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Venlafaxine versus Mirtazapine in the Treatment of Undifferentiated Somatoform Disorder

A 12-Week Prospective, Open-Label, Randomized, Parallel-Group Trial

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Abstract

Objective: We set out to compare the efficacy and tolerability of mirtazapine versus venlafaxine in patients with undifferentiated somatoform disorder (USD) using the Patient Health Questionnaire-15 (PHQ-15).

Methods: This was a 12-week prospective, open-label, randomized, parallel-group trial. The trial consisted of six visits that included baseline and weeks 1, 2, 4, 8 and 12. The primary effectiveness measure was the mean change in PHQ-15 total score from baseline to the end of treatment. Secondary effectiveness measures included the mean changes in total scores on the Beck Depression Inventory (BDI) and the 12-item General Health Questionnaire (GHQ) from baseline to the end of treatment. Ninety-five subjects were randomized to either mirtazapine (n = 50) or venlafaxine (n = 45); 71 subjects completed the study (mirtazapine: n = 39/50 [78%]; venlafaxine: n = 32/45 [71%]).

Results: The mean total score on the PHQ-15 decreased by 34.7% (–8.4, $p < 0.0001$) from baseline to endpoint in the mirtazapine group and by 26.6% (–6.1, $p < 0.0001$) in the venlafaxine group. A marginally significant between-group difference was observed for the mean change in total score on the PHQ-15 from baseline to endpoint ($F = 4.126$, $p = 0.046$). The mean total scores on the GHQ-12 and BDI from baseline to endpoint decreased by –4.9 (29.4%, $p < 0.0001$) and –13.5 (55.9%, $p < 0.0001$), respectively, in the mirtazapine group, and by –4.3 (26.2%, $p = 0.001$) and –9.02 (46.0%, $p < 0.0001$), respectively, in the venlafaxine group. No between-group difference was observed for the mean

changes in total scores on the secondary effectiveness measures from baseline to endpoint. Both treatments were well tolerated.

Conclusion: Our findings suggest that both mirtazapine and venlafaxine may be effective and well tolerated in the treatment of patients with USD. Double-blind, placebo-controlled and/or head-to-head comparison studies are required to allow definite conclusions to be drawn.

Introduction

More than half of outpatients in primary care complain of medically unexplained somatic symptoms.[1,2] In fact, the prevalence of undifferentiated somatoform disorder (USD) is known to be relatively high, although it varies according to the criteria used to identify it. In a recent study, the prevalence of USD in primary-care patients was estimated at 16.1%, and as high as 21.9% if the severity of clinical impairment was ignored.[3] Furthermore, ≥25% of such symptoms may persist at the 1-year follow-up, and they are chronic or recurrent in 20–25% of such patients.[4,5] It has also been shown that somatic symptoms are strongly associated with co-morbid psychiatric disorders, such as depression and anxiety disorders.[5]

The potential association between psychiatric disorders and somatic symptoms has been explored in large epidemiological surveys, which show that approximately 60–70% of depressed or USD patients have a bidirectional relationship.[6,7] Additionally, a large European longitudinal study with a community-based population sample showed that somatic symptoms were frequently reported and were also strongly associated with depressive disorders.[8]

Furthermore, somatic symptoms may negatively impact on treatment outcomes of co-morbid psychiatric disorders,[9] quality of life and functional impairment in affected patients.[10,11] In fact, a recent placebo-controlled, randomized clinical trial (RCT) showed that patients who remitted (Hamilton Depression Rating Scale-17 item [HAMD-17] score ≤8) after 12 weeks of antidepressant treatment (fluoxetine 20 mg/day) had significantly greater early improvement in the HAMD-17 item concerning fatigue and general somatic symptoms than non-remitters.[12] Somatic symptoms were also found to be an important indicator of later occurrence of mood disorders, indicating the importance of appropriate and early intervention for such symptoms.[13]

Dysfunctions in both serotonergic and noradrenergic pathways are considered to be the main biological underpinnings of somatic symptoms.[5] A number of RCTs have demonstrated the efficacy of the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine in the treatment of major depressive disorder (MDD),[14,15] generalized anxiety disorder (GAD),[16-21] social anxiety disorder (SAD),[22] panic disorder,[23-25] post-traumatic stress disorder[26,27] and various pain syndromes.[28-32] Recently, Kroenke et al.[33] reported a 12-week, multicentre RCT that showed that venlafaxine was effective in treating multisomatoform patients in a primary-care setting.

