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EFFICACY OF VENLAFAXINE IN THE TREATMENT OF SEVERE DEPRESSION

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Although the efficacy of available antidepressants has been well established in the treatment of mild to moderate depression, clinical research literature on severe depression is more limited, due to lack of a standardized definition for the condition and the resulting inconsistent data. Given the heterogeneous nature of severe depression, reports suggesting noradrenergic as well as serotonergic system involvement in depressive disorders, and the substantive capability of both clomipramine and TCA-SSRI combination to treat severe depression, investigation of dual-action antidepressant agent efficacy in the treatment of severe depression is warranted. The merit of one such combined-action agent, venlafaxine, is reviewed. Efficacy findings from the limited number of comparative clinical trials conducted in the severely depressed patient population suggest that, while venlafaxine has been evaluated in a broad range of depressed patients, this compound may be particularly effective for the severely ill. Pharmacological features of venlafaxine, which may benefit the patient with severe depression, include the possibility of a rapid onset of action and a dose-response curve. Based upon studies comparing venlafaxine with both placebo and other first-line antidepressants, it is concluded that venlafaxine is safe, tolerable, and effective for the treatment of severe depression. Depression and Anxiety, Volume 12, Supplement 1:50–54, 2000.

Key words: ***severe depression; venlafaxine; melancholia; inpatient; antidepressant***

DEFINING SEVERE DEPRESSION

The severity of major depressive episodes has been measured in a variety of dimensions, including intensity, number, and type of symptoms, degree of impairment, degree or presence of suicidality, and hospitalization status. A significant minority (about 30%) of depressed outpatients and almost all individuals hospitalized for depression can be considered severely ill [Thase, 2000]. These patients with severe depressive episodes typically suffer from an illness of longer duration [Keitner et al., 1992]. In addition, the more severe the depression, the less likely it is to respond to placebo or result in spontaneous remission [Thase and Kupfer, 1987].

According to the ICD-10 Classification of Mental Health and Behavioral Disorders, the severely depressed patient often displays marked agitation and/or distress, except when retardation is a central feature [WHO, 1992]. Furthermore, somatic symptoms, loss of self-esteem, and/or feelings of guilt, worthlessness, or suicide are likely to be prominent. Severe depression also features the presence of additional symptoms in excess of those required for diagnosis. These symptoms markedly disrupt workplace functioning, relationships, and ability to interact in social situations. If untreated, potential complications of severe depression include refusal to eat, self-injury, suicide, and treatment resistance [Sonawalla and Fava, in press].

Co-morbidities often exacerbate the degree of severity in depression, and severe episodes are more likely to be complicated by co-morbid conditions [Lipsitz and Williams, 1994]. A 1994 report by Lipsitz and Williams found that major depression accompanied by either a personality disorder or by a co-morbid medical or psychiatric illness is usually more debilitating than

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major depression alone. In a study comparing social functioning in patients with anxious depression versus major depressive disorder, Sonawalla and colleagues [1999] found that anxious depression resulted in significantly greater impairment in overall adjustment when compared with its nonanxious counterpart. Keitner and colleagues [1992] found that over a 12 month follow-up time period, patients with compound depression reported significantly poorer functioning, as well as lower recovery rates, than patients with pure depression.

The heterogeneous nature of severe depression makes this debilitating condition one of the greatest challenges faced by clinical psychiatrists. A severe major depressive episode is more likely to be accompanied by psychotic features that include hallucinations or delusions, catatonia, anhedonia, melancholia, diurnal mood variations, or anger attacks [Broquet,1999; Fava and Rosenbaum, 1998].

TREATMENT STUDIES IN SEVERE DEPRESSION

The clinical research literature on severe depression is limited by the lack of a standardized definition for the condition and the inconsistent data resulting from the multiple methodologies among studies. As is often the case in psychiatry clinical trial research, definitions of response and adequate duration and intensity of treatment are significant issues. In treatment studies, the level of depression severity is often assessed by standard rating scales. Patients who are severely depressed may still present substantial symptomatology even after a 50% reduction in the Hamilton Rating Scale for Depression (HAM-D) at the end of a 6–8 week trial [Schatzberg, 1999]. Severely depressed patients may need a longer trial to achieve euthymia [Nierenberg, 1994]. In a report by Hirschfeld and colleagues [1998] responders to antidepressants had a significantly lower baseline depression severity score than nonresponders. It is also reported that index depressive episode severity predicts persistence of the depression [Sargeant et al., 1990]. A more appropriate definition of clinical response may be a HAM-D score ≤8–10 or a greater than 50% score reduction at the end of a trial.

