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Efficacy and tolerability of venlafaxine in the treatment of primary dysthymia

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Objective: Currently, there is no documentation of the efficacy of venlafaxine (a serotonin norepinephrine reuptake inhibitor) in the treatment of dysthymia. This open-label pilot investigation examined the efficacy and tolerability of venlafaxine in patients with primary dysthymia without concomitant major depression. **Methods:** Fifteen patients were treated with venlafaxine for 12 weeks, with a dose range of 75 mg to 225 mg daily (taken orally), and symptom changes were measured using standard instruments including the Hamilton Depression Rating Scale (HAM-D). **Results:** Significant changes from pretreatment to posttreatment were observed ($p < 0.001$). Using the standard criteria of a 50% reduction in HAM-D scores, 73.3% of patients were rated as responders. About two-thirds of the patients reported adverse events, which were mostly mild and brief in duration. **Conclusion:** Venlafaxine may be useful in the treatment of primary dysthymia but placebo-controlled studies are required for confirmation.

Objectif : Il n'existe actuellement aucune documentation sur l'efficacité de la venlafaxine (inhibiteur de la réabsorption de la norépinéphrine et de la sérotonine) dans le traitement de la dysthymie. Dans le cadre de cette étude pilote, on a examiné l'efficacité et la tolérabilité de la venlafaxine chez des patients souffrant de dysthymie primaire sans dépression majeure concomitante. **Méthodes :** Quinze patients ont été traités à la venlafaxine pendant 12 semaines, recevant une dose variant de 75 à 225 mg par jour (prise oralement) et l'on a mesuré les changements des symptômes au moyen d'instruments standard, y compris l'échelle d'évaluation de la dépression de Hamilton (HAM-D). **Résultats :** On a observé des changements importants après le traitement ($p < 0,001$). En utilisant le critère normalisé qui consiste à réduire de 50 % les résultats HAM-D, on a évalué que 73,3 % des patients répondaient au traitement. Environ les deux tiers des patients ont signalé des effets indésirables, pour la plupart bénins et de brève durée. **Conclusion :** La venlafaxine peut être utile dans le traitement de la dysthymie primaire, mais il faut réaliser des études contrôlées par placebo pour le confirmer.

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Dysthymia, an illness characterized by chronic low-grade depression of at least 2 years in duration, is estimated to affect 2% to 5% of the population, and has significant morbidity.[1,2] In addition to significant depressive symptoms, patients with dysthymia experience considerable social dysfunction and disability.[2]

It has been suggested that dysthymia is underrecognized and undertreated.[2,3] Until recently, these patients were viewed as having a characterological disorder and often treated with only psychotherapy.[4] There is now clear evidence to suggest that a significant proportion of patients with dysthymia improve with antidepressant treatment.[5-7]

Although the older generation of antidepressants, such as tricyclic antidepressants (TCAs) and monamine oxidase inhibitors (MAOIs), have been found to be effective in treating depressive disorders (including dysthymia), they often cause significant adverse effects.[7] The newer generation of antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), appear to be equally effective and much better tolerated.[7,8]

Venlafaxine is a novel antidepressant with a phenethylamine bicyclic structure that is distinct from other antidepressants.[9] Like TCAs, venlafaxine has a significant effect on the reuptake of both serotonin and norepinephrine. In contrast to the TCAs, venlafaxine does not show affinity for muscarinic, α- or ß-adrenergic receptors, nor does it inhibit monoamine oxidase.[10] Venlafaxine has been documented to be effective for the treatment of major depression with or without melancholia[11] and treatment-refractory depression.[11,12]

Currently, there are no published reports of the use of venlafaxine in the treatment of dysthymia. (While this manuscript was under review, a paper on the efficacy of venlafaxine in a similar number of patients with dysthymia was published.[13]) This pilot investigation was conducted to examine the efficacy and tolerability of venlafaxine in the treatment of people with primary dysthymia without comorbid major depression.

Method

Subjects

A total of 17 patients (8 men, 9 women) referred to the mood disorders clinic at the Royal Ottawa Hospital in Ottawa were studied. All patients met the DSM-III-R or DSM-IV criteria for primary dysthymia but did not meet those for major depression. All had scores between 14 and 20 on the 17-item Hamilton Rating Scale for Depression (HAM-D) at screening. The exclusion criteria included the absence of any current Axis I or Axis II psychiatric disorders (determined by clinical interview) or any significant physical illness (determined by history). As well, patients were excluded if they had taken any other psychotropic medication during the previous month or if their HAM-D scores decreased 25% or more between screening and baseline.

