Manic Shift Due to the Use of Bupropion in Bipolar Depression: Two Case Reports

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SUMMARY

Bupropion is a selective norepinephrine and dopamine reuptake inhibitor. It is used in the treatment of depression and nicotine addiction. When compared to the other antidepressants, bupropion has a relatively lower risk of triggering shift to hypomania or mania in bipolar depression treatment. Here we report two cases of bipolar depression patients with manic shift when bupropion was used as an adjunct to mood stabilizer treatment. The first was a 43-year old female patient. Manic symptoms occurred after bupropion was added to lithium and quetiapine treatment for bipolar disorder (BD) depressive episode. Her manic symptoms regressed rapidly after discontinuing bupropion treatment. The second patient was a 26-year old male on lithium and valproate therapy with a BD diagnosis. After bupropion was added to his treatment for depressive symptoms, psychotic mania ensued and he had to be admitted to the hospital. Significant improvement was noted shortly after bupropion was discontinued and antipsychotic treatment was initiated.

Keywords: Bupropion, bipolar disorder, depression, mania

INTRODUCTION

Bupropion is the only antidepressant with an inhibitory effect on both noradrenaline and dopamine reuptake. Bupropion is also a non-competitive inhibitor of nicotinic acetylcholine receptors. Hence, it is also used in the treatment of nicotine addiction beside its use as an antidepressant (Yüksel 2010). Antidepressant induced manic shifts were detected in 20-40% of bipolar patients with all antidepressant classes (Goldberg and Truman 2003). Bupropion has a lower risk of inducing manic shift when compared to other antidepressants. Case reports on manic shift during unipolar depression treatment with bupropion are rare in the literature (Giasson-Gariépy and Jutras-Aswad 2013). Bupropion is reported to be the preferred treatment in bipolar depression for its lower hypomania / mania shift risk (Post et al. 2006).

Two cases with manic shift during treatment with bupropion are presented below.

CASE 1

K.E., a 43-year old primary school graduate housewife, had been for 6 years under treatment with lithium (1200 mg/day- blood level 0.50 mmol/L) and quetiapine XR (800 mg/day) for bipolar disorder diagnosis. She was admitted to the psychiatric clinic of Trakya University Medical Faculty for a month for a depressive episode. Her score was 23 on the Hamilton Depression Rating Scale (HAM-D). Her treatment was reorganised as lithium (1200 mg/day), quetiapine XR (800 mg/day) and bupropion XL (300 mg/day). Although discharged in complete remission, she was readmitted to the psychiatry clinic 3 months later with symptoms of decreased need for sleep, increased physical mobility, with varying thought contents and increased and continual speech especially about her childhood. She had complied with her recommended medication, maintaining a serum lithium level of 0.88 mmol/L. In her psychiatric examination, her orientation was normal, involuntary attention, amount of speech, and

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speed of speech were increased. Her mood was euphoric and grandiose ideas were present in her thought content. Perception examination was normal. The thought flow was accelerated and the associations were disorganized. Her psychomotor activity had increased, and her need for sleep had decreased. Her Young Mania Rating Scale (YMRS) score was 19. She was diagnosed with manic shift due to bupropion therapy which was stopped while continuing with lithium and her other antipsychotic drugs at the previous doses.

There was no history of mental disorder in her family. It was learnt that her first complaints started after pregnancy at the age of 21 and that she had received treatment for postpartum depression. She had been admitted to psychiatry clinics for 5 depressive and 2 manic periods since 2008. She had a history of manic shift after treatment with sertraline (50 mg/day) for BD depressive episode in April 2013. She had not been under drug treatment for any other disease after her last discharge from hospital.

It was decided that there was no need for hospitalization and the patient was followed as outpatient. After stopping bupropion treatment, the manic symptoms regressed in two weeks and disappeared totally at the end of the first month. Her functionality improved totally. The patient is still euthymic.

