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A comparison of the efficacy and tolerability of reboxetine and sertraline versus venlafaxine in major depressive disorder: A randomized, open-labeled clinical trial

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Abstract

The aim of the study was to compare the efficacy and tolerability of the combination of reboxetine and sertraline to venlafaxine XR (extended release) in major depressive disorder (MDD). The study consisted of 40 patients with MDD, aged 18–65 years. Patients were evaluated six times during a 10-week period. Treatment was started as venlafaxine XR 75 mg/day once a day (od) or reboxetine 4 mg/day twice a day (bid)+sertraline 50 mg/day od. In the second week, venlafaxine XR was increased to 150 mg/day od and reboxetine 8 mg/day bid while sertraline was kept at the same dose. The Hamilton Depression Rating Scale (HDRS), Montgomery and Asberg Depression Rating Scale, Clinical Global Impressions-Severity of Illness and Clinical Global Impressions-Global Improvement Scale were applied on each visit. Beginning from the second visit, both groups showed significant declines in each scale. There were no significant differences between treatment response rates. Remission rates defined as HDRS ≤ 10 were significantly higher in the venlafaxine XR group at visit 4 only. However, when remission was accepted as HDRS ≤ 7, no significant difference was observed. Side effect frequency was similar between the treatment groups. We may suggest that the reboxetine+sertraline combination is not superior to venlafaxine treatment.

Keywords: Depression; Reboxetine; Sertraline; Venlafaxine

1. Introduction

Major depressive disorder (MDD) has a multifactorial etiology. Biological factors, especially neurotransmitters, are reported to play an important role in the ethiopathogenesis. It is usually agreed that the mechanism of depression cannot be explained solely by the dysfunction of only one neurotransmitter but by the interaction of several neurotransmitters (Kirli, 2000; Tamam and Zeren, 2002). The clinical impact of monoamine-based antidepressant medications supports the view that alterations in both serotonin and noradrenalin function contribute to the syndrome of depression (Schatzberg, 2000; Versiani et al., 2000). Several findings support the view that combined serotonin and noradrenalin enhancement has greater therapeutic efficacy compared with the enhancement of either neurotransmitter alone (Akkaya et al., 2003; Anderson, 2000; Danish University Antidepressant Group, 1986, 1990; Faravelli et al., 2003; Kaplan, 2002; Mehtonen et al., 2000; Roose et al., 1994).

Despite the recent advances in the understanding of the pathophysiology and etiology of MDD and the availability of different effective treatments, as many as 20–45% of patients still fail to respond adequately to antidepressant therapy (Fava

Abbreviations: CGI-GI, Clinical Global Impressions-Global Improvement; CGI-SI, Clinical Global Impressions-Severity of Illness; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ECG, Electrocardiography; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery and Asberg Depression Rating Scale; MDD, Major Depressive Disorder; S.D., Standard Deviation; SSRI, Selective Serotonin Reuptake Inhibitor; venlafaxine XR, venlafaxine (extended release).

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and Davidson, 1996). This situation causes a high rate of relapse and recurrence, worsens the prognosis (Judd et al., 1998) and decreases the functionality (Judd et al., 1997), which emphasizes the importance of achieving the remission (Nierenberg and Wright, 1999). Thus, remission should be the main goal of antidepressant therapy.

To achieve remission, augmenting the ongoing treatment with a selective serotonin reuptake inhibitor (SSRI) (Amsterdam et al., 1997; Carpenter et al., 2002; DeBattista et al., 2003; Kennedy et al., 2002) or switching to venlafaxine (Mitchell et al., 2000; Nierenberg et al., 1994; Saiz-Ruiz et al., 2002) are frequently preferred strategies. Devarajan and Dursun (2000) reported that citalopram+reboxetine combination was effective in patients unresponsive to high dose venlafaxine. As they can be more effective in achieving the remission, there is growing emphasis on drugs with dual effect in the treatment of MDD. From this point of view venlafaxine seems to be a promising agent; however, as suggested by Devarajan and Dursun, there is the possibility that two different molecules can act more effectively on the two neurotransmitter systems. Based on their conclusion, we hypothesized that using the SSRI+reboxetine combination may be more effective than venlafaxine therapy in the treatment of depression. So in the present study, we aimed to compare the efficacy and tolerability of reboxetine+sertraline combination to venlafaxine XR in patients with MDD.

2. Methods

2.1. Patient population

The study group consisted of 33 females and 7 males. Patients aged 18–65 years with a diagnosis of MDD were eligible for participation in the study (*Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV)*, American Psychiatric Association, 1994). The patients were required to have a score of at least 16 at baseline on the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960).

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 who had a history of psychoses and patients with significant suicide risk were excluded from the study following a semi-structured psychiatric interview. Patients who had not responded to venlafaxine XR, reboxetine or sertraline in previous episodes of depression, patients who have or had history of treatment resistance (continuation of the depressive episode despite the use of two different antidepressants in the appropriate dose and duration), patients who have had electroshock therapy within the last 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), patients with any clinically significant medical disorder or laboratory abnormality were not eligible for participation in the study. Women were excluded if pregnant or if not using a reliable method of contraception throughout the study.

2.2. Drug administration

Patients who met the study inclusion criteria were randomly assigned to venlafaxine XR 75 mg/day od or reboxetine 4 mg/day bid+sertraline 50 mg/day od. At the second visit, venlafaxine XR was increased to 150 mg/day od and reboxetine 8 mg/day bid while sertraline was kept at the same dose. Patients were kept on the same dose for 10 weeks.

2.3. Study design

The study was designed as an open-label study; thus researcher and patients were not blind to the study drugs. Subjects were randomized in a 1:1 ratio to treatment with fixed doses of venlafaxine XR or reboxetine+sertraline for 10 weeks. Throughout the study, the patients were assessed six times; on the day of the screening visit (− 7th day), at baseline (day 0), and on the 14th (2nd visit), 28th (3rd visit), 49th (4th visit) and 70th (5th visit) days after the baseline. All patients underwent a detailed psychiatric evaluation on the screening visit day where inclusion and exclusion criteria as well as MDD diagnosis were assessed according to DSM-IV criteria. Physical examination and laboratory work-out including biochemical blood and urine analysis, complete blood count, electrocardiography (ECG) were carried out and vital signs were measured at the screening visit and at the end of study. Socio-demographic data were also recorded at the screening visit.

The study protocol was approved by the relevant ethics committee, and was conducted in accordance with the Declaration of Helsinki (1996). All subjects gave written informed consent to participate.

2.4. Assessment instruments

The following physician-rated instruments were used in the study: the Turkish version of HDRS (Akdemir et al., 1996), the Turkish version of Montgomery and Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979; Torun et al., 2002), and the Clinical Global Impression-Severity of Illness scale (CGI-SI) (Guy, 1976) were applied at all assessment points. The Clinical Global Impression-Global Improvement scale (CGI-GI) (Guy, 1976) was applied at the 2nd, 3rd, 4th, and 5th visits.

Adverse events spontaneously reported by patients and assessed by a checklist were recorded at 2nd, 3rd, 4th, and 5th visits. The severity of the adverse effects and the need for an intervention was also assessed on these forms. All the scales and forms were applied by only one investigator.

2.5. Data analysis

Statistical analysis was performed using SPSS 11.0 version for windows (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean±standard deviation and median. Categorical variables are presented as frequencies (*n*, %). Student's *t*-test and when necessary Mann-Whitney *U* test were used for comparison of the means between the drug