Procedures

Informed consent was obtained from participants after details of the treatment had been provided. At the beginning of the study, demographic information, characteristics of the current episode, psychiatric history and family history were obtained.

All patients were treated with venlafaxine on a starting oral dose of 37.5 mg twice a day. This dose was gradually increased, depending on clinical improvement and presence of adverse effects, by increments of 37.5 mg weekly, to a total daily dose of 375 mg. The screening and baseline visits were followed by 3 monthly visits. The total treatment period was 12 weeks.

Measurement instruments

The presence of depressive symptoms were measured using the 17-item HAM-D,[14] the Hamilton Anxiety Scale (HAM-A),[15] the Montgomery-Asberg Depression Rating Scale (MADRS), and the global improvement subscale of the Clinical Global Impressions (CGI). Efficacy measures were taken at screening and baseline visits as well as during the 3 monthly follow-up visits.

Results

Table 1 shows the characteristics of all patients in the

Table 1: Characteristics of patients at baseline

Mean age, yr (± SEM)	41.7 (2.14)
Sex	
Men	8
Women	9
Probable family history of depression	
No	9/17
Yes	8/17
Age of onset, yr (± SEM)	24.7 (2.87)

Note: SEM = standard error of the mean

study; the average age was 41.7 ± 2.14 years and the average age of onset was 24.7 ± 2.87 years. Three patients dropped out of the study; 2 for personal reasons not connected with treatment and 1 because of severe nausea during treatment. Therefore, all statistical analyses were performed on data from 15 patients.

To determine treatment efficacy, a series of pairwise *t*-tests were performed for each clinical measure. Bonferroni corrections were used to achieve more stringent α levels.

Figure 1 shows the decline of HAM-D (17-item), HAM-A, MADRS and the CGI (+SD) from baseline (week 0) to week 12 of treatment. Statistical analyses confirmed that all measures of efficacy were lower with venlafaxine treatment, t_{12} = 7.45, 7.01, 7.22, 9.00 respectively, $p < 0.0001$. Subsequent analyses showed reductions in CGI, HAM-A and MADRS scores as early as week 4 of treatment t_{15} =3.65, 5.09, 6.44, $p < 0.01$, respectively. HAM-D (17-item) scores also declined significantly by week 8 of treatment, t_{11} = 5.32, $p < 0.0001$. It is of interest to note that there were also significant treatment effects for both the HAM-D atypical items (items 23–28) and HAM-D 29-item totals, $p < 0.0001$ (data not shown).

Table 2 shows the overall treatment response and reported adverse events. Eleven of the 15 subjects