Similarly, the noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine has also been reported to be beneficial in the treatment of MDD, anxiety and various pain symptoms.[34-36]

Despite the fact that both drugs have shown potential benefit in patients with somatic symptoms, there has been a paucity of clinical trials investigating the effectiveness and tolerability of venlafaxine or mirtazapine in patients with USD. Hence, we set out to compare the effectiveness and tolerability of venlafaxine versus mirtazapine in this setting, using

the Patient Health Questionnaire-15 (PHQ-15),[37] which was designed specifically for assessing the severity of somatic symptoms.

Subjects and Methods

Design

This was a randomized, 12-week, open-label, parallel-group trial comparing the effectiveness and tolerability of venlafaxine and mirtazapine in outpatients with USD.

Subjects

The study was reviewed and approved by the institutional review board of Ansan Hospital, Korea University Medical Center, Ansan, Korea. All subjects provided written informed consent prior to participating in the study.

Eligible subjects with USD, based on the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) criteria,[38] were those aged ≥18 years (male or female) who had somatic symptoms almost every day for ≥6 months and were not taking any active prescription medications to control their somatic complaint (over-the-counter [OTC] medications such as paracetamol [acetaminophen] up to 2 g/day and ibuprofen up to 1.2 g/day were allowed). In addition, if the patient was a woman of reproductive age, she had to agree to use adequate contraception.

Subjects were excluded if they had a history of (and/or current) psychotic disorders (such as schizophrenia, schizoaffective disorder and bipolar disorder) or had current DSM Axis I disorders that could possibly account for the somatic symptoms (e.g. MDD, anxiety disorders, factitious disorder, malingering or another somatoform disorder such as somatization disorder). In addition, those exhibiting substance abuse or dependence in the previous 12 months, those with a history of hypersensitivity to venlafaxine or mirtazapine, and those currently being treated with any psychotropic medication were excluded. Subjects who had participated in any clinical trials in the previous 30 days or were involved in workers' compensation, disability or related litigation were also ineligible. Women who were breast-feeding or who were pregnant were also excluded.

Diagnosis

The Axis I diagnosis of USD was evaluated according to DSM-IV criteria by consensus between two board-certified psychiatrists (CH, BHL) upon study entry.

Medication

The allocation of each medication was based on a computer-generated randomization code. The two medications were dosed using a flexible titration strategy, starting at 15 mg/day and 37.5 mg/day, increasing weekly in 15 mg/day and 37.5–75 mg/day increments, and reaching maximum doses of 60 mg/day and 225 mg/day for mirtazapine and venlafaxine, respectively, depending on clinical response and tolerability. No other psychotropic medications were permitted during the study, other than hypnosedatives for insomnia and benzodiazepines for anxiety; use of these for temporary control only of these symptoms was allowed. Use of prescription analgesics, muscle relaxants and corticosteroids was not allowed during the study. Use of concomitant medications, such as OTC paracetamol, was allowed only on an as-needed basis.

Assessment

The study lasted for 12 weeks with six visits: at baseline and at weeks 1, 2, 4, 8 and 12. Assessments for effectiveness and tolerability were made at each visit.

Effectiveness

Primary Endpoint

The primary effectiveness measure was the mean change in PHQ-15[37] total scores from baseline to the end of treatment.

Secondary Endpoints

Secondary effectiveness measures were the mean changes in total scores on the Beck Depression Inventory (BDI)[39] and the 12-item General Health Questionnaire (GHQ-12)[40] from baseline to the end of treatment.

Tolerability

Physical examination, electrocardiogram (ECG), complete blood count, blood chemistry, urinary analysis and pregnancy tests were performed at baseline and at the end of treatment. Vital signs and weight were measured at each visit. All adverse events were recorded during the study and were assessed using the Systematic Assessment for Treatment Emergent Events–General Inquiry. A treatment-emergent adverse event was defined as any adverse event reported after subjects were given medications.

