

Mania/Hypomania Associated with Withdrawal of Antidepressants

Mehmet Guduk¹,
Ilke Yeser Erensoy²,
Filiz Ersumer³

¹Psychiatrist, Yedikule Private Psychiatry Center,
Istanbul - Turkey
²Psychiatrist, Besiktas Sait Ciftci State Hospital,
Istanbul - Turkey
³Psychiatrist, 75. Yil Milas State Hospital,
Mugla - Turkey



ABSTRACT

Mania/hypomania associated with withdrawal of antidepressants

Although paradoxical mania/hypomania due to antidepressant withdrawal is rarely reported in the literature as case report, it is possible that it may be observed more commonly in the clinical settings. Paradoxical mania/hypomania is reported to be associated with tricyclic antidepressants as well as selective serotonin reuptake inhibitors and other antidepressants. Although paradoxical mania/hypomania due to sertraline and paroxetine withdrawal are reported individually, we will discuss a patient with paradoxical mania/hypomania due to withdrawal of both antidepressants administered at two different time periods, since this is the only case reported so far.

Key words: Antidepressant withdrawal, hypomania, mania, paroxetine, sertraline

ÖZET

Antidepresan kesilmesine bağlı mani/hipomani

Antidepresan kesilmesi sonrası "paradoksal" mani/hipomani, literatürde az sayıda olgu bildirim şeklinde yer almakla birlikte, klinikte daha sık karşılaşıyor olması muhtemeldir. Sıklıkla trisiklik antidepresanlarla (TSA) bildirilmiş olup, selektif serotonin geri alım inhibitörleri (SSGI) ve daha nadir olarak diğer antidepresanlarla da bildirilmiştir. Sertralin ve paroksetin kesilmesine bağlı bildirilmiş olgular olmakla birlikte, aynı hastada farklı dönemlerde hem sertralin hem de paroksetin kesilmesine bağlı gelişen manik dönem olarak literatürdeki bilinen tek örnek olması açısından ilginç olduğunu düşündüğümüz bir olgu tartışılmıştır.

Anahtar kelimeler: Antidepresan kesilmesi, hipomani, mani, paroksetin, sertralin

Address reprint requests to / Yazışma adresi:
Psychiatrist Mehmet Guduk,
Yedikule Private Psychiatry Center,
Istanbul - Turkey

Phone / Telefon: +90-212-510-7410

E-mail address / Elektronik posta adresi:
memgdk@yahoo.com

Date of receipt / Geliş tarihi:
July 27, 2012 / 27 Temmuz 2012

Date of acceptance / Kabul tarihi:
August 26, 2012 / 26 Ağustos 2012

INTRODUCTION

Antidepressant drugs are safely used in the treatment of various psychiatric disorders. However, there are a great many of data on their undesired effects. An important undesired effect of antidepressants is mood switches emerging during their use. Current literature contains a lot of studies focused on this point (1). Another effect is related to the "withdrawal syndrome" resulting from discontinuance or rapid dose reduction of antidepressants. Withdrawal signs are frequently restlessness, anxiety, headache, fatigue, nausea and sleep disorders, and rarely mood changes, psychosis, delirium and similar psychiatric conditions (2).

Mood switches associated with withdrawal of antidepressants, which are generally reported as case reports in the literature, have first been defined as a

result of use of TSA, and later, similar cases have been reported also for other antidepressants (3,4). Mania associated with withdrawal of antidepressant will be discussed in this article.

CASE

A female patient of twenty-one years old was brought by her relatives to Kars State Hospital Psychiatry outpatient unit with logorrhea, hyperactivity, nervousness, intolerance and insomnia complaints. The patient was characterized with nervousness and intolerance towards her family members and entourage, and buttonholing of non-acquaintances, and preference of more vivid colors, and over-embellished make-up. In medical examination, she was conscious and cooperative with full orientation. She had grandiose attitude, and

her psychomotor activity was increased. Her affect was vivid, and mood was irritable. Quantity and rate of her speech were increased. Her associations have speeded up. Her self-confidence was increased. An increase in her interest to opposite sex was also reported. Psychotic findings were not detected. Her complaints were present for one week and had started three days after the discontinuation of sertraline (50 mg/day) used for three months. The patient, considered to be in manic episode, is hospitalized for treatment.