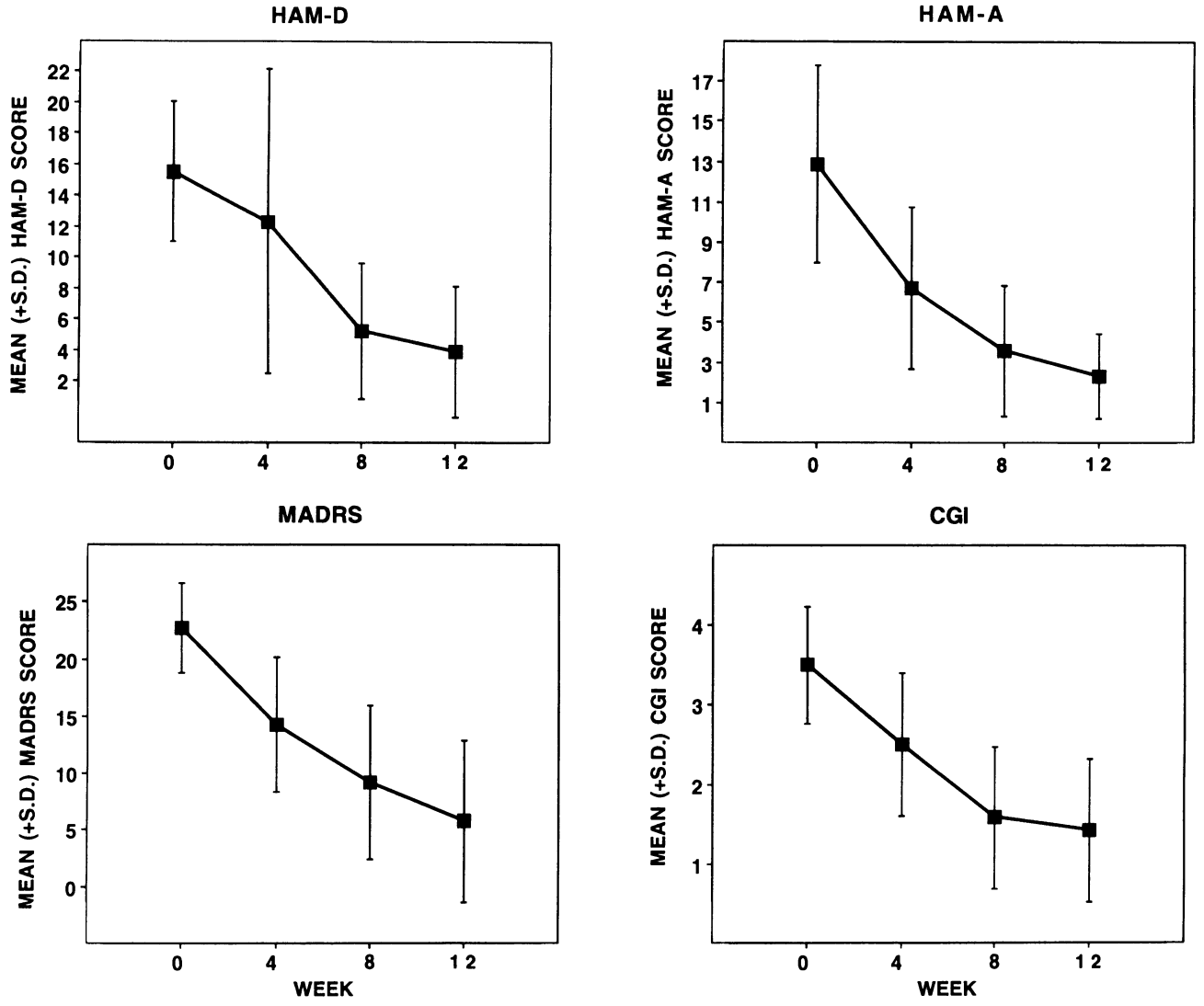

Fig. 1: Mean (+SD) HAM-D (17-item), MADRS, HAM-A and CGI scores of people with dysthymia treated with venlafaxine at baseline (week 0), and at weeks 4, 8, and 12 of treatment.

(73.3%) demonstrated a significant treatment response. However, the incidence of adverse events reported in our sample was relatively low (Table 2).

Discussion

Several recent reports have confirmed that, like the older TCAs and MAOIs,[5,16] the newer generation of antidepressants may also be effective in the treatment of primary dysthymia. These include the SSRIs.[6,7,17] Placebo-controlled studies report the response to treatment to be between 50% and 60% and open-label studies report the response to be about 70%. In our study, the HAM-D scores of 11 of the 15 subjects (73.3%) indicated a significant clinical improvement. A significant reduction was also observed in total HAM-A scores, suggesting that venlafaxine may be particularly useful in treating people with dysthymia who have concomitant anxiety. Moreover, these clinical changes were observed as early as 4 weeks into treatment, suggesting that the antidepressant properties of venlafaxine are relatively rapid. Significant and early reduction in anxiety has also been reported in people with major depression treated with venlafaxine.[18]

The effective dose in this study was between 75 mg and 225 mg daily (average approximately 160 mg). This dose range is similar to that previously reported to be effective in major depression.[19] Likewise, the presence of residual symptoms, as indicated by posttreatment HAM-D scores, are similar to those previously reported in studies using SSRIs to treat dysthymia.[6–8,18]

The profile, type and frequency of adverse effects of venlafaxine observed in this study are similar to those reported among people with major depression.[18,20] Common side effects including headaches, nausea, decreased energy, mild jitteriness and diminished libido were mild and brief in duration. One person dropped out because of severe nausea. Thus, systematic study of adverse effects in placebo-controlled studies is warranted.

Table 2: Number of the 15 patients reporting adverse events during the 12-week treatment period

Adverse event	No. of patients
Insomnia	3
Nausea	3
Decreased energy	2
Fatigue	2
Jitteriness or anxiety	2
Diminished libido	1
Delayed ejaculation	1
Weight gain	1
Persistent yawning	1
Episodic thirst	1
Decreased appetite	1
Perspiration	1

The TCA imipramine, which inhibits the reuptake of both norepinephrine and serotonin (in addition to hisatmine and acetylcholine), has been show to be effective in dysthymia. Because its effects are specific to norepinephrine and serotonin, venlafaxine may be effective without causing adverse events due to the effects on other neurotransmitter systems.[5] Thus, venlafaxine may be particularly useful for depressed patients who are refractory to treatment with SSRIs.[12,20]

The data from this small pilot study suggest that venlafaxine is useful in the treatment of dysthymia. However, larger multicentre, placebo-controlled studies are required to confirm these findings.

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