

Anxiolytic effects of venlafaxine/olanzapine combination in treatment of anxious depression

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Abstract

OBJECTIVE: Both venlafaxine and olanzapine have been previously found to have anxiolytic properties, however no study examined the effect of their combination on anxiety in anxious MDD. The aim of this study was to reveal if and when venlafaxine/olanzapine combination (VOC) can reduce the anxiety and depressive symptoms in patients with severe MDD at the level of patients with moderate-severe depression treated with venlafaxine monotherapy.

METHODS: Fifty seven patients were included into the study. Symptoms of depression were objectively assessed by Montgomery-Asberg Depression Rating Scale and subjectively scored by BECK Depression scale, symptoms of anxiety were objectively assessed by Hamilton Anxiety scale and subjectively evaluated by ZUNG Self-Rating Anxiety scale before treatment and after each following week until the fourth week of treatment.

RESULTS: VOC eliminated the pre-treatment score differences in all the scales within the first week of treatment. At the third week, VOC group had significantly lower level of anxiety symptoms and the effect maintained through the fourth week of medication.

CONCLUSION: Our results indicate that VOC could replace another anxiolytic medication in managing the symptoms of anxiety in patients with severe anxious MDD already within the first week of treatment.

Abbreviations:

MDD	- major depressive disorder
VOC	- venlafaxine/olanzapine combination
SNRI	- serotonin and noradrenaline reuptake inhibitor
VEN	- venlafaxine
OLA	- olanzapine
MADRS	- Montgomery-Asberg Depression Rating Scale
HAM-A	- Hamilton Anxiety scale
SAS	- Zung Self-Rating Anxiety scale
SARS	- Structured Adverse Effects Rating Scale

INTRODUCTION

Major depression is a debilitating mental disorder with lifetime prevalence 8–23.2% (Andrade *et al.* 2003; Carvalho *et al.* 2014; Shahpesandy 2005) associated with extensive severity of symptoms and role impairment (Kessler *et al.* 2003; Maes 2015; Sedlackova *et al.* 2015). Anxiety disorders are present in 57.4–67.6% of patients with depression (Zimmerman *et al.* 2000). Anxiety, somatization or both occurs in 75% of depressive patients (Moller 2002). The current psychopharmacological approaches prefer medication with effects on all or at least the majority of patient's symptoms as the first-choice drug. Venlafaxine has been shown to improve both symptoms of depression and anxiety in depressive disorders in several studies (Il'ina 2009; Silverstone & Ravindran 1999; Smith *et al.* 2002), moreover was effective in symptoms of anxiety in anxiety disorders (Gelenberg *et al.* 2000; Allgulander *et al.* 2004; Katzman 2004; Nimatoudis *et al.* 2004; Pollack *et al.* 2007). In patients with severe depressive symptoms, antipsychotics are added to antidepressant medication (Davidson 2010). Atypical antipsychotics are currently preferred due to their better efficacy and adverse effects profiles compared to traditional antipsychotics. Except antipsychotic and mood-improvement effects, olanzapine has been shown to have anxiolytic properties in patients with bipolar depression (Gao *et al.* 2006), schizophrenia (Littrell *et al.* 2003; Hosak, Hosakova, 2015), social anxiety disorder (Barnett *et al.* 2002) and vascular dementia (Moretti *et al.* 2004) and has improved the symptoms of anxiety as augmentation therapy in panic disorder (Sepede *et al.* 2006; Chao 2004) and generalized anxiety disorder (Pollack *et al.* 2006).

In clinical practice, the combination of venlafaxine plus olanzapine is widely used in patients with severe depression with excellent and fast improvement of depressive symptoms. However, there is lack of evidence of venlafaxine and olanzapine combination (VOC) effects on anxiety symptoms and rate of their improvement in patients with anxious MDD, a depression in which the symptoms of anxiety do not fulfill the criteria of any of anxiety disorders. Therefore, we decided to evaluate the magnitude and the rate of VOC effectivity on anxiety and depressive symptoms in patients with severe anxious MDD. The VOC effects were evaluated as compared to effects of venlafaxine monotherapy in patients which did not require antipsychotic drug administration, thus those with moderate to less severe depressive symptoms. The aim of this study was to examine if and when the VOC can reduce the symptoms of anxiety and depression in patients with severe anxious MDD at the level of patients with moderate-severe anxious depression treated with venlafaxine monotherapy. This is the naturalistic study in the standard clinical conditions with the relevance to understand the anxiety pharmacological management

by medication not primary administered to manage the symptoms of anxiety in patients with MDD.