Data Analysis

All patients who received at least one dose of a study medication and had at least one post-baseline visit assessment were included in the intent-to-treat (ITT) population. The last available post-baseline measurement was assigned as an endpoint (last observation carried forward [LOCF]). An ITT with LOCF approach was conducted for the analysis of effectiveness outcomes. The primary and secondary endpoints relative to continuous variables between the venlafaxine and mirtazapine groups were compared by analysis of variance (ANOVA), with repeated measurements. Categorical variables were analysed by chi-squared (χ^2) or Fisher's exact test. Descriptive statistics were also used when appropriate. All statistical significance was two-tailed and set at $p < 0.05$. Statistical analysis was carried out using STATA software version 10.0 (StataCorp, College Station, TX, USA).

Results

Subjects

Ninety-five subjects were enrolled in the study; of those, 50 and 45 were assigned to receive either mirtazapine or venlafaxine, respectively. No statistically significant difference was detected in any baseline data between the groups (table I). In both treatment groups the duration of somatic symptoms clearly reflected the chronic nature of the condition, being >3 years (mean ± SD 32.5 ± 22.3 months) in many cases. The mean (± SD) number of medical/surgical clinics before psychiatric visits was 3.0 ± 2.2. Overall, at study entry in the two treatment groups, the number of somatic complaints was high (mean ± SD 5.0 ± 5.5 for all subjects, maximum 15). Socioeconomic, marital, educational, alcohol and smoking status were similarly distributed, with no difference between treatment groups (table I).

Seventy-one subjects completed the study (mirtazapine: n = 39/50 [78%]; venlafaxine: n = 32/45 [71%]); 11 and 13 subjects, respectively, dropped out. Eight subjects in the mirtazapine group and nine in the venlafaxine group discontinued the medication for personal reasons, without further medical consultation. Failure to follow up was the most common reason, with withdrawal of consent being next. Three subjects in the mirtazapine group and four subjects in the venlafaxine group stopped the study because of adverse events. However, all patients returned for at least one post-baseline follow-up visit in both treatment groups, yielding an ITT with LOCF population of 77 (39 mirtazapine, 38 venlafaxine).

Table I. Baseline characteristics of subjects in the mirtazapine and venlafaxine treatment groups[a]

Demographic variables	Mirtazapine group (n = 50)	Venlafaxine group (n = 45)
Female [no. (%)]	30 (60.0)	28 (62.2)
Age (y) [mean (SD)]	45.9 (13.1)	44.5 (12.0)
Income status [no. (%)]		
high	3 (6.0)	1 (2.2)
middle	39 (78.0)	36 (80.0)
low	8 (16.0)	8 (17.8)
Marital status [no. (%)]		
married	42 (84.0)	37 (82.2)
single	3 (6.0)	4 (8.9)
divorced	0 (0.0)	2 (4.4)
widowed	5 (10.0)	2 (4.4)
Education (y)		
≤12	25 (50.0)	21 (46.7)
>12	25 (50.0)	24 (53.3)
Alcohol use [no. (%)][b]		
never use	12 (24.0)	12 (26.7)
1 drink per week	32 (64.0)	30 (66.7)
≥2 drinks per week	6 (12.0)	3 (6.7)
Smoking history [no. (%)]		
no	42 (84.0)	34 (75.6)
yes	8 (16.0)	11 (24.4)
Admission history [no. (%)]		
no	11 (22.0)	6 (13.3)
yes	39 (78.0)	39 (86.7)
No. previously seeking treatment for somatic symptoms [no. (%)][c]	2.7 (2.1)	3.4 (2.2)
Duration of somatic symptoms (mo) [mean (SD)]	35.1 (26.8)	29.6 (15.7)
No. of somatic symptoms by self-report [mean (SD)][d]	5.6 (5.4)	4.2 (5.5)
PHQ-15 total score [mean (SD)]	24.4 (4.2)	22.9 (4.2)
BDI total score [mean (SD)]	23.5 (15.2)	18.8 (11.3)
GHQ total score [mean (SD)]	16.3 (3.5)	16.5 (3.9)

a All comparisons were non-significant. Diagnosis was evaluated and confirmed at study entry.

b No patient met alcohol abuse or dependence criteria according to Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV).[38]

c Number who previously visited a clinic department, i.e. internal medicine, family medicine, etc.

d Number obtained from patients' self-report before evaluating PHQ-15 score.

BDI = Beck Depression Inventory; **GHQ** = General Health Questionnaire; **PHQ-15** = Patient Health Questionnaire.