CASE 2

O.D., a 26-year old high school graduate bachelor male worker, had been diagnosed with BD 8 years previously. He hed been admitted to the psychiatric clinic of Trakya University Medical Faculty two times for psycothic mania episodes. He also had a history of two depressive attacks that were managed on an outpatient basis. Bupropion XL (150 mg/day) was added to lithium (1500 mg/day- serum level 0.69 mmol/L) and valproate (1500 mg/day- serum level 49.1 ug/ml) for his second depressive episode. He was brought to the emergency reception 1.5 months after starting bupropion treatment, with complaints of hearing various sounds, decreased sleep, and increased religious preoccupation, increased self-confidence and increased tendency to spend money.

In his psychiatric examination, his orientation was normal, involuntary attention, amount of speech, and speed of speech were increased. His mood was euphoric, grandiose and mystical ideas were present in his thought content. Perception examination was normal. The thought flow was accelerated, idea flights were present and he had pressurised speech. His psychomotor activity was increased and his need for sleep had decreased. He did not have a history of any known disease and was not on any drugs other than his psychiatric medication. There was not a history of mental disorder in his family.

He was admitted to the clinic as an inpatient with the diagnosis of BD psychotic manic episode. His score on the YMRS was 34 and was attributed to manic shift due to bupropion therapy. Bupropion treatment was discontinued and olanzapine (20 mg/day) was added to the existing therapy with lithium and valproate. After two weeks, the symptoms improved and the olanzapine dose was reduced to 15 mg/day. As psychotic manic episode improved clinically, he was discharged after 4 weeks of hospitalization with olanzapine (10 mg/day), lithium (1200 mg/day) and valproate (1500 mg/day). The patient came to the outpatient clinic regularly after his discharge. Olanzapine treatment was stopped and lithium and valproate treatment was continued. The patient is still euthymic.

DISCUSSION

Use of antidepressants in BD is a potential risk for manic shift. A family history of BD, of manic shift caused by antidepressant thearpy and the use of multiple antidepressants have been shown to be associated with an increased risk of manic shift (Goldberg and Truman 2003). The first patient discussed here had a history of manic shift due to sertraline treatment. She had increased risk of manic shift with antidepressant use because of her previous manic shift episode history. Therefore, treatment with bupropion was preferred as an antidepressant with a low risk of shift.

Among the first-line therapies for the treatment of BD is the addition of an antidepressant with a relatively low risk of manic shift when combined with mood stabilizers (Vahıp and Aydemır 2010). In the meta-analysis of Peet et al. (1994), the use of tricyclic antidepressants in bipolar patients resulted in a higher risk of manic shift when compared to selective serotonin reuptake inhibitors (SSRIs). In a study comparing venlafaxine, sertraline and bupropion in the treatment of bipolar depression, venlafaxine was found to have a higher risk and bupropion was found to have a lowerrisk in terms of manic/hypomanic shift (Leverich et al. 2006). In a study involving bipolar depressive patients, the risk of hypomania or mania was found to be higher after venlafaxine as compared to bupropion and sertraline. While clinicians select antidepressants for treating bipolar depression, venlafaxine should be taken into account for its relatively higher risk of manic shift (Post et al. 2006). Post et al. (2001) observed in their study a 14% incidence of manic / hypomanic shift during acute treatment with bupropion, sertraline and venlafaxine. Bupropion was suggested to trigger mood shifts in bipolar depression less frequently than other antidepressants, and in both cases it was regarded appropriate to add bupropion to mood stabilizer treatment as antidepressant.

It should be especially remembered that in such cases as discussed here the differential diagnoses of drug-induced manic and the manic/hypomanic episodes withing the

natural course of BD can be difficult. Manic/hypomanic shift due to antidepressant medication has been reported to be higher in the first weeks of treatment (Wada et al. 2006). Initiaton of the symptoms was approximately 3 months after the addition of bupropion in our first patient and 1.5 months in our second patient. Both of these patients had regular outpatient follow-up. Their social support and compliance with drug treatment were good, and the blood levels of mood stabilizing drugs were in the protective range. The first patient was followed at the outpatient clinic and bupropion was discontinued. The second patient was hospitalised; bupropion was discontinued and an antipsychotic drug was started. In the first patient, a short time was needed for recovery without additional medication. When the previous manic episodes of the first patient were analyzed, it was found that the patient had psychotic features. Unlike in the reported current manic episode, she had stayed in hospital for a long term when antipsychotic drugs were used. Similarly, the second patient showed a rapid improvement in manic symptoms after stopping bupropion. The previous manic episodes of the second patient also had psychotic features, and only after prolonged inpatient treatment was he in remission with dual mood regulator therapy. These situations suggest that the manic symptoms seen in both cases discussed here were not spontaneous manic episodes.