MATERIALS AND METHODS

Subjects and treatment

Patients were recruited from the Clinic of Psychiatry, Jessenius Faculty of Medicine, Comenius University, Martin University Hospital in Martin, Slovakia. Seventy-six patients were included into the study. Fifty-seven patients finished the study and were included into the statistical evaluations. All subjects were in-patients of adult department with the diagnosis of single depressive episode and recurrent depressive disorder (F32, F33 according to ICD-10), or major depressive disorder, single episode or recurrent, according to DSM-V) with anxious symptoms. Written informed consent was obtained from the participating patients. The protocol was approved by the Ethics Committee of Martin University Hospital. The study conformed to the code of ethics stated in the Declaration of Helsinki.

The range age of the patients was 18–65 years. Twenty two of patients who finished the study were males ($n_{VEN}=11$, $n_{VEN/OLZ}=11$) and thirty five were females ($n_{VEN}=12$, $n_{VEN/OLZ}=23$). The clinical diagnosis of depression with anxiety symptoms was made by experienced senior consultant psychiatrist based on a clinical observation and extensive interview with the patient based on DSM-V criteria.

After the diagnostic process, patients were medicated by monotherapy with SNRI antidepressant venlafaxine ($n=23$) or combined treatment, venlafaxine and atypical antipsychotic of second generation olanzapine ($n=34$). Venlafaxine dose range at the end of the fourth week was between 150–375mg/d and olanzapine dose range was between 10–20 mg/d. The titration of drugs followed the prescribing regulations according to The State Institute for Drug Control. The effect of medication was evaluated at the end of the second week. Reduction 30% of MADRS pre-treatment score was evaluated as a clinical response. Non-responders were excluded from the study and were not included into the statistical evaluation. The total drop-out from the study was 19 patients. The reasons of drop-out were non-responsivity to treatment, non-compliance and severe adverse effects. Exclusion criteria included psychotic symptoms, serious medical or neurological illness, severe cognitive impairment, lack of cooperation and serious sensory deficit.

Assessment of symptoms

Patients underwent evaluation with MADRS (Montgomery-Asberg Depression Rating Scale) and HAM-A (Hamilton Anxiety scale) at baseline and each week during the following four weeks of treatment. Patients filled Beck Depression scale and Zung Self-Rating Anxiety scale (SAS) at baseline and each week during the following four weeks of treatment. Structured Adverse

Effects Rating Scale (SARS) was evaluated after the first week of treatment and in the following three weeks.

Depressive symptoms were quantified by the MADRS administered and scored by clinicians based on a clinical observation and interview with the patients. The scale consists of 10 items. Each item is scored on a 6-point scale. Higher MADRS score indicates more severe depression. The overall score ranges from 0 to 60. Usual cutoff points are: 0 to 6 – normal/symptom absent, 7 to 19 – mild depression, 20 to 34 – moderate depression, >34 – severe depression (Montgomery 1979).

Self-rated evaluation for depression was quantified by the Beck Depression Inventory II scale (Beck), modified version of 13 questions. According to the author, this version has a correlation coefficient of 0.96 comparing with the 21 item version. Each item is rated on a scale of 0 to 3 according to the severity. The overall score ranges from 0 to 39. The suggested cutoffs points are: 0–4 none or minimal depression, 5–7 mild depression, 8–15 moderate depression, 16 and more severe depression (Beck 1972).