Medication

The mean modal dose throughout the study was 31.7 ± 25.4 mg/day and 105.5 ± 168.6 mg/day in the mirtazapine and venlafaxine groups, respectively. Eighteen (46%) and four (10%) patients were given lorazepam and alprazolam, respectively, as needed in the mirtazapine group; similarly, 12 (32%) and 11 (29%) patients were administered lorazepam and alprazolam, respectively, as needed in the venlafaxine group.

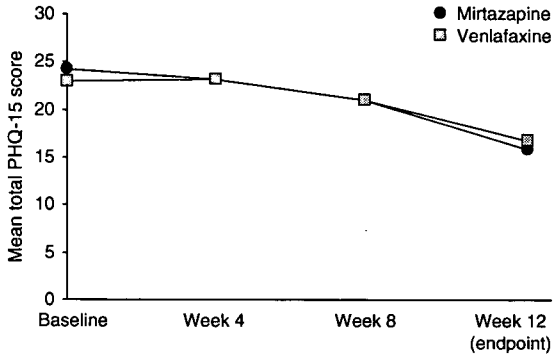

Fig. 1. Change in mean total score on the Patient Health Questionnaire-15 (PHQ-15) by visit throughout the study in the two treatment groups. The mean total score on the PHQ-15 decreased significantly at week 8 ($p < 0.01$ in both groups) and at study endpoint ($p < 0.0001$ in the mirtazapine group, $p < 0.0001$ in the venlafaxine group) compared with baseline in both treatment groups. There was a marginal between-group difference in reduction of the mean total score on PHQ-15 from baseline to endpoint during the study ($F = 4.126$, $p = 0.046$).

Effectiveness

Primary Endpoint

The total score on the PHQ-15 decreased significantly by 34.7% (–8.4, $p < 0.0001$) from baseline to endpoint in the mirtazapine group and by 26.6% (–6.1, $p < 0.0001$) in the venlafaxine group. A marginal significance was observed in the between-group difference for the mean change in total score on the PHQ-15 from baseline to endpoint ($F = 4.126$, $p = 0.046$); however, the observed difference for the mean change in total score on the PHQ-15 was 8.1%, favouring mirtazapine over venlafaxine. Among completers, no significant difference was observed in the between-group mean changes in total score on the PHQ-15 from baseline to endpoint ($F = 3.18$, $p = 0.08$).

In no case did the PHQ-15 total score worsen at the end of treatment in either treatment group. The mean total scores on the PHQ-15 throughout the study by visit are summarized in figure 1 (ITT population).

Secondary Endpoints

The mean total scores on the GHQ-12 and BDI from baseline to endpoint decreased significantly by –4.9 (29.4%, $p < 0.0001$) and –13.5 (55.9%, $p < 0.0001$), respectively, in the mirtazapine group. Similarly, the mean total scores on the GHQ-12 and BDI from baseline to endpoint decreased significantly by –4.3 (26.2%, $p = 0.001$) and –9.02 (46.0%, $p < 0.0001$), respectively, in the venlafaxine group ($p < 0.0001$). However, no between-group difference was observed for the mean changes in total scores on the secondary effectiveness measures from baseline to endpoint. The mean changes in secondary effectiveness measures from baseline to endpoint in both treatment groups are shown in figure 2.

Tolerability

Overall, both treatments were well tolerated (table II). The most common adverse experiences reported during the 12-week treatment period were dry mouth ($n = 5$ in the mirtazapine and $n = 6$ in the venlafaxine group), followed by somnolence ($n = 4$), yawning ($n = 3$) and dizziness ($n = 3$) in the mirtazapine group and nausea ($n = 4$) in the venlafaxine group. Three subjects in the mirtazapine group (all for somnolence) and four subjects in the

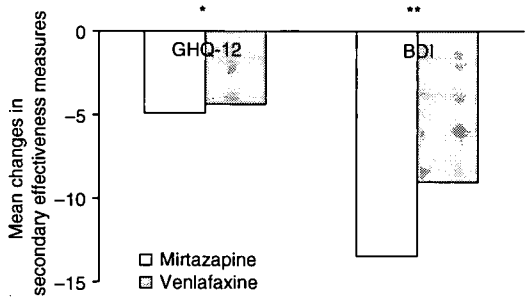

Fig. 2. Mean changes in secondary effectiveness measures from baseline to endpoint in the two treatment groups. There were no between-group differences in any measures. **BDI** = Beck Depression Inventory; **GHQ-12** = 12-item General Health Questionnaire; p-values shown vs baseline. * Mirtazapine $p < 0.0001$ vs venlafaxine $p = 0.001$; ** mirtazapine $p < 0.0001$ vs venlafaxine $p < 0.0001$.

