Combined Treatment With Venlafaxine and Tricyclic Antidepressants in Depressed Patients Who Had Partial Response to Clomipramine or Imipramine: Initial Findings

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Background: We report, after 3 years of work, a case series showing our initial results (efficacy, tolerability, and safety) with the addition of venlafaxine immediate release (IR) to either clomipramine or imipramine in depressed patients who had shown only partial response to maximal doses of one of those tricyclic antidepressants (TCAs) and no further improvement after addition of usual augmentation drugs.

Method: Eleven patients were treated, 10 of them having a recurrent depressive disorder (DSM-IV) and all of them having current major depression (DSM-IV) that in 9 patients was moderate or severe despite intense TCA treatment as well as usual augmentations. Under open and outpatient conditions, we maintained TCA doses, discontinued previous augmentations, and then added venlafaxine IR to a maximum dosage, if necessary, of 150 mg every 12 hours. There was no control group. Response was assessed using the 17-item Hamilton Rating Scale for Depression (HAM-D), DSM-IV criteria, the Clinical Global Impressions-Severity of Illness scale, and persistence of improvements after 6 months. We measured clinical tolerance (using the UKU Side Effect Rating Scale), blood pressure and heart rate, electrocardiogram (ECG), and blood TCA levels after adding venlafaxine IR.

Results: A sustained improvement (> 50% decrease in HAM-D score plus decrease in DSM-IV severity level) appeared in 9 patients, and sustained full remission (DSM-IV criteria plus HAM-D score < 5) in 7. Panic-agoraphobic symptoms improved in the 2 patients suffering from them. There were no dropouts, and tolerability was good. No significant changes in blood pressure and heart rate, ECG, or blood tricyclic levels were found.

Conclusion: Addition of venlafaxine to clomipramine or imipramine could be an effective and safe augmentation strategy in depressive patients with partial response to maximum-dose monotherapy. A consistent replication of these initial findings is strongly needed.

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Usual augmentation drugs[1] seem to be effective in no more than 50% of treatment-resistant depressed patients,[2] and many of them may induce disturbing and/or dangerous side effects,[2] toxicity,[2] or severe drug interactions[2,3]; have medical contraindications; or require laboratory monitoring.[2] Most problems coincide in the more widely used strategies: lithium salts and tricyclic antidepressant (TCA)/selective serotonin reuptake inhibitor (SSRI) combinations. We thus consider venlafaxine to be an alternative augmentation drug with some advantages: (1) intrinsic serotonergic (5-HT) and noradrenergic effect,[3–6] especially suited for resistant depression[7]; (2) acceptable tolerability[8]; (3) lack of known significant drug interactions[4,8–11]; and (4) relative lack of known medical risks, except for the appearance of dose-dependent, elevated supine blood pressure in some cases (according to Danjou and Hackett,[8] 3.9% [systolic] and 5.1% [diastolic] of 509 patients taking > 200 mg/day; significant systolic increase was defined as 20 mm Hg [and systolic blood pressure ≥ 180 mm Hg], and diastolic increase as 15 mm Hg [and diastolic blood pressure ≥ 105 mm Hg] in at least one blood pressure measurement).

METHOD

Description of the Sample

For the past 3 years, we have augmented TCAs with venlafaxine in 11 patients (10 of them women) aged 35 to 54 years (mean = 44 years). Ten patients had a recurrent depressive disorder (DSM-IV) lasting 7 to 25 years

Table 1. Summary of Results of Combined Treatment With Venlafaxine and Tricyclic Antidepressants in Partially Resistant Depressed Patients (N = 11)[a]

			Baseline[b]					With Venlafaxine Treatment[c]			
Patient	TCA, mg/d	Other Augmentation	Blood TCA Level (ng/mL)	DSM-IV Severity	CGI-S Score	17-Item HAM-D Score	Venlafaxine mg/d[d]	DSM-IV Severity	CGI-S Score	17-Item HAM-D Score	Change in Blood TCA Level[e]
1	Imipramine, 250	Lithium, T_4	> 250	Severe chronic	6	29	300	Mild	3	12	+10%
2	Clomipramine, 225	Lithium	> 250	Severe chronic	5	25	225	Full remission	1	< 5	None
3	Clomipramine, 150	Lithium, T_4	> 250	Severe chronic	5	26	300	Unchanged	5	27	None
4	Imipramine, 200	Citalopram	< 200	Severe	5	27	300	Mild	3	12	–10%
5	Clomipramine, 150	Citalopram, T_4	< 200	Severe	5	25	150	Full remission	1	< 5	None
6	Clomipramine, 150	Pindolol, buspirone	> 250	Moderate	4	23	150	Full remission	1	< 5	None
7	Clomipramine, 150	Lithium, citalopram	> 250	Moderate	4	21	300	Unchanged	4	23	+12%
8	Clomipramine, 225	Pindolol, T_4	> 250	Moderate	4	23	150	Full remission	1	< 5	None
9	Clomipramine, 187	…	> 250	Moderate	4	24	150	Full remission	1	< 5	None
10	Clomipramine, 375	Methylphenidate, pindolol	> 250	Mild	3	19	225	Full remission	1	< 5	None
11	Imipramine, 200	…	< 200	Mild	3	20	75	Full remission	1	< 5	None