Anxious symptoms were quantified by the HAM-A scale administered and scored by clinicians. The scale consists of 14 items, each of them contains a number of symptoms and each group of symptoms is rated on a scale of 0 to 4, with 4 being the most severe (0 = not present, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe). The overall score ranges from 0 to 56. Score of 17 or less indicates mild anxiety severity. Score from 18 to 24 indicates mild to moderate anxiety severity. Score of 25 to 30 indicates a moderate to severe anxiety severity (Hamilton 1959).

Subjective symptoms of anxiety were measured by Zung Self-Rating Anxiety Scale (SAS). This is a 20-item self-report assessment based on scoring in 4 groups of manifestations: cognitive, autonomic, motor and central nervous system symptoms. Each item is scored from 1 to 4 (1 = a little of the time, 2 = some of the time, 3 = good part of the time, 4 = most of the time). The total scores range from 20–80. Cutoff points are: 20–44 normal range, 45–59 mild to moderate anxiety levels, 60–74 marked to severe anxiety levels, 75–80 extreme anxiety levels (Zung 1971).

Adverse effects were evaluated by SARS. The scale consist of 33 questions, each symptom is rated on scale of 0 – 3 according to the relation of the symptom with the therapy (0 = no relation, 1 = maybe, 2 = probable, 3 = highly probable) (Alda 1985).

Statistical analyses

Non-parametric tests were used due to relatively small number of subjects in both treatment groups and the condition of normality of values distribution failure. Friedman ANOVA, a non-parametric alternative to ANOVA of repeated measures, was used to evaluate the effectivity of pharmacotherapy in both groups. This test examines if the observed value is changed by

the measure repeating. We used Friedman ANOVA to test the time effect on the MADRS, BECK, HAMA and SAS score decrease. Compared to ANOVA of repeated measures, Friedman ANOVA loses the possibility to measure the combined influence of time plus group score difference on measure repeating. As we wanted to examine the difference between the separate scales' scores dynamics, in spite of the data features, ANOVA of repeated measure was used to solve the combined effect, thus to compare the curves of the scale score decline between the two treatment groups. Mann-Whitney test was used to evaluate the score difference between the two treatment groups in particular weeks 0–4 to examine the scales' score differences in the separate weeks.

RESULTS

Pre-treatment differences

As we expected, we found statistically significant differences between groups in pre-treatment score of MADRS, HAMA and SAS scales. MADRS, HAMA and SAS scores were significantly higher in the VOC group. Pre-treatment BECK score was also higher in the VOC group, but did not reach the statistical significance (Tables 1–4).

Treatment effects in particular weeks

The pre-treatment differences were eliminated by the first week of treatment. Moreover, BECK and HAMA scores were lower in the VOC group but did not reach the statistical significance. The decrease of the scores of all the scales continued to the second week without the significant differences between groups. In the third week, MADRS, BECK and SAS scale scores did not significantly differ, however we found the statistical significant difference in HAMA scale score. VOC group had significantly lower scores than group treated by venlafaxine alone. In the fourth week the decrease of all the scales' scores continued without the statistically significant difference between groups (Tables 1–4).

Overall treatment effects

The changes of all the scales' scores were statistically significant in both groups during treatment. The dynamics of all the scales' scores decrease was significantly different between groups during treatment as proved by ANOVA of repeated measures (Figures 1–4).

Tolerability of medication

Adverse effects manifested in VOC group during treatment were drowsiness, collapse states, palpitations, nausea, obstipation, diarrhea, dyspeptic difficulties, accommodation disorders, dry mouth, increased sweating, akathisia, tremor, muscle weakness and dizziness. Adverse effects manifested in venlafaxine group were collapse states, palpitations, nausea, obstipation, diarrhea, dyspeptic difficulties, dry mouth, increased

Tab. 1. MADRS (Montgomery-Asberg Depression Rating Scale).

	VEN group		VOC group		p(M-W)
	d	sd	d	sd	
MADRS0	36.26	10.13	43.32	6.35	0.010*
MADRS1	30.26	10.22	30.65	8.63	0.935
MADRS2	22.39	9.37	21.38	8.70	0.690
MADRS3	14.87	6.74	14.41	8.79	0.647
MADRS4	9.96	6.77	9.94	8.79	0.486

Score before and after each week until the fourth week of treatment. VEN-venlafaxine, VOC-venlafaxine/olanzapine combination

Tab. 2. Beck Depression scale score before and after each week until the fourth week of treatment.