All available antidepressants have been generally effective for the treatment of mild to moderate depression. The advent of the newer antidepressants such as the SSRIs and dual-action agents has improved outcome in depressed patients, since these compounds are not only equally efficacious but are better tolerated than the older tricyclics. Yet many treatment studies of antidepressants may not be generalizable to the severely depressed. Gravely ill patients may show a better response to more intense treatment regimens of longer duration, aggressive dose titration, and/or combination therapy [Elkin et al., 1989; Nierenberg, 1994; Schatzburg, 1999; Zanardi et al., 2000].

A controversial issue in the treatment of severe depression has been the differential efficacy of TCAs and SSRIs, where the data are mixed [Hirschfeld, 1999]. However, the same proportions of patients treated with either class of drugs are classified as treatment responders and the average reduction of symptom severity in each treatment group is approximately equal despite differences in the impact of the different antidepressant medications on presynaptic and postsynaptic receptors [Nierenberg, 1994]. Some research has attempted to identify symptoms or factors that might be used to predict response to individual antidepressants or drug classes [Joyce and Paykel, 1989; Nelson and Charney, 1981]. While most of these attempts have failed to find substantive predictors, other findings support the hypothesis that there are differences in symptom response to different antidepressants [Nelson et al., 1984; Montgomery, 1997], suggesting the potential for additive or synergistic effects with the combination of mechanisms of action.

COMBINATION THERAPY

Given the heterogeneous nature of severe depression as well as reports that suggest that more severe depressive states are more likely to be associated with disturbances of neurobehavioral response systems regulated by both noradrenergic and serotonergic systems [Thase, 1996; Stahl 1997], it is not surprising that the dual action antidepressant clomipramine, the most serotonergic TCA, as well as SSRI-TCA combination treatment have demonstrated considerable efficacy in treating severe depression. In randomized comparison studies with over 100 inpatients each, the Danish University Antidepressant Group (DUAG) reported clomipramine (n=52[1986]; n=46[1990]) to be superior to the SSRIs citalopram [DUAG, 1986] (n=50) and paroxetine [DUAG, 1990] (n=56) in the treatment of severe depression. Desipramine and fluoxetine have been used in combination to produce a more rapid and efficacious treatment of inpatients with major depression and melancholia than had previously been seen with desipramine alone [Nelson et al., 1991]. This study of combination treatment was prompted by the finding that the drug combination down-regulates beta-adrenergic receptors more rapidly than either desipramine or fluoxetine alone [Baron et al., 1988]. Results showed complete remission (HAM-D score reduction ≥ 75%) for 10 of the 14 depressed inpatients treated with the TCA-SSRI combination within a 4 week period while only 6 of the 42 who received desipramine alone remitted.

This psychopharmacologic combination, however, is not ideal. When SSRI-TCA therapy is prescribed, plasma TCA levels must be monitored, as hepatic metabolism of TCAs may be inhibited by some SSRIs [Nemeroff et al., 1996; Hirschfeld, 1999]. In addition, TCAs are associated with pharmacodynamic and pharmacokinetic drug interactions as well as such adverse

effects as dry mouth, constipation, urinary retention, blurred vision, and cognitive impairment. Low initial doses and titration is indicated for TCAs. Also to be considered is the potential significant drop in patient compliance that occurs when a second medication is added to a treatment regimen. In order to both reduce the adverse-effect discomfort among those who continue treatment and minimize the number of patients suffering from major depression who discontinue treatment, treatment advances in the areas of improved efficacy, faster onset of action, and lessened side-effects are needed.

A SINGLE THERAPY WITH COMBINED ACTION

Antidepressants can be distinguished by differing effects on receptor blockade and neurotransmitter reuptake. Because it is not possible to predict which patients will respond to noradrenergic or serotonergic agents or the combination thereof, there is a rationale for the use of a dual-action antidepressant in the treatment of severe depression. Similar to the SSRIs, venlafaxine, compared to TCAs, has no significant affinity for muscarinic cholinergic, histaminergic, or α_1-adrenergic receptors and thus does not have the anticholinergic effects, orthostasis, antihistamine-related sedation, or weight gain, nor cardiotoxicity or increased risk for seizure [Muth et al., 1986; Ballenger, 1996; Broquet, 1999]. Main side effects include nausea, headaches, nervousness/stimulation, and sweating [Broquet, 1999; Rudolph and Derivan, 1996] However, in contrast to the SSRIs but similar to TCAs in higher doses, venlafaxine significantly inhibits norepinephrine reuptake with a dose-response relationship within the therapeutic range [Andrews et al., 1996].