Table II. Adverse events reported by the mirtazapine and venlafaxine treatment groups[a]

Adverse events	Mirtazapine group (n = 50)	Venlafaxine group (n = 45)
Nausea	2 (4.0)	4 (8.9)
Vomiting	1 (2.0)	2 (4.4)
Somnolence	4 (8.0)	1 (2.2)
Dry mouth	5 (10.0)	6 (13.3)
Anorexia	1 (2.0)	2 (4.4)
Yawning	3 (6.0)	0 (0.0)
Sweating	2 (4.0)	1 (2.2)
Insomnia	0 (0.0)	2 (4.4)
Constipation	0 (0.0)	0 (0.0)
Dizziness	3 (6.0)	2 (4.4)
Headache	1 (2.0)	1 (2.2)

a Data represent number (%). Three subjects (somnolence 3) in the mirtazapine group and four (nausea 3, dry mouth 1) in the venlafaxine group discontinued because of drug adverse effects.

venlafaxine group (three for nausea and one for dry mouth) stopped the study because of adverse events. However, no serious adverse events were reported in either group.

Discussion

This was the first study to compare the effectiveness and tolerability of mirtazapine and venlafaxine over 12 weeks in psychiatric outpatients with USD. After the 12-week treatment, the primary effectiveness measure, the mean change in total score on the PHQ-15 from baseline to endpoint, decreased significantly in both groups, indicating no large difference in effectiveness between the two antidepressants. Compared with baseline, the magnitude of improvement on the primary endpoint was approximately 35% and 27% in the mirtazapine and venlafaxine treatment groups, respectively. No studies have investigated the comparative effectiveness of antidepressants, including SNRIs and NaSSAs, for patients with USD using the PHQ-15 total score as a primary endpoint.

Recently, venlafaxine was compared with placebo for the treatment of patients with multi-somatoform disorder over 12 weeks using the PHQ-15 total score as the measure of efficacy.[33] In that study, the magnitude of improvement in mean PHQ-15 total score was 46.1% and 36.5% in venlafaxine-treated and placebo-treated groups, respectively, with no between-group differences ($p = 0.097$).[33] In our study, the magnitude of improvement in the primary endpoint was numerically lower than that of either the venlafaxine-treated or the placebo-treated groups in the previous study.[33] These differences in results between our study and the previous RCT may have been related to the fact that subjects in our study had more chronic symptoms, with longer durations of illness. Additionally, the lower dose of venlafaxine (mean 105.5 mg/day) than the previous study (mean 177 mg/day) may also have played a role in the smaller reductions in mean PHQ-15 scores seen in our study. Differences in other sample characteristics such as age, sex and co-morbidities may also have contributed.

Another line of evidence supporting the effectiveness of mirtazapine and venlafaxine in USD arises from the results of several randomized studies that reported significant treatment effects on subscores of anxiety/somatization or somatic pain on the depression scale (HAMD-17) in patients with depressive or anxiety disorders.[41,42] When considered in light of these results, our findings in terms of the effect of treatment on the primary endpoint indicate the potential effectiveness of mirtazapine and venlafaxine, with no significant between-group difference for these symptoms.

Most somatic symptoms are considered to be modulated by both serotonin and norepinephrine neurotransmitters. Hence, dual action antidepressants, such as SNRIs and NaSSAs, may be more effective against such symptoms than unimodal antidepressants (duloxetine[43] and milanacipran,[44] for example, have proven efficacy for treatment of fibromyalgia and neuropathic pain disorders), although there has been a paucity of direct comparisons between such medications.[4] However, there is

no evidence to support the superiority of venlafaxine or mirtazapine over other antidepressants to date, and this should be addressed in future randomized, double-blind, active drug-controlled clinical trials.