	VEN group		VOC group		p(M-W)
	d	sd	d	sd	
BECK0	26.04	8.13	28.24	6.56	0.297
BECK1	22.96	7.11	20.62	6.53	0.234
BECK2	17.87	7.27	16.12	6.63	0.328
BECK3	12.35	6.01	11.32	6.72	0.320
BECK4	8.09	5.66	8.44	5.87	0.909

VEN-venlafaxine, VOC-venlafaxine/olanzapine combination

Tab. 3. HAMA (Hamilton Anxiety scale) score before and after each week until the fourth week of treatment.

	VEN group		VOC group		p(M-W)
	d	sd	d	sd	
HAMA0	34.00	7.99	40.62	5.29	0.001*
HAMA1	29.00	9.01	28.41	8.75	0.961
HAMA2	22.39	9.01	19.94	9.50	0.317
HAMA3	16.61	7.59	13.12	9.93	0.022*
HAMA4	11.26	8.51	9.32	9.80	0.168

VEN-venlafaxine, VOC-venlafaxine/olanzapine combination.

Tab. 4. SAS (Zung Self-Rating Anxiety scale) score before and after each week until the fourth week of treatment.

	VEN group		VOC group		p(M-W)
	d	sd	d	sd	
SAS0	41.78	4.18	45.71	4.72	0.004*
SAS1	40.22	3.55	41.41	3.37	0.343
SAS2	37.91	3.49	37.41	3.54	0.573
SAS3	36.83	2.95	35.91	3.43	0.317
SAS4	35.74	2.82	34.44	5.00	0.800

VEN-venlafaxine, VOC-venlafaxine/olanzapine combination.

sweating, decrease of libido, akatisia, tremor and dizziness. All adverse effects in patients who continued in the study till the fourth week were slight to moderate and almost all of them disappeared at the end of the fourth week of treatment. The list of adverse effects with the dynamics in particular weeks is present in Table 5.

Tab. 5. Adverse effects evaluated by SARS (Structured Adverse Effects Rating Sscale) in weeks 1-4 in venlafaxine/olanzapine combination (VOC) and venlafaxine (VEN) group.

	Week 1		Week 2		Week 3		Week 4	
	VOC	VEN	VOC	VEN	VOC	VEN	VOC	VEN
Insomnia	0	0	1	0	1	0	1	0
Drowsiness	12	0	11	0	8	0	5	0
Orientation disorders	0	0	0	0	0	0	0	0
Halucinations	0	0	0	0	0	0	0	0
Manic syndrome	0	0	0	0	0	0	0	0
Depressive syndrome	0	0	0	0	0	0	0	0
Collapse states	10	6	9	5	4	1	3	0
Palpitations	8	6	5	5	3	4	1	1
Nauzea	2	1	1	0	0	1	0	0
Obstipation	7	0	6	0	3	0	0	1
Diarhhea	1	1	0	2	0	0	0	0
Dyspeptic difficulties	4	7	1	2	0	0	0	0
Accomodation disorders	7	0	5	0	2	0	0	0
Dry mouth	11	0	9	1	4	0	0	0
Increased salivation	0	0	0	0	0	0	0	0
Swell of nasal mucosa	0	0	0	0	0	0	0	0
Increased sweating	8	7	8	6	3	5	2	3
Micturition difficulties	0	0	0	0	0	0	0	0
Decrease of libido	0	2	0	4	0	3	0	1
Increase of libido	0	0	0	0	0	0	0	0
Ejaculation/ orgasm difficulties	0	0	0	0	0	0	0	0
Menstrual cycle disorders	0	0	0	0	0	0	0	0
Galactorhea	0	0	0	0	0	0	0	0
Dyskineses	0	0	0	0	0	0	0	0
Rigid face	0	0	0	0	0	0	0	0
Walking pertubations	0	0	0	0	0	0	0	0
Rigid forearm and wrist	0	0	0	0	0	0	0	0
Akatisia	3	2	4	2	0	0	0	0
Tremor	1	1	0	0	0	0	0	0
Muscle weakness	4	0	3	0	1	0	0	0
Dizziness (not orthostatic)	6	2	4	2	0	0	0	0
Tongue tremor	0	0	0	0	0	0	0	0
Erection difficulties	0	0	0	0	0	0	0	0

Numbers in columns express number of patients with adverse effect.