Venlafaxine has been evaluated in a broad range of patients, and while both inpatient and outpatient studies have demonstrated equivalent efficacy for different antidepressant classes, venlafaxine has been shown to be particularly effective in hospitalized patients with severe depression and melancholia when compared to placebo [Guelfi et al., 1995]. A 1995 controlled, randomized, double-blind study by Guelfi and colleagues evaluated the safety and efficacy of venlafaxine in 93 severely depressed inpatients (baseline MADRS scores ≥ 25) weekly for 4 weeks (Fig. 1). The mean baseline HAM-D scores for the two groups were 28.2 (venlafaxine) and 28.6 (placebo) and the total daily dose was within the range of 150–375mg. Mean HAM-D total scores were significantly better than the placebo group at every evaluation point during treatment, beginning at week 1 and improving through week 4. Similarly, mean MADRS scores were significantly better in the venlafaxine group than in the placebo group at every evaluation point. No statistically significant differences between the venlafaxine and placebo treatment groups in the frequency of study discontinuation due to adverse events were reported.

The Guelfi et al. [1995] study also demonstrated a relatively rapid onset of venlafaxine effects, a pharmacological feature clearly important for the severely ill patient. As early as day 4, statistically significant improvement in MADRS scores of the venlafaxine treated group were observed. Several mechanisms have been proposed to explain venlafaxine's rapid onset [Derivan et al., 1995], and multiple studies suggest that venlafaxine may have an onset of activity within 1 to 2 weeks of initiating therapy [Guelfi et al., 1995; Rudolph and Derivan, 1996; Benkert et al., 1996]. In 1996, Benkert and colleagues reported rapidly escalating doses of venlafaxine to produce a significantly faster time to response as well as time to sustained response than rap-

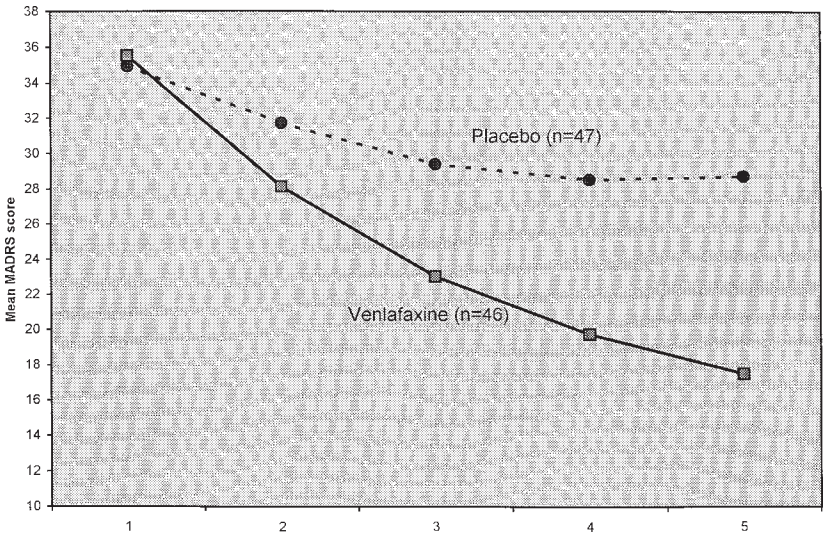

Figure 1. Improvement in MADRS total scores in severely depressed inpatients. Statistically significant improvements began at week 1 and continued through week 4. Data adapted from Guelfi et al. [1995].

idly increased imipramine in inpatients with major depression and melancholia [Benkert et al., 1996]. The daily dose of venlafaxine was increased to 375 mg/day over a 5 day period, maintained for 10 days, and reduced to 150 mg/day for the remaining 4 weeks in a group of 85 patients. Despite the rapid dose increase, adverse effects were well tolerated with nausea being the most common, reported by 17% of the venlafaxine treated group. In the other 82 patients, imipramine was rapidly raised to 200 mg/day and maintained throughout the study. The median time to response on the HAM-D among responders was 14 days with venlafaxine and 21 days with imipramine.

