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LETTER TO THE EDITOR

Mania associated with venlafaxine discontinuation

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Switch to hypomania, mania, or rapid-cycling has been reported with virtually every class of antidepressant medication (Montgomery et al., 2000). Mania and hypomania have been also reported as a result of antidepressant discontinuation in bipolar disorder, whether or not patients were also taking a mood stabilizer (Goldstein et al., 1999). Venlafaxine-associated mania (Shulman et al., 2001; Stoner et al., 1999) and a paradoxical shift to mania upon its discontinuation despite adequate lithium treatment have been reported (Goldstein et al., 1999). We describe here, however, a case which has some interesting features by virtue of its longitudinal development.

Case report

Mr A was a 59-yr-old male patient who referred himself to our Affective Disorders Programme, seeking psychotherapy as a prevention of his recurrent depression. A psychiatrist and a psychologist, independently using the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer, 1978), reached a consensus about diagnosis of bipolar disorder, type I, according to research diagnostic criteria (Spitzer et al., 1989). This diagnosis had never been formulated before and the patient had never been treated with mood stabilizers. The first reported affective episode occurred in his early twenties, when he was a college student. He subsequently had at least 18 episodes of either major depression or mania, each lasting several months. The severity and frequency of episodes increased with age and led to three hospitalizations during the depressed phases. There were no hospitalizations during mania, which was characterized by intensive work and absence of psychotic symptoms. He had been treated with a variety of antidepressant drugs. His last depressive episode (which took place a year previously) was severe and was treated with 8 sessions of bilateral ECT. This period was preceded by an extended period of mania (10 months). At the time of assessment he appeared to be euthymic and was taking extended-release venlafaxine (37.5 mg/d) for 2 months and lorazepam (1 mg three times daily) for 10 yr. He had no identified history of alcohol or drug abuse. He was told that a mood stabilizer (lithium) was required first, and that psychotherapy might have to be considered at a later date. The psychiatrist prescribed a medical regimen for lithium and discontinued venlafaxine without tapering (because of the brief period of administration). The patient was, however, warned to call if any problems occurred. Lorezapam was kept at the same dosage. After 3 d Mr A began to present with the typical symptoms of venlafaxine discontinuation (Fava et al., 1997): dizziness, light-headedness, excessive sweating, nausea and chills. He also became irritable, grandiose, hyperactive, mildly paranoid, restless, with elated mood, pressure of speech and 3–4 h of sleep a night, which satisfied the research diagnostic criteria for mania, except for their duration (Spitzer et al., 1989). One week after discontinuation, venlafaxine was reinstated at the previous dosage (37.5 mg/d). Both physical and manic symptoms were resolved in a few days. The patient was then started on lithium carbonate, associated with clonazepam (0.5 mg three times daily), in addition to venlafaxine and lorazepam. When lithium achieved satisfactory blood levels (0.84 mmol/l at a daily dosage of 1500 mg), which occurred about 3 months after the manic episode, venlafaxine was again discontinued, with the same modality of the first time. Similar withdrawal symptoms developed, even though to a milder degree, and subsided in 2 wk. There was, however, no manifestation of mania. At a 6-month follow-up, the patient was euthymic.

This case suffers from many of the limitations that are characteristic of individual case reports. The emergence of mania after discontinuation of venlafaxine could have been a coincidence. There is no way of knowing whether lithium prevented the occurrence of venlafaxine-withdrawal-associated mania the second time, or whether this was due to the combination of lithium and clonazepam, or clonazepam only, or even a consequence of spontaneous fluctuations of bipolar illness.

This case, however, presents some specific features. Venlafaxine discontinuation was associated with both

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physical and psychiatric symptoms. Both subsided with re-institution of venlafaxine. Discontinuation of venlafaxine after lithium and clonazepam treatment was associated with the physical disturbances typical of venlafaxine withdrawal, which mirrored those of the first episode, but without manic symptoms. The case (including the anti-manic effect of venlafaxine re-institution) can be interpreted in light of the sensitization hypothesis related to antidepressant drugs (Fava, 1999), encompassing cycle acceleration and paradoxical effects, such as the emergence of depressive symptoms during treatment of panic disorder with an SSRI and abatement of these symptoms when discontinued (Fux et al., 1993), or mood elevation associated with antidepressant drug decrease (Corral et al., 1987). Further investigations of this neglected aspect of depression treatment research appear to be extremely important. It cannot be ruled out that antidepressant drugs may trigger manic episodes in a specific phase of bipolar illness, while in another phase in the same patient they may display anti-manic properties.

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