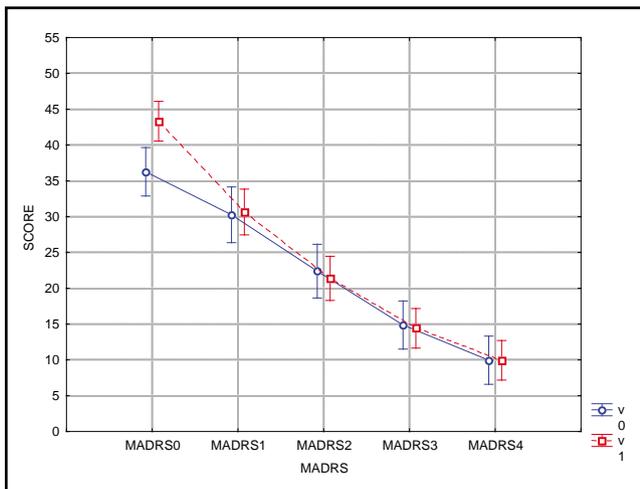


Fig. 1. The dynamics of MADRS score decline during venlafaxine (V0) and combined venlafaxine/olanzapine (V1) medication before and after each week until the fourth week of treatment. Friedman ANOVA: $p_{V0} < 0.000005$, $p_{V1} < 0.000005$. ANOVA of repeated measures $p = 0.001$.

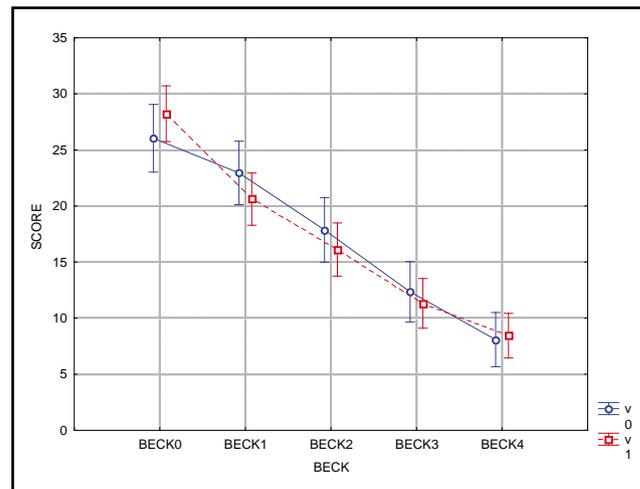


Fig. 2. The dynamics of BECK score decline during venlafaxine (V0) and combined venlafaxine/olanzapine (V1) medication before and after each week until the fourth week of treatment. Friedman ANOVA: $p_{V0} < 0.000005$, $p_{V1} < 0.000005$. ANOVA of repeated measures $p = 0.036$.

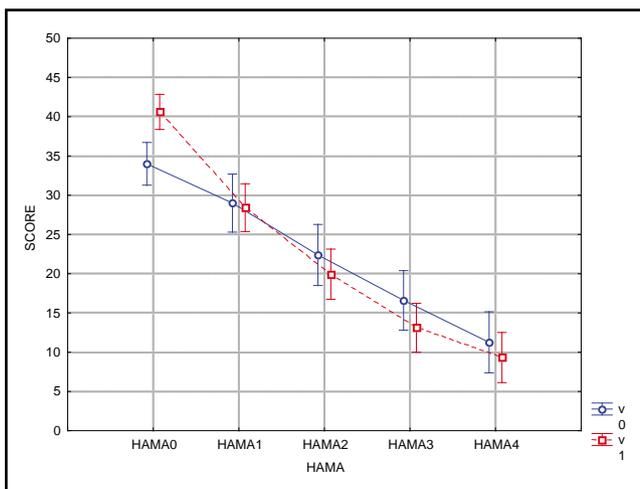


Fig. 3. The dynamics of HAMA score decline during venlafaxine (V0) and combined venlafaxine/olanzapine (V1) medication before and after each week until the fourth week of treatment. Friedman ANOVA: $p_{V0} < 0.000005$, $p_{V1} < 0.000005$. ANOVA of repeated measures $p = 0.001$.