The patient was suffering from the disease for three years, and first she admitted to a psychiatrist with depressed mood, anhedonia and social withdrawal three years ago, and used paroxetine for four months. Treatment was useful, but three days after she discontinued the treatment by herself, her logorrhea, hyperactivity, nervousness, and increase in interest to opposite sex complaints have started, and after one week, her complaints ceased automatically. After one year, due to her depressive complaints, paroxetine was restarted at a dose of 30 mg/day, and after a treatment period of five month discontinuation of paroxetine for four days, increase in quantity and rate of speech, insomnia, nervousness and increase in interest to opposite sex have started again, and after ten days, her complaints ceased automatically. Three months thereafter, she started to take paroxetine by herself, and after two months, the drug was discontinued by her psychiatrist by dose reduction, and no problem was emerged during this period. Three months prior to her last admission, she was started to take sertraline 50 mg/day upon demand of her psychiatrist due to her depressive complaints, and discontinued the drug treatment by herself after three months, and three days after discontinuation, she was brought to the hospital following her severe family and professional problems due to manic symptoms.

The patient had no other medical disorder, and her family history did not indicate any specific problem, nor has any finding been detected in her post-hospitalization analyses. Risperidon 2 mg/day treatment was started. Upon observation of a rapid improvement in her symptoms, she was discharged with clinical improvement in the tenth day of her hospitalization.

DISCUSSION

It is known that use of antidepressants in bipolar disorder triggers manic switch at such a high rate of 35% (1). Furthermore, though rarely, there are case study reports indicating that mood switches may also be triggered paradoxically in association with withdrawal of antidepressants. In these reports dealing with mood switches considered as a type of "withdrawal syndrome" emerging upon reduction or sudden discontinuation of antidepressants, various different clinical effects such as mood elevation, hypomania and mania are described (1,3-6).

Though the cases of mania or hypomania in association with withdrawal of antidepressants have mostly been reported in bipolar and unipolar depression patients, the literature also contains, one case report related to schizophrenia and one related to OKB (1,3,7).

It is believed that though they remain only at the case report level, the number of reports is fairly below the actual number of cases in clinical practice (3). Furthermore, it is stated that mood switches are generally slight in severity and tend to improve automatically, and are considered as an automatic episode occurring as a natural part of the improvement process, and for these reasons, they affect the detection and identification of manic or hypomanic switches in association with withdrawal of antidepressants (3,7,8).

The literature contains only two studies focused on frequency, and both of those studies have included only patients with bipolar disorder. In the first study, it is determined that 12 out of 79 manic episodes (15.2%) observed in 39 patients have occurred within fifteen days after discontinuation of antidepressants (1,5). Also in another prospective follow-up study, post-discontinuation mania has been reported in 6 out of 73 patients (8.2%) (7). There exists no study investigating the frequency of mood switches occurring after discontinuation of drug treatment in unipolar depression.

According to the diagnostic systems which are commonly used in our day, though manic or hypomanic switches occurring in association with withdrawal of drug treatment are not considered within the bipolar

disorder diagnosis group, the opinion defending that this should be considered within “bipolar spectrum” is gaining weight (9,10).

In differential diagnosis of manic/hypomanic switches in association with reduction or withdrawal of antidepressants, one must take the following conditions in consideration: the antidepressant withdrawal syndrome, the mania/hypomania triggered by antidepressants, the agitated depression, and the mania/hypomania occurring in the natural course of disease (1,5,7). As in our case the somatic symptoms of antidepressant withdrawal syndrome are not observed, and a more severe clinical situation is reported in comparison with the mood symptoms which may normally be seen during a withdrawal syndrome, the case cannot only be described with a withdrawal syndrome (1,7). During the patient’s disease history of three years, as no mood symptom is observed during administration of paroxetine for different periods at different times and lastly, sertraline for three months, and as mania/hypomania triggered by the drug is reported generally within the initial 4 to 8 weeks of treatment, and as manic episodes emerge upon discontinuation of drug at each time, the mania triggered by antidepressant is excluded. As depressive symptoms are not observed in the case, and due to such dominating symptoms as grandiosity, speeding in associations, increase of self-confidence, and as DSM-IV diagnosis criteria are met for manic episode, the agitated depression diagnosis is also excluded. The lack of any finding indicating a pretreatment mania/hypomania reduces the probability of mania/hypomania occurring in the natural course of disease. In addition, the probability of discontinuation of drug treatment by the patient herself due to a manic switch under antidepressant treatment is also excluded through detailed inquiry of the patient and her family members about the time immediately before the discontinuation of drug treatment, and as her medical records related to these periods did not contain any finding suggested a mania/hypomania.

In case reports, first, manic/hypomanic switches associated to discontinuation of TSAs have been

reported, and later, upon increase of use of non-TSA antidepressants, it has been noted that this is not related only to TSAs, and may occur in almost all antidepressants, and by the time, the manic/hypomanic switch cases in association with withdrawal of antidepressants have also increased (1,2,4,5,8,11-13). Our case with manic/hypomanic episodes triggered by discontinuation of paroxetine twice, and discontinuation of sertraline immediately before hospitalization, is the single example known in the literature in terms of mood episodes occurring in association of withdrawal of different antidepressants.