[a]Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness Scale, HAM-D = Hamilton Rating Scale for Depression, T_4 = levothyroxine, TCA = tricyclic antidepressant.
[b]Two weeks after discontinuing previous augmentations, before venlafaxine addition.
[c]After 2 months of taking the final dose of venlafaxine, and persistent during 6 months of treatment.
[d]Twice-daily regimen.
[e]Compared with baseline blood level.

(mean = 12.5 years), and the remaining patient had a first severe major depressive episode (DSM-IV) lasting 18 months. Duration of the current major depressive episode at the time we added venlafaxine ranged from 8 to 36 months (mean = 15.6 months, > 24 months in 3 cases). Nine patients previously had been given fluoxetine or paroxetine, 20 mg/day, for 2 months without any improvement, and all 11 achieved only partial remission with a trial of clomipramine or imipramine at maximum doses, without further improvement after adding usual augmentation drugs. (See ahead in this section and Table 1.) The stages of resistance defined by Thase and Rush[12] could not be applied to our subjects owing to our early use of TCAs and augmentors. Diagnosis and baseline severity assessments (before adding venlafaxine, after therapy with TCAs and usual augmentation drugs) used DSM-IV criteria[13,14] (major depressive episode, mild, N = 2; moderate, N = 4; severe without psychotic features, N = 5), 17-item Hamilton Rating Scale for Depression (HAM-D)[15] scores (range, 19–29; mean = 23.8), and Clinical Global Impressions-Severity of Illness scale (CGI-S)[16] scores (range, 3–6; mean = 4.4). Before TCA monotherapy, 3 patients had moderate major depression, and 8 had a severe major depressive episode without psychotic features; HAM-D scores ranged from 25 to 33 (mean = 28.2), and improvement with that TCA therapy ranged from 0 to 2 levels of DSM-IV severity (mean = 0.45). Two patients (patients 2 and 11; see Table 1) had comorbid panic disorder with agoraphobia, and 1 patient (patient 9; see Table 1) had comorbid obsessive-compulsive disorder. Nine patients were taking benzodiazepines (diazepam [N = 7], 5–20 mg/day, mean = 10.1 mg/day; alprazolam immediate release [IR; N = 2], 0.5–3.5 mg/day, mean = 2.0 mg/day). Exclusion criteria were as follows: (1) age > 60 years; (2) known medical illness (neurologic, endocrinologic, metabolic, cardiovascular, liver/renal dysfunction, glaucoma) or any ongoing pharmacologic medical treatment; (3) history of major depressive episode with psychotic features or bipolar, psychotic, or substance abuse disorder; (4) suicidal risk; (5) use of drugs other than clomipramine, imipramine, venlafaxine, and benzodiazepines prescribed before adding venlafaxine; and (6) abnormalities on baseline medical screening. (See Clinical and Medical Evaluations below.) All patients were informed about the aims of the combined treatment and its possible side effects and gave their informed consent.

TCAs and Usual Augmentations

Eight patients were treated with clomipramine (150–375 mg/day, mean = 201.5 mg/day), and 3 received imipramine (200–250 mg/day, mean = 217 mg/day). Overall blood TCA levels during monotherapy were > 250 ng/mL (at the top of therapeutic ranges for imipramine and clomipramine[3,17]) in 8 patients, while intolerance (anticholinergic side effects, overweight, sexual dysfunction) made maintenance of such high blood drug levels impossible for 3 patients. We kept TCA doses steady for 2 months, and then we augmented them in 9 patients with 1 or 2 usual

augmentation drugs, each one for 6 weeks: lithium carbonate, 0.7 to 1.0 mEq/L (first week, 0.3–0.6 mEq/L); levothyroxine, 50 to 100 μg/day; citalopram, 20 to 40 mg/day; pindolol, 2.5 mg t.i.d.; methylphenidate, 15 mg/day; and buspirone, 30 mg/day.