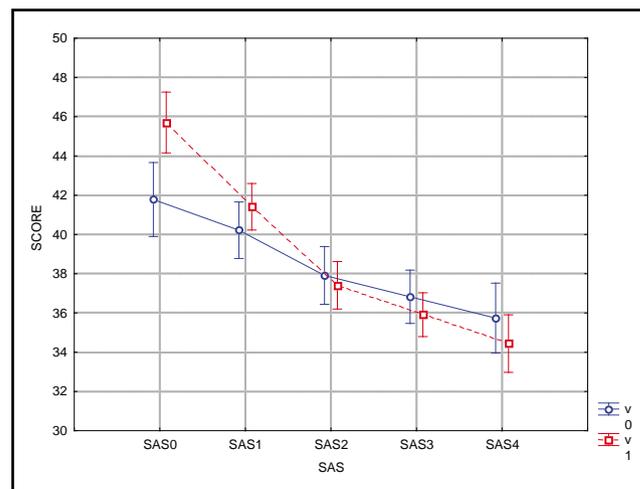


Fig. 4. The dynamics of SAS score decline during venlafaxine (V0) and combined venlafaxine/olanzapine (V1) medication before and after each week until the fourth week of treatment. Friedman ANOVA: $p_{V0} < 0.000005$, $p_{V1} < 0.000005$. ANOVA of repeated measures $p = 0.001$.

DISCUSSION

To our best knowledge, this is the first study evaluating the effects of venlafaxine+olanzapine combination on the rate and the magnitude decrease of anxiety and depressive symptoms in patients with anxious major depressive disorder. We found that VOC decreases the symptoms of anxiety and depression within the first week of treatment and keeps them on the level of patients with less severe depression treated with venlafaxine monotherapy. Moreover, VOC was more effective than venlafaxine monotherapy in objectively evaluated anxiety symptoms (HAMA) in the third week of treatment. Both venlafaxine monotherapy and VOC were effective in reduction of objectively and

subjectively assessed symptoms of anxiety and depression, however we found the significant differences in the dynamics of the symptoms decrease between the anxiety and depressive symptoms. ANOVA of repeated measures revealed the significant results in the effect of time+score difference in all the scales, however there was a slight difference between the anxiety and the depression symptoms decline. Concerning the depressive symptoms, the graphs of the objectively and the subjectively assessed depression (Figures 1 and 2) show that these differences are the most probably caused by more effective/faster symptoms reduction in the VOC group within the first week, whereas in the next weeks of treatment the rate of the score decline in both scales is approximately similar without statistically signifi-

cant differences between groups in any of the following weeks. The symptoms of anxiety are reduced in a different way. The pre-treatment significant differences between groups disappeared already within the first week of treatment and the reduction continued to the second week like in depressive symptoms, however the objectively assessed score evaluated by HAMA decreases in the third week of treatment at significantly lower level compared to the group medicated by venlafaxine monotherapy. Subjectively assessed score by SAS scale was also lower in the VOC group but did not reach statistical significance. We believe that the statistical significance would be achieved in the treatment groups with higher number of subjects. The anxiety scores continued to be slightly lower in the VOC group also in the fourth week of treatment.

Our study indicates two facts. First, in spite of the fact that VOC group had more severe symptoms of both depression and anxiety before treatment, the combination of venlafaxine and olanzapine therapy was more effective in anxiety symptoms reduction than venlafaxine monotherapy from the third week of treatment. Second, the VOC combination was demonstrably more effective in reduction only the symptoms of anxiety, not the symptoms of depression. Interestingly, the depressive symptoms were fastly reduced at the level of less depressive patients within one week of treatment, however the potential additive effect of venlafaxine and olanzapine did not continued to the next weeks. These results are discussed in the following paragraph.

