The Combined Treatment of Venlafaxine and Quetiapine for Treatment-Resistant Depression: A Clinical Study

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The authors studied the efficacy and safety of combined venlafaxine and quetiapine treatment for treatment-resistant depression (TRD) by dividing 95 TRD patients into two treatment groups: a combined venlafaxine (225 mg/day) and quetiapine (400 mg/day) group and a venlafaxine-only (225 mg/day) group for 8 weeks. Efficacy was assessed with the Hamilton Rating Scale for Depression, 17 items (Ham-D–17) and the Hamilton Rating Scale for Anxiety (Ham-A); safety was assessed with the Treatment-Emergent Symptom Scale (TESS). The two groups showed significant differences for the Ham-D–17 and Ham-A and no differences on the TESS. Combined venlafaxine and quetiapine treatment showed good efficacy and safety in TRD.

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The incidence of clinical depression is high, affecting as many as 4.3% of Chinese residents.[1] Antidepressant monotherapies are ineffective in many patients.[2] Moreover, about one-third of patients with major depressive disorder do not experience satisfactory improvement with their treatments, and thus have their diagnoses modified to treatment-resistant depression (TRD).[2] The TRD diagnosis is made when patients who, despite receiving appropriate treatments (in terms of both dose and time-course) with at least two different antidepressants, do not show clear improvement as indicated by a Hamilton Rating Scale for Depression–17 item (Ham-D–17) score reduction of less than 50%.[3,4]

Previous studies have examined therapeutic options for TRD, including augmentation therapies.[4–6] Good results have been reported for combining lithium with classical antidepressants, as well as for combining triiodothyronine with buspirone.[7] Also, it has been suggested that atypical antipsychotics (AAPs), such as olanzapine, may be used as a synergist with fluoxetine therapy.[8]

Depression is thought to be a neuromodulatory disorder involving the norepinephrine (NE) and serotonin (5-HT) systems; some studies have also implicated dopamine transmission in the limbic system in depression.[9] Venlafaxine is a dual NE and 5-HT reuptake inhibitor that has been recommended for bipolar depression by the U.S. Food and Drug Administration. Venlafaxine has previously been shown to be helpful for improving emotional and cognitive symptoms[9] and was an effective treatment for major depression.[2,10] It has been suggested that AAPs that antagonize 5-HT_2 receptors might enhance the antidepressant effects of serotonin-reuptake inhibitors.[9] Thus, we hypothesized that quetiapine, which antagonizes 5-HT_2, as well as type 1 and 3 dopaminergic receptors and type 1 histaminergic receptors, may enhance the therapeutic efficacy of venlafaxine by increasing synaptic 5-HT and DA levels. The present study examined whether the efficacy of venlafaxine in the treatment of TRD could be improved by combining it with quetiapine.

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TABLE 1. Treatment Efficacy at the End of the 8-Week Treatment Period, N (%)

Group	N	Cure	Substantial Improvement	Low-Level Improvement	No Effect	Effective Rate
Control	46	12 (26.09%)	20 (43.48%)	10 (21.74%)	4 (8.69%)	32 (69.57%)
Experimental	49	19 (38.78%)	24 (48.98%)	5 (10.20%)	1 (2.04%)	43 (87.76%)*

*$p < 0.05$.

MATERIALS AND METHODS

Clinical Data

A cohort of 95 patients (46 men, 49 women) with TRD were enrolled in this study from January 2009 to June 2011. The patients were randomly divided into an experimental (N=49; 24 men, 25 women) and a control group (N=46; 22 men, 24 women) by coin-toss. The control group ranged in age from 23 to 66 years old, with an average age of 42.6 (SD: 5.4) years, and the experimental group ranged in age from 21 to 63 years, with an average age of 41.8 (SD: 5.9) years. The study was approved by our local ethics committee. Written consent was obtained from all patients when they enrolled in the study.

