

Mania induced by antidepressant withdrawal

- case report and review -

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Context

The emergence of manic and hypomanic episodes is frequently triggered by antidepressants. Paradoxically, there are rare cases reporting manic states induced by antidepressant withdrawal, in patients treated for major depression in the absence of previously diagnosed bipolar disorder.

This poster aims to report a clinical case accompanied by the authors in the emergency department, consisting of a manic state induced by the abrupt discontinuation of escitalopram. Moreover, we intend to review the extent of this phenomenon, determine which drugs are more commonly involved and present possible explanations for this occurrence.

Psychiatrists should bear in mind the possibility of mania induced by antidepressants withdrawal, a phenomenon that illustrates our lack of understanding of the neural circuits.

Proposed diagnostic criteria for antidepressant withdrawal hypomania/mania [1]

1. A manic state that starts after stopping or reducing the dose of an antidepressant
2. No pharmacological confounders are present that could account for the manic state, e.g. stimulant misuse or stoppage of an antimanic drug (lithium, valproate, carbamazepine, an antipsychotic) prior to the onset of the manic state
3. Continuous antidepressant treatment should have been administered for at least four weeks before the manic state begins
4. Symptoms begin within one week of antidepressant stoppage or dose reduction

Review of the literature

As reviewed by Narayan V and Haddad PM [1], up until 2011 there had only been reported 19 cases of hypomanic/manic episodes induced by antidepressant discontinuation in patients with unipolar depression. Only a minority of those cases (n=6) fulfilled the criteria for mania, and even less required admission (n=2).

This phenomenon has been described with all classes of antidepressants, and is more common with [1]:

- Tricyclic antidepressants
- Drugs with a short half-life (particularly paroxetine)
- Abrupt withdrawal (compared to tapered discontinuation)

These factors suggest that rapid elimination of the antidepressant is a relevant aetiological factor. Since 2011, only a handful more of anecdotal reports [2-5] were published. As far as we know, there has only been one previous report of such occurrence with escitalopram [2].

In terms of disease management, most cases were treated with antimanic drugs [1], according to the recommendations for the treatment of functional mania unrelated to antidepressant stoppage. However, at least 5 cases were managed with the reintroduction of the original or a related antidepressant [1,2]. In all of those cases there was full resolution of symptoms, similarly to what happens in discontinuation syndromes after the reinstatement of antidepressants.

References

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Case report

A 60 years old male patient (Mr. X) was admitted in 2017 at the psychiatric emergency department of Oporto due to behaviour changes. The patient presented:

- Elevated mood
- Pressured speech
- Delusions of grandeur
- Impulsivity and psychomotor agitation
- Increased irritability
- Excessive spending

Mr. X was being treated for a major depressive episode with **escitalopram 20mg** for less than 12 months. He had history of a previous major depressive episode 3 years before, and for which he was also medicated with escitalopram. The family denied any suggestive manic or hypomanic episodes in the past and history of family psychiatric disorders.

According to Mr. X's daughter, who took him to the hospital, the patient had been in his usual state until he went on holidays with his family and forgot to bring his medication. In the first few days of vacations he suddenly developed the above mentioned symptomatology, coinciding with escitalopram withdrawal.

The existence of organic causes was excluded by performing a brain CT scan and laboratory tests (including substance abuse screening), whose results were within reference ranges. Mr. X had no insight for his condition and refused any therapeutic intervention, reason for which he had to be compulsorily hospitalized.

According to the diagnostic criteria suggested by Narayan V and Haddad PM [1], we believe this case represents a manic episode triggered by withdrawal of antidepressant.

Pathophysiology

Whether antidepressant discontinuation manic states indicate a latent bipolar disorder is unclear. However, constitutional factors must play a part as only a proportion of patients develop discontinuation symptoms [1].

Several explanatory models have been presented to explain antidepressant withdrawal-induced mania, none of which have received adequate experimental testing. The prevailing theories are [1,2,5,6]:

- *The cholinergic-monoaminergic interaction hypothesis* – (the most studied hypothesis) withdrawal of tricyclic antidepressants precipitates cholinergic overdrive, which activates the monoaminergic synthetic pathways in an effort to maintain homeostasis. When the cholinergic overdrive abates, the monoaminergic system should downregulate in tandem. However, in some patients, the system fails to downregulate, which leads to relative monoaminergic excess and resultant mania and hypomania
- *Hypo-serotonergic mania* – synaptic reduction of monoamines during antidepressant withdrawal may lead to acute upregulation of monoaminergic postsynaptic receptors that were downregulated during treatment with antidepressants. An ensuing rapid receptor upregulation may increase monoaminergic transmission and trigger a manic switch
- *Noradrenergic hyperactivity* – noradrenergic hyperactivity has been documented after discontinuation of tricyclic antidepressants, although most patients exhibiting these changes did not exhibit mania
- *Hyperdopaminergic mania* – discontinuation of MAOI induces a loss of the agonist autoreceptor effects, which should lead to hyperdopaminergia, owing to decreased uptake of dopamine by the autoreceptor

In the clinical case presented here, the “hypo-serotonergic mania” hypothesis appears to be the most appropriate theory to explain the symptomatology [2].