Combined Treatment With a TCA and Venlafaxine

After completion of treatment with TCAs and usual augmentation drugs, we kept clomipramine/imipramine doses, discontinued usual augmentation drugs, and, 2 weeks later, added venlafaxine in the following fixed titration sequence (dose increases only if complete recovery was not achieved and if there was good tolerance and absence of medical abnormalities): 37.5 mg in the morning for 2 days; 37.5 mg every 12 hours for 15 days; 75 mg every 12 hours for 2 months; 112.5 mg every 12 hours for 2 months; and 150 mg every 12 hours for 2 months. No psychotherapeutic approach was added to the ongoing supportive therapy for any patient.

Clinical and Medical Evaluations

Clinical and medical evaluations were performed before adding venlafaxine, at day 15 of venlafaxine treatment, and then every 2 months (the last evaluations after 6 months of using final doses). Our criteria for sustained positive response to venlafaxine addition were (1) reduction in baseline HAM-D score of > 50%, (2) decrease in baseline DSM-IV and CGI-S level (taking into account both patient and family reports), and (3) persistence of all those improvements for > 6 months (all 3 criteria must have been met). We further distinguished patients who, meeting all 3 previous requirements, showed a marked improvement (decrease of 2 or more DSM-IV severity levels) or a full remission (DSM-IV criteria plus HAM-D score < 5 and CGI-S score of 1). Statistical analysis, performed using the SPSS for Windows 8.0 software package (Spanish version, SPSS, Inc., Chicago, Ill.), included descriptive measures and a t test for paired samples to assess clinical improvements (baseline HAM-D score/final HAM-D score). Medical controls included (1) clinical tolerance (UKU Side Effect Rating Scale); (2) blood pressure-heart rate using Danjou-Hackett criteria[8]; (3) blood analyses (measures of blood count, sedimentation rate, electrolytes, glucose, serum urea nitrogen, creatinine, calcium, cholesterol and other lipids, liver enzymes, alkaline phosphatase, bilirubin, proteins, and thyrotropin); (4) electrocardiogram (ECG); and (5) blood TCA levels.

RESULTS

We found a sustained positive response to venlafaxine addition in 9 patients (82% of the sample). This response was always marked, excluding 2 patients with mild baseline level, and achieved the criteria for full remission in 7 patients (64%). A t test comparison of mean ± SD HAM-D scores (baseline vs. final) showed a statistically significant difference (23.8 ± 3.3 vs. 9.9 ± 8.01, $p < .005$). If we take into account baseline DSM-IV severities, full remission was found in the 2 mildly depressed patients, in 3 of 4 moderately depressed patients, and in 2 of 5 severely depressed patients (with 2 more severely depressed patients showing a marked improvement and becoming mildly depressed).

These full remissions and marked improvements are still present in 8 patients, for over 2 years in the first ones treated. Improvements were found in both the presence and absence of blood levels > 250 ng/mL at baseline, and in both clomipramine and imipramine treatments (but the 2 nonresponders received clomipramine and venlafaxine and had baseline blood clomipramine levels > 250 ng/mL). Patients 2 and 11 reported a clear improvement (not tested) in their panic-agoraphobic symptoms and discontinued alprazolam IR without difficulty. There was no improvement in the obsessive-compulsive symptoms of patient 9. Response during the first 3 weeks of adding venlafaxine appeared only in the 2 mildly depressed patients. The range of venlafaxine doses that allowed maximum improvement was 75 to 300 mg/day (mean = 191.6 mg/day). There were no dropouts. Initial tolerance was always acceptable, and no patient presented tolerability problems that interfered with dose increases. We did not find significant changes and/or abnormalities in blood pressure or heart rate, blood analyses, ECG, or blood TCA level during or after the trial. From a clinical point of view (UKU), we found initial (first few days) mild hypersomnia with low doses (N = 4), initial (first month) sexual difficulties after dose increases (anorgasmia/delayed orgasm, erectile dysfunction in men; N = 7), initial (first month) increase in constipation with doses > 75 mg every 12 hours (N = 6), and overweight (> 5 kg; N = 5). All improved patients decreased or discontinued benzodiazepine use. Blood TCA levels showed only slight changes (< 15%) in some of the patients (N = 3) treated with high venlafaxine doses.

DISCUSSION

We have found that the addition of venlafaxine seems to increase the efficacy of clomipramine or imipramine in some of the depressed patients who achieve only a partial improvement with these TCAs, and that this could be a well-tolerated combined treatment, almost free from medical risks. However, we must be cautious, keeping in mind that our initial results belong to only a small, uncontrolled, and open sample. A clear replication of these findings, under more rigorous methodological conditions,[1] is thus strongly needed (attending to efficacy, tolerability, and safety, particularly in relation to blood pressure increases). A remaining issue that would need clarification is the mechanism acting in this suggested augmentation effect of venlafaxine.

