Manic states related to antidepressant withdrawal – a case report and literature review

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Abstract

Background: A manic state induced by antidepressant withdrawal is a rare clinical occurrence that has been increasingly reported in the last decades and currently represents a nosological entity with specified criteria. **Objectives:** This paper aims to report a case of mania induced by escitalopram withdrawal in a patient with unipolar depression. Furtherly, we intend to review the published case reports of manic states induced by antidepressant withdrawal, analysing its epidemiology and discussing the current theories concerning its pathophysiology. **Methods:** We conducted a search in PubMed database in July 2019, without restriction by year of publication, and selected case reports and literature reviews in English, which were fully read. **Results:** Only 29 reported cases fulfil the most accepted diagnostic criteria. This phenomenon is more frequent in patients with unipolar depression, may occur with any major class of antidepressant and it is still unclear whether it indicates a latent bipolar disorder. Our case report is the third case associated with the use of escitalopram published in the literature. **Conclusion:** Although a rare phenomenon, mania induced by antidepressant withdrawal poses relevant clinical challenges and its possible pathophysiological processes may shed some light on the mechanisms underlying affective disorders.

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Keywords: Mania, hypomania, antidepressant withdrawal, major depressive disorder, escitalopram

Introduction

Antidepressant discontinuation syndrome (or antidepressant withdrawal syndrome) is triggered by the interruption, reduction or discontinuation of all major antidepressant classes[1]. Symptoms may include increased anxiety, nausea, vertigo, insomnia, sensory changes, among others[1]. Although the most common mood disturbances related to this syndrome are depressive symptoms, some authors have reported cases of paradoxical manic shifts induced by antidepressant withdrawal.

It is a rare clinical occurrence that has been increasingly reported in the last decades. The most commonly used diagnostic criteria were published in 2007 by Haddad and Anderson[1], and included four items:

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.

This paper aims to review all published case reports of manic states induced by antidepressant withdrawal, analyse its epidemiology and discuss the current theories concerning its pathophysiology. We will also report an extremely rare case of mania induced by escitalopram withdrawal in a patient with unipolar depression.

Methods

We conducted a search in PubMed database in July 2019, using the query first published by Narayan and Haddad[2], and later used by Kassm et al.[2]: "antidepressant withdrawal" or "antidepressant discontinuation" plus "mania" or "hypomania". From the articles retrieved we selected the relevant case reports written in English, without restriction by year of publication, according to the previously described diagnostic criteria. The relevant articles were fully read, and the papers' references were searched for additional reports and for articles regarding explanatory theories. Additionally, we report a clinical case attended by the authors in the emergency department in late 2017.

From the query used we retrieved 579 articles, fifty-three of which regarding case reports of antidepressant withdrawal manic states. Twenty-four of those reports were excluded for not fulfilling all the inclusion criteria: two case reports were not written in English, one case had a possible confounding vascular aetiology for

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the manic symptoms, and in another there was not sufficient clinical data to ascertain the diagnostic criteria. The remaining twenty cases were excluded for not meeting all the diagnostic criteria outlined by Haddad and Anderson[1]: three cases for criterion 1, one for criterion 2, three for criterion 3 and thirteen for criterion 4. Twenty-nine case reports were then retained.

Case report

We present the case of a 60-year old male patient that was referred by his family to the emergency department due to a two weeks behavioural disturbance. According to his family, during vacation, he presented psychomotor agitation, increased irritability, excessive spending and incoherent speech. On admission, he presented other characteristic symptoms of a manic state such as elevated mood, pressured speech and delusions of grandeur. He had no relevant history of medical diseases or family psychiatric disorders, and the family denied previous hypomanic episodes.

At that time the patient was being treated for a major depressive episode with escitalopram 20mg for less than 12 months, medication he had already taken three years before during another major depressive episode. The aforementioned symptoms started after abrupt discontinuation of escitalopram during family vacations. An organic evaluation was performed through CT scan and laboratory tests (including substance abuse screening). All results were within reference ranges. Due to a lack of insight for his condition and treatment need, the patient had to be compulsorily hospitalized in a psychiatric ward.

Literature review

The twenty-nine case reports selected for analysis are in accordance with the results compiled by two literature reviews previously published[2,3], corresponding to two different time frames. Narayan and Haddad[3] reviewed all existing case reports until 2007 and concluded that 24 clinical cases met their proposed diagnostic criteria. These authors found that all major antidepressant classes were involved, with a majority of cases occurring with tricyclic antidepressants (n = 13), followed by selective serotonin reuptake inhibitors (n = 5), monoamine oxidase inhibitors (n = 3) and serotonin-norepinephrine reuptake inhibitors (n = 2). Manic states induced by antidepressant discontinuation were more frequent in patients with unipolar depression, compared with patients previously diagnosed with bipolar disorder (n = 19 vs n = 4). They also concluded that drugs with a short half-life (particularly paroxetine) and the abrupt stoppage of an antidepressant (comparing with a slow dose reduction) were risk factors. Interestingly, the hypomanic/manic symptoms were resolved in two patients with bipolar disorder by reinstating the antidepressant, while the rest were medicated with antipsychotics. As for patients with unipolar depression, the symptoms remitted spontaneously in 9 patients after a median of 25.5 days. The remaining cases of patients with unipolar depression were treated with mood stabilizers (n = 2), antipsychotics (n = 2) or by reinstating an antidepressant (n = 2). The symptoms presented in most cases were mild, only six patients fulfilled all the criteria for mania, and even less required admission (n = 2).

