

# Hypomania/Mania Induced by Cessation of Antidepressant Drugs

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## Abstract

Although rarely reported, the induction of hypomanic/manic episodes due to sudden or gradual cessation of antidepressant drugs is a phenomenon observed in clinical settings. Herein we present 2 patients that had manic episodes induced by gradual cessation of antidepressant drugs. Common features of both cases were as follows: patients were female; a major depressive episode was the reason for starting treatment; familial loading for unipolar depressive disorder; venlafaxine was administered for treatment of the episode; mood elevation symptoms while gradually decreasing the medication dose; absence of physical symptoms related to withdrawal; antipsychotic and mood stabilizing drugs were required for the treatment of the episode. In both cases 1) a hypomanic/manic episode induced by the use of antidepressants, 2) agitated depression, 3) physical withdrawal syndrome, and 4) spontaneous episodes in the natural course of the illness were the 4 different states that were taken into consideration for differential diagnosis. Hypomanic/manic episodes induced by cessation of antidepressant drugs are thought to shed light on the etiology of bipolar disorder, which this report discusses with reference to the case reports.

**Key Words:** Antidepressive drug, mania, hypomania, cessation

## INTRODUCTION

It is reported that the prevalence of induced mania/hypomania in patients with mood disorders (especially bipolar disorder) that are treated with antidepressants is 10%-40% and, thus, should be investigated. (Fava and Mangelli, 2003; Goldberg and Truman, 2003; Sherese and Milev, 2003). Patients suffering from induced mania/hypomania during antidepressant drug treatment that were never diagnosed with bipolar disorder are not considered to be bipolar according to the diagnostic criteria in general use (World Health Organization, 1992; American Psychiatric Association, 1994), yet researchers have been classifying these patients as bipolar (Ghaemi et al., 2001; Akiskal et al., 2003; Chun and Dunner, 2004; Berk and Dodd, 2005). Variables such as duration of antidepressant drug use and dose, and their relationship to the induction of mania/hypomania isn't explicitly known; however, it is reported that variables

such as a family history of bipolarity and having bipolar signs prior to antidepressant use increases the risk of induced mania/hypomania (Goodwin and Jamison, 1990; Goldberg and Truman, 2003). It is reported that all antidepressant drugs, especially tricyclic antidepressants, can lead to induced mania/hypomania (Fava and Mangelli, 2003; Sherese and Milev, 2003). Some questions remain unanswered: Does induction of mania/hypomania arise in people who are expected to experience spontaneous attacks; do people with a history of induced mania tend to experience additional attacks, and does exposure to the drug that induced mania always induce mania (Post, 2000)?

In clinical settings, although not as common as during drug use, it is observed that mania/hypomania is induced during dose reduction or subsequent to drug cessation. Nonetheless, it is thought that it is observed in clinical settings much more frequently than reported in

Received: 12.01.2007 – Accepted: 01.04.2008

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the literature, which might be because it isn't observed, is attributed to other causes, or is considered to be a totally different condition (Andrade, 2004). The present study aimed to discuss induced mania/hypomania related to drug cessation in the light of 2 cases. The cases are considered to be important because they highlight the biochemical origin of induced mania/hypomania and offer an opportunity to consider new protective treatment approaches.

### CASE 1

The patient was a 25-year-old unmarried female, the second of 3 siblings. She presented to the emergency outpatient clinic complaining of sudden nervousness, conversing with strangers, exploding with anger, decreased need for sleep, rapid speech, racing thoughts, hypersexuality, impulsive spending, engagement in risky sexual activity, and mood swings.

According to the case history, the complaints began 1 week prior to presentation and then in increased severity; her sleep time decreased to 3-4 hours and she couldn't continue to work. Two years earlier she presented to the Marmara University Hospital, Psychiatry Outpatient Unit, complaining of a depressed mood, and feelings of worthlessness and guilt accompanied by suicidal thoughts. At that time she was diagnosed with dysthymia and double depression, and was prescribed sertraline 50 mg/day. She was on medication for 1 year but she used them irregularly. Eventually, specialists thought that she couldn't get regular treatment and she was hospitalized in a psychiatric inpatient unit and was prescribed clomipramine 150 mg/day and lithium 900mg/day for augmentation. She was discharged from the hospital with partial recovery and was followed-up at an outpatient unit.