To our best knowledge, the combination of venlafaxine and olanzapine has not been previously compared to the venlafaxine monotherapy in the treatment of depression. However olanzapine in the combination with fluoxetine has been more effective than olanzapine or fluoxetine (Thase *et al.* 2007) and olanzapine, fluoxetine or venlafaxine (Corya *et al.* 2006) administered separately in the treatment of treatment resistant depression and more effective than olanzapine and placebo in the therapy of bipolar I depression (Tohen *et al.* 2003). Moreover, olanzapine augmentation to paroxetine and fluoxetine has been shown to be effective in treatment of symptoms of anxiety in panic disorder and generalized anxiety disorder respectively (Chao 2004; Pollack *et al.* 2006). Venlafaxine has been shown to be more effective than SSRIs in depression treatment (Smith *et al.* 2002) and more effective than citalopram in generalized anxiety disorder (Zhang *et al.* 2013) and paroxetine in social anxiety disorder (Allgulander *et al.* 2004) treatment. The therapeutical effects of olanzapine and fluoxetine combination have been observed already from the first week in therapy of treatment resistant depression (Corya *et al.* 2006) and from the fourth week of bipolar I depression therapy (Tohen *et al.* 2003). Thus, the previous studies indicate that olanzapine and venlafaxine combination should be more effective than venlafaxine monotherapy in management of symptoms of both depression and anxiety. Interestingly,

we observed prompt improvement of both depressive and anxiety symptoms within the first week of treatment by olanzapine and venlafaxine combination followed by maintainance of antidepressive effects at the level of venlafaxine monotherapy whereas anxiolytic effects were even greater from the third week of combined therapy. The combination maintainance of antidepressive effects at the level of patients at monotherapy was probably caused by the fact that patients medicated by venlafaxine/olanzapine had more severe symptoms which include prolonged periods and resistency to medication. The depressive symptoms in patients with MDD are primary, more prominent and thus probably more resistant to treatment than the symptoms of anxiety. The augmented effect of venlafaxine/olanzapine combination on anxiety symptoms could have the implications in pharmacodynamic interactions. Olanzapine, a serotonin (5HT_{2A/2C}) and dopamine (D₁₋₄) antagonist could increase the effects of venlafaxine's serotonin antagonism (Ghio *et al.* 2011). Moreover, olanzapine's anxiolytic effects could be mediated by inceasing of plasma and whole brain progesterin as shown in ovariectomized rats (Frye & Seliga 2003). These effects could combine and could positively affect the symptoms of anxiety which are potentially easily curable than symptoms of depression in patients with severe MDD.

Interesting is also the promptness of effect of venlafaxine/olanzapine combination on both anxiety and depressive symptoms. Our results are consistent with the cases of patients with severe psychotic major depressive disorder in which venlafaxine/olanzapine combination reduced the psychotic depressive symptoms within the first week of treatment (Ghio *et al.* 2011). Authors of the study propose that it could be related to the olanzapine's combined antidepressant and antipsychotic effects mediated by dopamine and serotonin antagonism and dual serotonergic-noradrenergic effect of venlafaxine (Ghio *et al.* 2011). Moreover, both venlafaxine and olanzapine have been shown to increase brain-derived neurotrophic factor in hippocampus (Czubak *et al.* 2009; Li *et al.* 2011) thus their combination could lead to augmented and faster therapeutical effect.

This is the first study revealing better anxiolytic effects of venlafaxine/olanzapine combination than those of venlafaxine monotherapy in patients with anxious MDD. Our results indicate that venlafaxine/olanzapine combination could replace another anxiolytic medication, e.g. benzodiazepines recommended by some guidelines in managing the symptoms of anxiety in patients with MDD (Davidson 2010) already within the first week of treatment. Further research without the limitations of our study including pre-treatment differences and an absence of placebo group is necessary to investigate the anxiolytic and augmented antidepressant effects of venlafaxine and olanzapine combination.

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