The most recent literature review, conducted by Kassm et al.[2], assessed articles published from January 2008 to January 2018. This article identified 11 case reports but considered that only 5 met the diagnostic criteria. In those ones, manic states were triggered by the withdrawal of amitriptyline, fluoxetine, escitalopram (n = 2) and mirtazapine. Both escitalopram-related cases happened in patients with unipolar depression. As stated by the previous review, the majority of cases occurred after the abrupt discontinuation of antidepressants (n = 3). The therapeutic approach was variable: in two cases the original antidepressant was reinstated, and in the rest antipsychotics or/and humour stabilizers were started. After January 2018 until July 2019 no further cases have been reported.

Table 1. Summary of the number of case reports by antidepressant, in descending order

Antidepressant	Number of Cases	References
Amitriptyline	6	Mirin et al., 1981 (4 cases)[4] Charney et al., 1982[5] Uppal et al., 2009[6]
Imipramine	4	Mirin et al., 1981[4] Jones et al., 1984[7] Gupta and Narang, 1986[8] Kusalic and Ghadirian, 1990[9]
Paroxetine	3	Bloch et al.,1995 (2 cases)[10] Landry and Roy, 1997[11]
Escitalopram	2	De Berardis et al., 2014[12] Kwok and Lim, 2017[13]
Venlafaxine	2	Fava and Mangelli, 2003[14] Khazaal, 2007[15]
Desipramine	2	Nelson et al., 1983[16]
Isocarboxazid	2	Rothschild, 1985[17]
Mirtazapine	2	MacCall and Callender, 1999[18] Verma and Mohapatra, 2015[19]
Fluoxetine	1	Özcan et al, 2013[20]
Sertraline	1	Goldstein et al., 1999[21]
Fluvoxamine	1	Szabadi, 1992[22]
Protriptyline	1	Mirin et al., 1981[4]
Nortriptyline	1	Ali and Milev, 2003[23]
Phenelzine	1	Hartmann, 1990[24]

Several explanatory models have been suggested for this phenomenon, none of which have received adequate experimental testing. The most studied theory has been the cholinergic–monoaminergic interaction hypothesis[25,26] that has more applicability to the discontinuation of tricyclic antidepressants. It is thought that the monoaminergic synthetic pathways are stimulated by the cholinergic overdrive induced by the sudden lack of the antidepressant. In these patients the monoaminergic synthetic pathways do not downregulate after the cholinergic overdrive declines, which may lead to mania and hypomania. The noradrenergic hyperactivity[5] has also been proposed has a possible mechanism involved in the discontinuation of tricyclic antidepressants, although most patients exhibiting these changes did not exhibit mania.

One relevant theory has been named as the hyposerotonergic mania[27]. It has been hypothesized that the antidepressant withdrawal, and consequent lack of synaptic monoamines, may fuel an acute upregulation of monoaminergic postsynaptic receptors, which could increase monoaminergic transmission and trigger a manic switch. Finally, the discontinuation of monoamine inhibitors has been related to the hyperdopaminergic mania theory[17].

Discussion

Manic states following antidepressant withdrawal are a rare condition, and only 29 reported cases in the past 37 years fulfil the most accepted diagnostic criteria. Since Haddad and Anderson[1] established those criteria in 2007, no further refinements have

been proposed. However, some issues can be raised, in particular the application of the temporal criterion has led to the exclusion of a considerable number of cases of patients whose symptoms appeared after 1 week of the antidepressant discontinuation. In the first review[2] 11 cases were excluded because they did not meet this criterion, and in the most recent review[3] two cases were excluded for the same reason. All those patients appeared to fulfil the remaining criteria, and the clinical evaluation and treatment was very similar to the ones that were included.

Although Narayan and Anderson[2] concluded that this phenomenon is more frequent in patients with unipolar depression, it is still unclear whether antidepressant discontinuation manic states indicate a latent bipolar disorder. Kassm et al.[3] claim that half of all the published cases display a very suspicious history for bipolar spectrum disorder. What is certain is that constitutional factors must play a part as only a proportion of patients develop discontinuation symptoms[2]. What can also be ascertained is that the rapid elimination of the antidepressant is a relevant risk factor.

Our case report meets all the diagnostic criteria for a manic episode induced by antidepressant withdrawal: the manic state started after the abrupt stoppage of escitalopram, the patient was not under any other medication that could be considered as a pharmacological confounder, the treatment with antidepressant lasted longer than four weeks and symptoms started in less than one week. Therefore, we believe it is safe to consider it as the third case report related to the use of escitalopram. As previously discussed by Berardis et al.[12], the "hypo-serotonergic mania" hypothesis appears to be in accordance with the symptoms displayed. However, one major limitation of our report is that we did not followed the patient after admission to the inpatient unit.

Although our knowledge of the mechanisms underlying antidepressant withdrawal manic states in the absence of previously diagnosed bipolar disorder is scarce, its occurrence underlies the importance of tapered discontinuation of antidepressants, alongside an adequate clinical follow-up. To the best of our knowledge, it is the only way to decrease the risk of the emergence of this phenomenon.

Conflicts of interest

The authors do not report any conflicts of interest. This clinical case was previously presented at the 31st European College of Neuropsychopharmacology Congress, 6-9 October 2018, Barcelona (Spain).

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