Case Report

Mirtazapine withdrawal-induced mania

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ABSTRACT

Antidepressant withdrawal mania is not a commonly reported occurrence. To date, there is only one published report of hypomanic episode on withdrawal of mirtazapine. A case is presented herein of a patient who experienced manic episode on withdrawal of mirtazapine.

Key words: Antidepressant, mania, mirtazapine, withdrawal

INTRODUCTION

Manic episode induced by antidepressants is well reported in the literature. However, a paradoxical shift to hypomania or mania upon withdrawal of an antidepressant is not a commonly reported occurrence. These mood switches are considered as a type of "withdrawal or discontinuation syndrome" emerging upon sudden discontinuation or reduction in dose of antidepressants. Earlier it was reported in patients of unipolar depression but it can also occur in bipolar patients.[1] Though this phenomenon is rare, but described with all classes of antidepressants.[2-6] To date, there is only one published report of hypomanic episode on withdrawal of mirtazapine.[7] A case is presented herein of a patient who experienced manic episode on withdrawal of low dose (15 mg) mirtazapine.

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CASE REPORT

Mr. A., 54-year-old male, presented to Psychiatry outpatient department (OPD) with complaints of over talkativeness, grandiose talks, irritability, exhibiting poor boundaries, decreased sleep, increased physical activity for last 7 days. He was receiving treatment from our institution since last 10 years with a diagnosis of bipolar affective disorder. He was maintained on lithium carbonate 800 mg and mirtazapine 15 mg per day for past 6 months. He was euthymic over past 3 months after which it was decided to taper and stop mirtazapine and maintain him on lithium carbonate 800 mg per day. After 1 week of stopping mirtazapine, the patient presented with above-mentioned symptoms. Past history revealed five manic and three depressive episodes in the last 25 years. Last episode was moderate depression, after which mirtazapine was added to lithium. Family history and personal history were insignificant. There was no history of any substance of abuse. He was not taking any other medication (e.g., any herbal medication or medication for any other disorder) except lithium carbonate and mirtazapine. Physical examination of the patient did not reveal any abnormality. Laboratory investigations including hemogram, thyroid function tests, liver function tests, renal function tests were within normal limits. Serum lithium level was 0.98 meq/L [normal range (0.8-1.1 meq/L)]. Olanzapine

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10 mg per day was added. The patient improved slowly and olanzapine was stopped after 2 weeks. He was asymptomatic after 4 weeks and maintained on lithium 800 mg per day.

DISCUSSION

In the present case withdrawal of mirtazapine could be contributed to the development of mania based on the criteria for antidepressant discontinuation or withdrawal "manic state" proposed by Narayan and Haddad.[8] The patient developed manic episode within 1 week of stoppage of mirtazapine and was not taking any other medication other than lithium carbonate and mirtazapine. So no pharmacological confounders present prior to onset of the manic state that could account for it (e.g., stimulant misuse, discontinuation of antimanic or antipsychotic drug). The patient has received mirtazapine for more than 4 weeks which is consistent with the diagnostic criteria proposed by Narayan and Haddad.

Most reported cases of antidepressant withdrawal mania are due to sudden discontinuation.[9] Sudden withdrawal of mirtazapine can cause anxiety, restlessness, depression, insomnia, diarrhoea, vomiting and rarely hypomania or mania. The patient did not report any other symptom except manic episode. Several hypotheses have been postulated to explain the pathophysiology of antidepressant withdrawal–induced mania. But withdrawal-induced cholinergic overdrive and the action of the cholinergic–noradrenergic system remain the most investigated hypothesis for explaining antidepressant withdrawal-induced mania.[10] This hypothesis proposes that, upon cholinergic overdrive, the monoaminergic synthetic pathways are activated in an effort to maintain homeostatic balance. Once the cholinergic overdrive abates, the monoaminergic system usually downregulates in parallel. In some patients, the system fails to downregulate, leading to a state of relative monoaminergic (serotonergic and adrenergic) excess and associated hypomania or mania. Previous report of mirtazapine withdrawal hypomania[7] was at high dose (30 mg). At higher dose mirtazapine sequentially blocks the 5HT2A receptor and then the alpha2 adrenergic receptor. But in our case, hypomania occurred at low dose (15 mg). So this explains that only serotonergic excess caused by mirtazapine withdrawal is sufficient to cause mania.

In this case, the clinical presentation of mirtazapine withdrawal-induced manic episode was almost similar to the presentation of his previous five manic episodes. Also, in previous reported cases[2-6] with other antidepressants no such significant difference was noted.

Mirtazapine is metabolized by 2D6, 3A3/4 (without clinically relevant inhibition), making it less susceptible to pharmacokinetic drug–drug interactions. In the present case no significant drug interaction between mirtazapine and lithium can contribute for the manic episode.

The manic episode may be self-limiting or may require antidepressant drug or specific antimanic treatments. The true incidence of antidepressant withdrawal mania is unknown because it may be underreported as a consequence of under recognition or misattribution.

Psychiatrists should remain aware of the phenomenon of antidepressant withdrawal mania. More studies should be conducted on this subject, which will provide data required for identification of risk factors and for clarification of the relations of sociodemographic and clinical criteria with mania and hypomania triggered by withdrawal of antidepressants.

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