Venlafaxine has been shown to be superior to fluoxetine in the treatment of depressed inpatients in a 1994 study by Clerc et al. [1994] (Table 1). This randomized, double-blind, 6 week comparative study of fluoxetine 40 mg/day (n=34) and venlafaxine 200 mg/day (n=33) in patients hospitalized for melancholic depression found venlafaxine to be the more effective agent, as reflected in its significantly greater reduction in HAM-D (–18.0 vs. –12.4; *P*=0.02) and MADRS (–22.8 vs. –15.7; *P*=0.028) scores. Response to treatment was demonstrated at both of the last two evaluation points: weeks 4 and 6. There were significantly more responders in the venlafaxine group than in the fluoxetine group at week 4 according to the MADRS (76% vs. 46%; *P*=0.024), HAM-D (76% vs. 41%; *P*=0.006) and CGI-Improvement (73% vs. 53%; *P*= 0.13) scales. At week 6, the venlafaxine group continued to have a higher proportion of responders than the fluoxetine group for HAM-D (73% vs. 50%; *P*=0.08). Although differences did not reach significance, fewer venlafaxine-treated than fluoxetine-treated patients withdrew from the study (18% vs. 35%). The safety and tolerability profiles of the two therapies were reported to be similar.

Venlafaxine also appears to be effective in the treatment of delusional depression, a particularly severe form of mood disorder with a prevalence estimated to be about 25% in hospitalized patients [Roose and Glassman, 1988]. A recent pilot study suggests that venlafaxine may be an effective compound for the treatment of delusional depression [Zanardi et al., 2000]. Under double-blind conditions, 28 patients hospitalized for major depression with psychotic features were randomly assigned to receive venlafaxine or fluvoxamine, 300 mg/day, for 6 weeks; 7 of the 12 patients treated with venlafaxine showed a reduction in the score of the 21 item HAM-D to 8 or below. In addition, the overall safety profile of venlafaxine was favorable. The results of this pilot trial provide the first evidence that venlafaxine may be a useful and safe compound in the treatment of delusional depression. Although this conclusion is based on a relatively small number of venlafaxine-treated patients, the evidence is promising and warrants further replication in a larger sample of patients.

CONCLUSION

There is no specific treatment algorithm for severe depression reported in the literature. While almost all antidepressants have been found effective in the treatment of mild to moderate depression, reports on severe depression are more limited. The available evidence suggests that venlafaxine, a newer antidepressant with favorable side-effect and drug-drug interaction profiles, may be particularly effective for the treatment of severely depressed patients. Venlafaxine is characterized by a unique dual mechanism of neurochemical action evident at higher doses (e.g., 150 mgm per day or greater), exerting its effects on both central-norepinephrine and serotonin systems. The combined inhibition of the two neurotransmitters may account for the greater efficacy and rapid onset compared to other antidepressants. This dual-action drug has shown promising results for severely depressed patients.

TABLE 1. Clinical trials evaluating velafaxine for severe depression*

Study	Patient population	Duration (weeks)	Drug mg daily (mean)	N (total)	Baseline average	Overall outcome
Geulfi et al., 1995	Inpatients; MDD and MEL	4	VEN, 150-375 (218) PLA	46 47 (93)	HAM-D 28.6 HAM-D 28.2	• VEN>PLA from week 1 onward • HAM-D ≤ 7 in 12 of 46 (26%) VEN
Clerc et al., 1994	Inpatients; MDD and MEL	6	VEN, 200 FLU, 40	33 34 (67)	HAM-D 29.1 HAM-D 29.7	• ≥ 50% reduction in HAM-D: VEN (73%) > FLU (50%)
Benkert et al., 1996	Inpatients; MDD and MEL	6	VEN, 375/150 IMI, 200	85 82 (167)	HAM-D 30.6 HAM-D 28.8	• significantly faster response onset in VEN • *sustained* ≥ 50% reduction in HAM-D: VEN (31%) > IMI (17%) • low VEN AEs despite rapid dose increase
Zanardi et al., 2000	Inpatients; MDD and MEL	6	VEN, 300 FVX, 300	14 14	HAM-D 35.8 HAM-D 36.8	• HAM-D ≤ 8 response in 7 of 12 (58%) VEN

**MDD, major depressive disorder; MEL, melancholia; DEL, psychosis/delusions; VEN, venlafaxine; FLU, fluoxetine; IMI, imipramine; FVX, fluvoxamine; PLA, placebo; HAM-D, Hamilton Rating Scale for Depression; AE, adverse effect.*

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