The usual final pharmacokinetic interaction in such an "added-drug" situation is an increase in the blood level of the first drug, in this case clomipramine or imipramine. Although our results suggest an absence of such changes and correspond to studies of venlafaxine interactions,[9–11] they also need replication. Published studies about TCA-venlafaxine interactions have used only in vitro designs, nonhuman subjects, or acute drug administrations (short-term blood level results), and they cannot be easily applied to a human steady-state situation.[18] Owen and Nemeroff[11] reviewed data obtained by Wyeth-Ayerst Laboratories under those limited methodological conditions and found unchanged imipramine area-under-the-curve, C_{max}, and C_{min} values and a mean increase of 35% in all of these parameters affecting its active desmethyl metabolite (desipramine). Nelson[19] recently considered that usual TCA doses could be used after or added to treatment with venlafaxine.

Despite the need for replication of our efficacy/pharmacokinetic results, we can also consider some pharmacodynamic explanations for this possible augmentation effect. All of our patients had experienced some initial improvement with a first drug (clomipramine or imipramine) that in fact shows a dynamic profile (5-HT + noradrenergic reuptake inhibition) similar to that of the added drug, venlafaxine. From this point of view, the question would be: Can venlafaxine bring added effect to those TCAs through that common mechanism of action? This effect would seem logical if blood clomipramine or imipramine levels were low at baseline (as was the case in 3 patients; all 3 improved). But the 8 remaining patients had blood TCA levels > 250 ng/mL at baseline, and, although they were supposed to be receiving a maximum therapeutic dose, 6 of them clearly improved when we added venlafaxine.

Could we suggest then the presence, at least in some patients, of a higher therapeutic margin in that common mechanism of action that could not be reached by TCAs only because of their toxicity, but that could be reached by adding venlafaxine to them? This explanation should not be seen as merely speculative: there exist several published reports (and clinical knowledge as well) about depressed patients who achieve full remission only when they reach blood imipramine levels higher than the usual range.[3] Additional support for this proposed augmentation effect comes from an experimental study by Debonnell et al.,[20] in which they concluded that desipramine and venlafaxine perhaps do not act through the same noradrenergic reuptake mechanism, although they both finally enhance through that mechanism the noradrenergic transmission in depressed patients (adding the possibility of a "qualitative" noradrenergic augmentation to the quantitative—5-HT and/or noradrenergic—augmentation we mentioned before).

It could also be considered, from our results, that the low dosages of venlafaxine we used in 5 patients (150 mg/day or less) could have had not a 5-HT–enhancing effect (as usual with low-dose venlafaxine monotherapy[4,20]), but mostly a noradrenergic-enhancing effect, since 1 severely ill patient in the sample, who had no response to clomipramine augmentation with citalopram, 40 mg/day, reached full remission when we added venlafaxine, 150 mg/day. Venlafaxine has shown affinity to imipramine 5-HT binding sites,[4] suggesting the possibility of a competitive imipramine-clomipramine interaction with the well-known preferential affinity and binding of venlafaxine to 5-HT reuptake structures,[4,20] leading thus to greater binding of venlafaxine to noradrenergic reuptake structures. Moreover, a severely depressed patient of ours who had no response to fluvoxamine, 200 mg/day, for 2 months recently achieved a sustained full remission 48 hours after adding venlafaxine at low doses (37.5 mg every 12 hours); in fact, treatment with this low dose was only planned as the beginning of a switch. This (unreplicated) response could suggest a similar mechanism: an intense SSRI competitive binding to 5-HT reuptake structures could also enhance noradrenergic binding and effects of venlafaxine using low doses. However, we must remember in this regard the preliminary data of Owen and Nemeroff[11]: addition of low-dose venlafaxine could merely increase blood level of the active desmethyl TCA metabolite (with a noradrenergic effect). Also, the simultaneous dopaminergic effect of venlafaxine must be considered.[4]

A last comment: venlafaxine tends to have a fast onset of action when it is rapidly titrated to doses > 200 mg/day.[21] It is possible that the delayed responses we have found could be due to the low initial dose and slowed sequence of increases that we preferred to use. Perhaps a higher initial dose, and/or faster dose increases, would help to reduce this latency time and make it similar to the one achieved with many usual augmentation drugs, although such dosage modifications could affect the acceptable overall tolerability that we have found.

Drug names: alprazolam (Xanax and others), buspirone (BuSpar), citalopram (Celexa), clomipramine (Anafranil and others), desipramine (Norpramin and others), diazepam (Valium and others), fluoxetine (Prozac), fluvoxamine (Luvox), levothyroxine (Synthroid and others), methylphenidate (Ritalin), paroxetine (Paxil), venlafaxine (Effexor).

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