The inclusion criteria were a diagnosis of TRD and no previous use of venlafaxine or quetiapine. A TRD diagnosis was accepted when the CCMD-3 and DSM-IV diagnostic criteria for depressive episodes was met; the patient's Ham-D–17 score was ≥20; and the patient had not achieved a Ham-D–17 score reduction of at least 50% with previous antidepressant treatments (at least two different antidepressant therapies with clinically-appropriate dosage and time-course).

Treatment

After a 1-week drug washout phase, the patients commenced an 8-week treatment period in accordance with their group assignments. During the first 4 days, all subjects received venlafaxine hydrochloride, sustained-release 75-mg capsules only (Yi-Nuo-Si, from Pfizer). From the 5th day onward, patients in the experimental group also received quetiapine (Si-Rui-Kang, from AstraZeneca, 200 mg per capsule) at 100 mg/day. The quetiapine dose was then increased by 50–100 mg/day every 3 days. The final dose of quetiapine was 200–400 mg/day, with an average dose of 324.42 (SD: 56.35) mg. At the same time, from the 7th day onward, the venlafaxine dose for both groups was increased to 225 mg/day and adjusted according to the patient's response to the drug(s).

Evaluation

The Ham-D–17 and Hamilton Anxiety Scale (Ham-A) were administered 1 day before the treatment period and biweekly thereafter during the treatment period. The Treatment-Emergent Symptom Scale (TESS) was administered biweekly during the treatment period, as well. A Ham-D–17 score <7: cure; a reduction rate more than 50% suggested efficacy; more than 25% suggested progress/improvement; and less than 25% change suggested a nonfunctional effect. The Ham-A and TESS scores were used as associated indices. The patients' blood pressure, body weight, complete blood count panel, full biochemical panel, plasma prolactin level, and electrocardiogram were assessed at the beginning of the study and 2 weeks after the beginning of treatment.

Statistical Analysis

All data were represented as means (standard deviations [SD]) and analyzed with SPSS 12.0 software (Chicago, IL, U.S.). χ^2 and *t*-tests were applied, and $\alpha < 0.05$ was considered to be statistically significant in all cases.

RESULTS

Dosages

In the experimental group, 12 patients had a final venlafaxine dose of 150 mg/day, and 37 patients had a final venlafaxine dose of 225 mg/day (mean: 206.63 [32.59] mg/day). In the control group, 10 patients had a final venlafaxine dose of 150 mg/day, and 36 patients had a final venlafaxine dose of 225 mg/day (mean: 208.70 [31.28] mg/day). The venlafaxine dosage did not differ significantly between the two groups (t=0.314; NS). Venlafaxine dosage did not correlate with patients' Ham-D–17 scores.

Treatment Efficacy

The efficacy data for the combined therapy and monotherapy are reported in Table 1. At the end of the 8-week

TABLE 2. Ham-D–17 and Ham-A Scale Scores in Experimental and Control Groups

	Ham-D–17 Score			Ham-A Score		
Time-Point	**Control**	**Experimental**	***t***	**Control**	**Experimental**	***t***
Pre-treatment	25.78 (4.37)	25.96 (4.36)	NS	23.96 (3.30)	23.98 (2.88)	0.108
2 weeks	20.52 (3.81)	19.16 (3.18)	1.510*	19.76 (2.64)	17.67 (2.55)	4.474*
4 weeks	18.48 (3.15)	14.67 (2.31)	5.213*	16.54 (2.35)	13.86 (1.78)	6.924*
6 weeks	15.78 (3.05)	11.65 (2.23)	5.046*	13.72 (2.00)	10.43 (1.38)	7.810*
8 weeks	14.24 (4.14)	10.08 (2.60)	5.899*	11.74 (2.50)	8.71 (2.11)	6.387*
t	15.12**	18.16**		20.44**	28.70**	

Values are mean (standard deviation).
*p<0.01 Experimental group versus Control group
**p <0.01 Before versus After treatment

experimental period, the effective rate in the experimental, combined-therapy group showed a significantly higher effective rate (87.6%; 43/49 cases) than the control, monotherapy group (69.57%; 32/46 cases; χ^2=4.723; p <0.05).