A question for clinicians and patients is whether an improvement in the PHQ-15 total score is clinically valuable or meaningful. The PHQ-15 has been extensively used as an outcome measure of the severity of somatic symptoms and has been validated in over 6000 patients.[33,37,45] However, the correlation between clinical improvement and changes in the PHQ-15 score and, in particular, the magnitude of improvement in the PHQ total score that corresponds to an actual benefit for patients in clinical practice have not been established. This question was also raised by the previous venlafaxine trial,[33] in which venlafaxine was indistinguishable from placebo in terms of change in the PHQ-15 total score as a primary endpoint. Although recent evidence has further supported the utility of PHQ-15 as a measure of somatization,[46,47] more efforts to develop and/or update objective assessment scales of somatic symptoms in such patients are needed. Importantly, other secondary outcome measures in our study did show statistically significant differences between the drug and placebo groups. This suggests that more clinical data are needed using the PHQ-15 total score as a primary outcome measure for treating medically unexplained somatic symptoms in antidepressant trials.

In our study, a trend toward significant reduction in mean PHQ-15 total scores by week 8 was observed, and this became significant through to the end of treatment in both treatment groups, suggesting a need for ≥8 weeks of antidepressant treatment for somatic symptoms. As somatic symptoms are considered chronic and recurrent,[4] the long-term effectiveness of treatments should also be investigated. In this context, the early improvement in mean total score on the PHQ-15 by week 8 and its persistence, demonstrated in both treatment groups in our study, may be relatively persuasive to clinicians.

We did not find any significant difference in the secondary effectiveness measure GHQ-12 between the two treatment groups. Not surprisingly, we did find significant reductions in mean total scores on the BDI from baseline to endpoint in both treatment groups, but there was no between-group difference.

A fundamental issue exists regarding whether the effect of antidepressants on somatic symptoms is a direct or indirect effect. An increasing number of studies have suggested that antidepressants may have a direct effect on somatic symptoms, outweighing possible indirect effects through improvement of psychological symptoms, such as depression or anxiety.[45,48-52] However, clinicians should be cautious on this point until sufficient evidence and clinical data are available.

The doses of mirtazapine and venlafaxine used in the study were within the ranges approved for the treatment of MDD and anxiety disorders by the US FDA. Comparison of the smaller reduction in the mean PHQ-15 total score observed in our study with the higher reduction observed in the previous report (in which a higher mean dose of venlafaxine was administered)[33] suggests that a dose-response relationship may exist in the treatment of somatic symptoms with venlafaxine. Therefore, it would be interesting to conduct a fixed-dose trial of venlafaxine to determine whether a dose-response relationship was present and to further assess treatment strategies for patients with USD.

Common adverse events seen in our study were no different from those reported in other randomized clinical trials of mirtazapine and venlafaxine.[53-57] No serious adverse event was reported in either treatment group. We found that both antidepressants were tolerated in the treatment of medically unexplained somatic symptoms.

Finally, our study may at least contribute to the psychopharmacological treatment field for patients

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with USD by demonstrating a tolerable profile for mirtazapine and venlafaxine in this setting; the open-label study design does not provide definite information with regard to the efficacy of the medications because of the lack of a placebo group. Our study may also encourage the conduct of future clinical trials for the treatment of USD since we observed a potential usefulness for both medications in the treatment of USD. This study is the first direct comparison study between mirtazapine and venlafaxine in USD that provides a preliminary possibility for control of USD. Future clinical trials should increase our understanding of the utility of both medications and other antidepressants for the treatment of somatic syndromes.

Limitations

The major shortcoming of the present study was its small sample size. Because the study design was open-label and did not include a placebo control group, the reduction in the PHQ-15 total scores may simply have been due to the natural course of USD; definite conclusions about the efficacy of the test drugs are therefore not possible. Observer bias should be also considered. We cannot exclude the effect of co-morbid psychiatric disorders on the antidepressants' effects because of the absence of a structured clinical interview, although patients were rigorously evaluated according to DSM-IV criteria. Finally, we should consider that concomitant use of benzodiazepines may also have confounded the effects of both antidepressants in the treatment of somatic symptoms.

Conclusion

Mirtazapine and venlafaxine may be useful in the treatment of patients with USD. Our results are encouraging, and double-blind, placebo-controlled and/or head-to-head comparison studies would be useful to allow more informative and definite conclusions to be drawn.

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