VENLAFAXINE-INDUCED MANIA
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ABSTRACT

Venlafaxine is a novel antidepressant with a rapid onset of action. It is highly efficacious in the treatment of depression and in comparison to the traditional tricyclic antidepressants, it has a favourable side effects profile. Although effective, venlafaxine too carries a risk for manic switch in bipolar affective disorder patients. Given the paucity of literature, we report a case of venlafaxine induced mania and discuss the possible neurochemical underpinnings of this adversity.

Key words: Venlafaxine, mania, hypomania, antidepressant-induced mania

Because of its quicker onset of action, i.e., within a week of initiation, venlafaxine is considered as a breakthrough in the treatment of depression. This novel bicyclic phenethylamine antidepressant has a well proven efficacy in the treatment of depression (Montgomery, 1993). Similar to tricyclic antidepressants (TCAs), venlafaxine too inhibits the reuptakes of serotonin, noradrenaline and, to some extent, dopamine, but in a dose dependent manner (Bezchlibnyk-Butler & Jeffries, 1998; Horst & Preskom, 1998). However, in contrast to the TCAs, due to lack of anticholinergic, antihistaminergic and antiadrenergic effects it is generally better tolerated (Montgomery, 1993).

Bipolar affective disorder is a common and disabling disorder. Although mood stabilizers remain the treatment of choice for bipolar depression, at times, when the depression is marked and not improving with mood stabilizers, a short course of antidepressant treatment is considered (APA, 1994). Although effective, almost all the antidepressants carry a risk of mania/hypomania in bipolar patients. This risk is high with the TCAs (Bottlender et al., 1998). A similar risk for mania/hypomania has been noted with venlafaxine too (Montgomery, 1993; Stoner et al., 1999). In a review (Montgomery, 1993), 0.04% has been proposed as the incidence rate of venlafaxine-induced mania. Since venlafaxine-induced mania has not been reported in Indian literature, we report a case and discuss the possible neurochemical underpinning of this adverse effect of venlafaxine.

CASE REPORT

A 45-year old female, having a history of unspecified mental illness in her maternal uncle, was brought to us with following complaints. Having had a manic episode 25 years ago, she developed a major depressive episode of severe intensity with psychotic features six months ago. Due to lack of improvement, after four months of onset of severe depressive episode, she was taken to a private psychiatrist. Treatment was initiated with venlafaxine 37.5 mg/day, which was increased to 150 mg/day at the end of first week. Additionally
she was also prescribed clonazepam 1 mg at night for her sleep and alprazolam SR 0.5 mg at morning for her restlessness. Within a fortnight, her depressive symptoms started improving steadily. At the end of 20 days of therapy, family members noted changes in her behaviour. She started talking more and became irritable and aggressive. Her sleep decreased and she started demanding good food. Family members who were unaware of this complication did not discontinue venlafaxine until they contacted us.

Patient was brought to us after five weeks of her manic symptomatology. Mental status examination at the time of consultation revealed overactivity, physical and verbal aggression, distractibility, overabundant speech, elated affect, delusions of grandiosity and persecution, second person auditory hallucination and absent insight. Physical examination revealed anteroinferior perforation of right tympanic membrane. She was diagnosed as a case of bipolar affective disorder, current episode being drug induced mania. Due to severe management problems, she was hospitalized. Venlafaxine was discontinued and treatment was initiated with carbamazepine (200-600 mg/day) and risperidone (2-6 mg/day). Investigations did not reveal any abnormality. Her psychopathology was rated with the scale for manic states (Cassidy et al., 1998). The total manic score was 55 at admission and it dropped to 29, 23 and 18 at the end of first, second and third week of treatment, respectively. Except psychotic items, all other manic items had significantly improved at the end of three weeks of hospitalization.

DISCUSSION

The temporal relationship noted between the beginning of venlafaxine therapy and the onset of mania suggests that in our patient venlafaxine could be the most probable cause for manic switch. Proposed risk factors for antidepressant-induced mania include female sex, premorbid cyclothymic personality and a history suggestive of manic proneness (Wehr & Goodwin, 1987). Except female sex, we did not observe any of the above mentioned risk factors in our patient. Lack of addition of a mood stabilizer and a faster titration of venlafaxine to 150 mg/day, however, might have additionally heightened to risk of mania.