The Ham-D–17 and Ham-A scores improved steadily (decreased) through the treatment period for both groups (Table 2). The Ham-D–17 and Ham-A scores did not differ between the groups at the initial pretreatment assessment. At all biweekly assessments thereafter, the experimental, combined-treatment group had lower Ham-D–17 and Ham-A scores than the control, monotherapy group (all p <0.01).

Secondary Drug Effects (Side Effects)

As shown in Table 3, the experimental group showed a greater incidence of excessive sedation and weight gain, and a lower incidence of insomnia, relative to the control group, as determined by the TESS. Other adverse reactions occurred at similar rates in the two groups. The overall adverse-reaction rate did not differ significantly between the two groups (Table 3).

DISCUSSION

In the present study, we observed a significantly better effective rate in patients given a combined venlafaxine and quetiapine treatment than in control patients given only venlafaxine for an 8-week study period. Patients did not drop out of the study, despite the presence of some side effects (as indicated by TESS assessments), which indicates that both treatment regimens were well tolerated.

These findings support the idea that the addition of an AAP, such as quetiapine, can improve antidepressant therapy efficacy in patients with TRD.[8,11–13] In their 2009 review, Carvalho et al.[8] found a convergence of evidence supporting the possible efficacy of some AAPs as augmentative agents delivered in combination with SSRIs, but they also underscored the need for adequately-powered, controlled trials on augmentation pharmacotherapies for TRD treatment. Shelton and Papakostas' review of the use of AAPs in TRD,[11] which also incated that AAPs can be effective add-on agents, expressed concern regarding risks for metabolic syndrome and tardive dyskinesia. However, in our patient populations, we did not observe any severe secondary effects. Longer-term studies will be needed to properly assess long-term risks.

In our control (monotherapy) group, 8 patients showed blood pressure elevation, including 2 patients who had previously had normal-range blood pressure. The blood

TABLE 3. Incidence Rates of Adverse Reactions According to the TESS

Symptom	**Control (N=46)**	**Experimental (N=49)**
Dry mouth	3 (6.52%)	2 (4.08%)
Constipation	1 (2.17%)	3 (6.12%)
Gastrointestinal reactions	4 (8.7%)	5 (10.2%)
Excessive sedation	3 (6.52%)	10 (20.41%)*
Excited agitation	4 (8.7%)	5 (10.2%)
Insomnia	8 (17.39%)	2 (4.08%)*
Tremor	2 (4.35%)	2 (4.08%)
Dizziness, headache	7 (15.22%)	9 (18.37%)
Weight gain	3 (6.52%)	8 (16.33%)*
Sexual dysfunction	2 (4.35%)	2 (4.08%)
Elevated blood lipids	4 (8.7%)	6 (12.24%)
Elevated blood pressure	8 (17.39%)	9 (18.37%)

TESS (Treatment-Emergent Symptom Scale): items with incidence rates of 0 for both groups are not listed here.
*p <0.01 Experimental group versus Control group

pressure of these 2 patients returned to normal range when their venlafaxine dose was decreased and captopril was added (25 mg, three times per day). There were also 9 patients whose blood pressure increased in the experimental (combined therapy) group; however, none reached an abnormal level. The mechanisms by which these drugs may interact with blood pressure regulation have not yet been clarified.

There are a few limitations of this study that should be noted. First, the trial was open-label (not blinded); and, second, the study cohort was small. Thus, it may be that more significant differences would be observed with larger study groups.

In conclusion, the present study showed that a combined treatment of venlafaxine and quetiapine provided benefits for TRD patients beyond those seen with venlafaxine alone. Also, a target venlafaxine dose of 225 mg/day was safe for patients in combination with quetiapine at a dose of 400 mg/day.

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