As she complained of adverse effects and wasn't improving, specialists withdrew clomipramine and lithium, and she was prescribed venlafaxine 75 mg/day. During the third month of treatment the venlafaxine dose was increased to 300 mg/day; treatment then continued at the same dose for the next 8 months. At the end of the eighth month of treatment the drug was gradually reduced and finally withdrawn because the patient was fully recovered. During the third week of dose reduction (venlafaxine 75 mg/day) she again presented to the emergency outpatient clinic, complaining of nervousness, hyperactivity, and decreased need for sleep, in addition to her prior complaints.

Her history was unremarkable, although her family

history revealed that her brother was hospitalized for alcohol dependency and treated numerous times, and that her sister had been diagnosed with major depression.

During her psychiatric examination she showed signs of irritable mood and racing thoughts. She didn't have unusual thoughts, except grandiosity. She had decreased need for sleep and showed signs of psychomotor agitation. She was prescribed valproate 1000 mg/day and wasn't hospitalized, but followed-up at the outpatient unit. At the end of 1 week, risperidone 2 mg/day was added to her treatment because she wasn't improving. After the first month of the treatment it was concluded that all her symptoms resolved and that she was functioning normally. Risperidone was then withdrawn and her treatment continued only with valproate.

### CASE 2

The patient was a 26-year-old unmarried female, the first of 2 siblings. She presented to the emergency outpatient unit complaining of rapid speech, decreased need for sleep, and explosions of anger. She got suspicious about her colleagues because she believed that they were testing her professional competency. She doubted her colleagues because she thought that they were testing her knowledge.

According to her case history, during the previous 2 days she started to feel increasingly angry, started arguing with her colleagues and close friends, did not sleep, believed that her friends were testing her professional competency in certain ways, and she frequently left home and wandered around.

Her complaints first began 8 months earlier: anhedonia, continuous feelings of worthlessness and sadness, frequent thoughts about being unsuccessful at work, unable to study because of a lack of concentration, fatigue, and decreased self-care. She presented to the Marmara University Hospital, Psychiatry Outpatient Unit, was diagnosed with major depressive disorder, and prescribed venlafaxine 75 mg/day. After 2 months venlafaxine was increased to 225 mg/day, as her symptoms didn't improve. With this dose her symptoms began to diminish and the medication continued at the same dose for 6 months. At the end of the sixth month the dose was gradually reduced and the medication was withdrawn upon full recovery.

During the third week of dose reduction (venlafaxine 75 mg/day) her previous complaints returned.

Her history was unremarkable, but her family history

included her father's suicide, committed when she was 12 years old. Her other first-degree family members had no psychiatric problems.

According to her psychiatric examination her mood was irritable, and she had racing thoughts, delusions of reference and grandiosity, psychomotor agitation, decreased need for sleep, and distractibility. Due to these symptoms she was diagnosed with acute mania and was prescribed olanzapine 10 mg/day and lithium 900 mg/day. At the end of the first month her symptoms resolved, olanzapine was withdrawn, and treatment continued only with lithium.

## DISCUSSION

One of the most important features of bipolar depression treatment is undoubtedly the risk of induced mania/hypomania triggered by antidepressants. It is known that induction of mania/hypomania frequently occurs during the first weeks of treatment (Wada et al., 2006). It is predominantly observed in patients with bipolar disorder, but also is seen in patients with recurrent depressive disorder (Goodwin and Jamison, 1990). On the other hand, the general opinion is that every patient that experiences induced mania/hypomania should be included in the bipolar spectrum (Ghaemi et al., 2001; Akiskal et al., 2003; Chun and Dunner, 2004; Berk and Dodd, 2005). Females (Post, 2000), adolescents, and patients with early onset (Goodwin and Jamison, 1990; Goldberg and Truman, 2003), and patients with a family history of psychiatric problems in first-degree family members (Goldberg and Truman, 2003; Wada, 2006) are more likely to experience induction of mania/hypomania. In contrast though, another study didn't find any relationship between age and the risk of induced mania/hypomania (Goodwin, 1990).

Induced mania/hypomania following antidepressant dose reduction or cessation is a subject that is not adequately reported, though a few studies do exist (Mirin, 1981; Nelson et al., 1983; Dilsaver and Greden, 1984; Pickar et al., 1984; Rothschild, 1985; Altintoprak et al., 2006). Induced mania/hypomania's course is generally mild and it recovers naturally. It's a process that can be considered to be the recovery phase of depression, but it is not always related to drug cessation and the timing of drug cessation, and it's a spontaneous attack of manic/hypomanic episode. These characteristics may be hindering clinicians' awareness of the subject (Goldstein, 1999; Andrade, 2004).