Dose dependent inhibition of the reuptakes of major three neurotransmitters is the unique feature of venlafaxine. At lower doses, it exclusively inhibits serotonin reuptake. At doses 150 mg/day or above, it inhibits reuptake of both serotonin and noradrenalin (Muth et al., 1986) and at still higher doses, it blocks dopamine reuptake (Bezehilbnyk-Butler & Jeffries, 1998). Antidepressant effect of venlafaxine is correlated with its serotonin and noradrenalin re-upt inhibition whereas the significance of dopamine reuptake blockade is presently unknown (Horst & Preskorn, 1998).

Both the phenomenology and course of manic switch of our patient suggest a few interesting conclusions regarding the dopaminergic action of venlafaxine. First, severe depression of our patient turned into psychotic mania within two weeks of venlafaxine 150 mg/day. This finding suggests that probably all three neurotransmitter systems, including dopaminergic system, as evidenced by psychotic features of our case, might have been activated at the doses 150 mg/day. Although this view is contracting to the existing data (Bezehilbnyk-Butler & Jeffries, 1998), we believe that at least in some persons who are prone for switch, e.g., female gender (Wehr & Goodwin, 1987), dopaminergic activation may be occurring at moderate doses of venlafaxine. Second, although mood, biological, cognitive and behavioral symptoms of mania of our patient significantly improved within a week of discontinuation of venlafaxine, psychotic features remained stable even at the end of three weeks of treatment. This finding leads to a query that whether venlafaxine-induced dopaminergic activation lasting longer than that of activation of other two neurotransmitter systems. This argument is, at least partly, supported by an earlier observation in which mania induced by a predominantly dopaminergic antidepressant,
bupropion, in a case of recurrent depressive disorder, persisted for a long period even after drug discontinuation (Bittman & Young, 1991). In summary, we state that although venlafaxine is considered as a safe agent in the treatment of women with bipolar II disorder (Amsterdam & Garcia-Espana, 2000), its utility in the treatment of depression of bipolar I disorder needs further evaluation. In addition, the clinical significance of venlafaxine induced dopaminergic activation should also be explored in detail. The present work is a singly case report, hence, welldesigned studies are essential to confirm our views.

REFERENCES

American Psychiatric Association Practice Guidelines (1994) Practice guidelines for the treatment of patients with bipolar disorder. American Journal of Psychiatry, 151 (Supplement).

Amsterdam, J. D. & Garcia-Espana, F. (2000) Venlafaxine monotherapy in women with bipolar II and unipolar major depression. Journal of Affective Disorders, 59, 225-229.

Bezehlibnyk-Butler, K. Z. & Jeffries, J. J. (1998) Clinical Handbook of psychotropic drugs, Ed. 9. Seattle, Hogrefe & Huber Publishers.

Bittman, B. J. & Young, R. C. (1991) Mania in an elderly man treated with bupropion. American Journal of Psychiatry, 148, 541.

Bottlender, R., Rudolf, D., Strauss, A. & Moller, H. J. (1998) Antidepressant associated maniform states in acute treatment of patients with bipolar I depression. European Archives of Psychiatry and Clinical Neurosciences, 248, 296-300.

Cassidy, F., Murry, E., Forest, K. & Carroll, B. J. (1998) Signs and symptoms of mania in pure and mixed episodes. Journal of Affective Disorders, 50, 187-201.

Horst, W. D. & Preskorn, S. H. (1998) Mechanisms of action and clinical characteristics of three atypical antidepressants: Venlafaxine, nefazodone, bupropion. Journal of Affective Disorders, 51, 237-254.

Montgomery, S.A. (1993) Venlafaxine: A new dimension in antidepressant pharmacotherapy. Journal of Clinical Psychiatry, 54, 199-217.

Muth, E. A., Haskins, J. A., Husbands, G. E. M., Nielsen, S. T. & Sigg, E. B. (1986) Antidepressant biochemical profile of the novel bicyclic compound Wy-45,030, an ethyl cycloexanol derivative. Biochemistry and Pharmacology, 35, 4493-4497.

Stoner, S. C., William, R. J., Worrel, J. & Ramlatchman, L. (1999) Possible venlafaxine-induced mania. Journal of Clinical Psychopharmacology, 19, 184-185.

Wehr, T. A., Goodwin, F. K. (1987) Can antidepressant cause mania nad worsen the course of affective illness. American Journal of Psychiatry, 144, 1403-1411.