Though gradual withdrawal has also been reported in the cases in medical literature, most of the case reports are related to results of sudden discontinuation of antidepressants (1-3). In our case, manic/hypomanic episodes have been detected upon sudden discontinuation of paroxetine twice and of sertraline once, but no such problem has been reported upon withdrawal through reduction of dose under the control of a psychiatrist.

The mechanism of mania/hypomania associated with withdrawal of antidepressants could not be described fully yet, but various hypotheses have been put forward. Noradrenergic hyperactivity model, cholinergic-monoaminergic interaction model, hyposerotonergic mania model, REM sleep rebound and hyperdopaminergic mania are the most commonly discussed hypotheses (1,4,5).

Reduction of serotonin in synaptic gap during withdrawal of SSRIs plays an important role in occurrence of withdrawal symptoms. Half lives and withdrawal rates of SSRIs are also important in occurrence of withdrawal symptoms. Withdrawal syndrome is more frequently reported especially in SSRIs with a shorter half life such as paroxetine and sertraline (14). Use of SSRIs leads to desensitization in serotonin receptors, resulting in a down-regulation in receptors. An evident reduction is noted in serotonin concentration in synapses as a result of elimination of recovery inhibition and recovery of presynaptic serotonin upon sudden discontinuation of SSRIs. It is argued that this hyposerotonergic situation may be

associated not only with the withdrawal symptoms, but also with mania/hypomania occurring in association with withdrawal (1,2). As mania/hypomania occurred with two SSRIs with a short half life such as paroxetine and sertraline, and in addition, as manic/hypomanic episodes are observed upon sudden discontinuation of both drugs, but a similar result is not obtained upon withdrawal of paroxetine through dose reduction, we concluded that hyposerotonergic mania model, as put

forward for description of mechanism of mania/hypomania associated with withdrawal of antidepressants, may explain our case.

Broad-scale and controlled studies are needed to be conducted on this subject, and the follow-up studies 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.

REFERENCES

1. Ali S, Milev R. Switch to mania upon discontinuation of antidepressants in patients with mood disorders: a review of the literature. *Can J Psychiatry* 2003; 48:258-264.
2. Zajecka J, Tracy KA, Mitchell S. Discontinuation symptoms after treatment with serotonin reuptake inhibitors: a literature review. *J Clin Psychiatry* 1997; 58:291-297.
3. Andrade C. Antidepressant-withdrawal mania: a critical review and synthesis of the literature. *J Clin Psychiatry* 2004; 65:987-993.
4. Narayan V, Haddad PM. Antidepressant discontinuation manic states: a critical review of the literature and suggested diagnostic criteria. *J Psychopharmacol* 2011; 25:306-313.
5. Altintoprak AE, Sertoz OO, Coskunol H. Antidepressant-discontinuation induced mania: A case report and review of the literature. *Bulletin of Clinical Psychopharmacology* 2006; 16:245-251 (in Turkish).
6. Dilsaver SC, Greden JF. Antidepressant withdrawal-induced activation (hypomania and mania): mechanism and theoretical significance. *Brain Res* 1984; 319:29-48.
7. Goldstein TR, Frye MA, Denicoff KD, Smith-Jackson E, Leverich GS, Bryan AL, Ali SO, Post RM. Antidepressant discontinuation-related mania: critical prospective observation and theoretical implications in bipolar disorder. *J Clin Psychiatry* 1999; 60:563-567.
8. Kora K, Kaplan P. Antidepressant-discontinuation induced hypomania/mania. *Turk Psikiyatri Derg* 2008; 19:329-333 (in Turkish).
9. Akiskal HS, Hantouche EG, Allilaire JF, Sechter D, Bourgeois ML, Azorin JM, Chatenêt-Duchêne L, Lancrenon S. Validating antidepressant-associated hypomania (bipolar III): a systematic comparison with spontaneous hypomania (bipolar II). *J Affect Disord* 2003; 73:65-74.
10. Ghaemi SN, Ko JY, Goodwin FK. The bipolar spectrum and the antidepressant view of the world. *J Psychiatr Pract* 2001; 7:287-297.
11. MacCall C, Callender J. Mirtazapine withdrawal causing hypomania. *Br J Psychiatry* 1999; 175:390.
12. Fava GA, Mangelli L. Mania associated with venlafaxine discontinuation. *Int J Neuropsychopharmacol* 2003; 6:89-90.
13. Michael N, Erfurth A, Arolt V. A case report of mania related to discontinuation of bupropion therapy for smoking cessation. *J Clin Psychiatry* 2004; 65:277.
14. Tamam L. Selective serotonin reuptake inhibitor discontinuation syndromes. *Clinical Psychiatry* 2001; 4:102-111 (in Turkish).