Two studies have reported prevalence rates, both of

which included patients with bipolar mood disorder. Shrivar et al. (1998) reported that 12 (15.2%) of 79 episodes among 39 patients were related to drug cessation. The only forward looking study that systematically evaluated risk factors (Goldstein et al., 1999) reported that 6 patients (8.2%) out of 73 had induced mania/hypomania subsequent to antidepressant drug cessation.

The first factors that should be dealt are the natural course of the disorder and the difficulty in making a differential diagnosis. There are 4 descriptions included in the differential diagnosis: induced mania triggered by antidepressant drug use, agitated depression, physical abstinence syndrome, and manic/hypomanic episode occurring during the natural course of bipolar disorder (Goldstein et al., 1999).

Induced mania/hypomania triggered by antidepressant drugs is typically expected to occur at the same time as antidepressant response, which is 4-8 weeks (Altshuler et al., 1995). In both of our presented cases, manic/hypomanic induction occurred after the sixth month of treatment so this weakens the forementioned possibility. Additionally, mania in both cases was induced when the drug dose was at its lowest level. Both cases met the criteria for manic episode according to DSM-IV (American Psychiatric Association, 1994), especially as symptoms like racing thoughts, grandiose thoughts, and decreased need for sleep are not consistent with the criteria for a diagnosis of agitated depression.

Both cases were taking venlafaxine and signs of withdrawal are common after its cessation; however, clinically there weren't any signs of withdrawal or increased cholinergic activity, which contradicts the models suggested by etiology, yet is consistent with Goldstein's (1999) findings and excludes the possibility of withdrawal syndrome.

Additionally, there weren't any signs or episodes before treatment, which led us to consider bipolarity; therefore, the probability is low that the manic episodes appeared as a part of the disorder's natural course. Of particular note is that both cases didn't have a genealogical history of unipolar depression and there were no signs of bipolarity.

When making the differential diagnosis one should consider that the drug might be withdrawn because of induced mania/hypomania and that the clinician, mistakenly, could think that the induction of mania/hypomania occurred because of drug cessation (Andrade, 2004). This seems to be improbable with regards to

the presented cases because in both cases there were no signs of mood elevation when the clinician decided to withdraw the drug, and symptoms of a manic episode appeared 6 months after drug treatment with the same dose and also appeared during drug reduction.

It is thought that biological mechanisms other than the effect of drug withdrawal triggered induced mania/hypomania. This unstable situation, which has a triggering effect on sensitive patients (Goodwin and Jamison, 1990) suggests that there should be alternative explanations for manic episodes. Noradrenergic hyperactivity and cholinergic-monoaminergic interaction are widely accepted and supported etiological theories, yet there are also hypotheses such as hyposerotonergic mania, REM rebound, and hyperdopaminergic mania (Sherese and Milev, 2003; Goldstein et al., 1999). The theory of noradrenergic mania is based on the increase of plasma and urinary MHPG (3-Methoxy-4-Hydroxyphenylglycol) subsequent to tricyclic antidepressant cessation, which are the signs of norepinephrine metabolism. These findings were observed in 7 patients, yet only 1 showed hypomanic behavior (Sherese and Milev, 2003). The cholinergic-monoaminergic interaction theory, as well, explains mania/hypomania cases following the cessation of antidepressant drugs as being due to anticholinergic effects. By withdrawing these kinds of drugs, cholinergic inhibition is replaced by cholinergic stimulation. Consequently, the monoaminergic system is activated

to maintain homeostasis. When the cholinergic stimulation is relieved, the down-regulation of the monoaminergic system is expected, yet sometimes doesn't occur and causes relative monoaminergic residuary, resulting in mania/hypomania. Both theories are based on cases treated with anticholinergic drugs and this is a limitation (Sherese and Milev, 2003). Both of our presented cases were prescribed venlafaxine, which is associated with high anticholinergic activity, and this is a supporting finding and an interesting coincidence.

It is reported that in some cases mood elevation signs automatically diminish without any additional treatment (Charney et al., 1982; Dilsaver and Greden, 1984; Ghadirian, 1986). In some cases, as with the 2 presented cases, the symptoms were controlled with mood stabilizers and antipsychotics (Sherese and Milev, 2003; Andrade, 2004). Other instances that can link the etiology of the induction of mania/hypomania to withdrawal are some cases with extinction of induction symptoms after restarting antidepressant medication (Nelson et al., 1983; Goldstein et al., 1999).

As induced mania/hypomania related to antidepressant drug cessation is a rare condition encountered in clinical settings, it is difficult to conduct large-scale controlled studies of it. Studies designed with an expanded scope will help us to better understand bipolar disorder and to find new treatment methods.

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