies at the beginning; however it created a dual-action like venlafaxine by visit 5. Naturally physicians avoid combination therapies because of increased risk for side effects; however the side effect profile of the sertraline-reboxetine combination was no different from that of the other treatment choices in the present study. Nevertheless it seems that, it is not advantageous to create a dual-action by combining two agents while the original dual-action agents already exist. There are studies in the literature reporting that a SSRI + reboxetine combination is effective in cases resistant to SSRIs alone or to high-dose venlafaxine; therefore, this combination can be rarely considered as an alternative in such treatment resistant cases.

The present study also clarified the uncertainty regarding the dose for the initiation of the dual-action of venlafaxine. It was observed that venlafaxine was superior to sertraline even at a dose of 75 mg/day and effective with respect to the same symptoms as reboxetine. These findings are good indicators of the initiation of the dual-action of venlafaxine at a dose of 75 mg/day.

In conclusion, antidepressants acting through different neurotransmitter systems display similar efficacy even though they are effective against different symptoms of depression. Despite the limitations mentioned above, the present study is a valuable preliminary study due to the dearth of studies discussing these issues in the literature. This study reveals the fact that there is a need for further multicenter, placebo controlled trials with larger patient groups to evaluate the efficacy and safety of these antidepressants.

Statement of Interest

No support was received from any pharmaceutical company for this study. The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

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