There are differing results in the studies evaluating the manic/hypomanic shift risk of antidepressant treatment combined with mood stabilizers as compared to antidepressant use alone in bipolar depression. It was observed that lithium use along with antidepressant treatment was effective in decreasing manic or hypomanic shift, while adding valproate to treatment had not made any difference (Henry et al. 2001). In another study, it was found that the combination of lithium or valproate treatment had not made a significant difference in antidepressant treatment for manic or hypomanic shift risk (Goldberg and Whiteside 2002). In a review by Bottlender et al. (2001), it was reported that when tricyclic antidepressants were added to the treatment of depressive BD patients on valproate or lithium, the risk of manic or hypomanic shift was reduced as compared to the absence of mood stabilizer. However, in patients using other antidepressant classes, such as SSRI or MAO inhibitors, it was observed that the presence of the mood stabilizer in the treatment did not make a significant difference in manic shift risk. It has been shown that the risk of shifting to mania or hypomania did not increase in patients when bupropion was added for the depressive episode while they were under mood stabilizer treatment (Sachs et al. 2007, Salvi et al. 2008). Long-term antidepressant treatment has been reported to reduce the development of new depressive episodes without a significant increase in the risk of manic/hypomanic shifts, especially in BD-II patients. In antidepressant monotherapy, increased risk of affective shift compared to mood regulator monotherapy was associated with the protective effect of mood stabilizer in reducing manic/hypomanic episodes (Liu et al. 2017). However, in both cases, manic shifts were observed after the addition of bupropion to the treatment while the blood levels were in the protective range and when the patients were under protective treatment.

There is not a definite explanation of the neurobiology of the shift phenomenon. Many factors like neurobiological problems, sleep deprivation and drugs, seem to be associated with mood shifts. Abnormalities in catecholamine level, hypothalamic pituitary adrenal axis hyperactivity, circadian rhythm disorders are among the major factors. Sleep deprivation, corticosteroids and dopaminergic drugs can induce mood shifts in BD (Salvadore et al. 2010).

Mania caused by bupropion therapy have been reported in the literature. Several cases started with with bupropion for unipolar depression resulting in hypomanic / manic shifts have been reported (Hussain and Butt 2008, Bittman and Young 1991, Masand and Stern 1993). There are also clinical studies reporting manic shift during bupropion treatment in bipolar depression treatment (Fogelson et al. 1992, Erfurth et al. 2002, Sachs et al. 2000). In a study by Fogelson et al. (1992), 6 of 11 patients had manic / hypomanic shifts necessitating discontinuation of bupropion treatment. These results were interpreted as bupropion therapy having the same risk of accelerating manic shifts as other antidepressants in depressive bipolar patients. There are some data suggesting that the relatively low risk of shifts after bupropion as compared to other antidepressants is related to not exceeding the recommended daily maximum dose (Goren and Levin 2000). However, in both of our patients manic shift occurred despite the daily dose of bupropion being below the maximal dose. In the first reported case, the shift was observed when using 300 mg/day bupropion, while in the second case a psychotic manic shift was observed with a dose of 150 mg/day.

In a recent meta-analysis, in contrast to previous data in the literature, the risk of manic / hypomanic shift was found not to be not relatively lower in bupropion use as compared to other antidepressants. It was emphasized in conclusion that despite the current clinical practice guidelines of treatment of BD, the risk of possible phase shift in prescribing bupropion should be kept in mind by the clinicians (Li et al. 2016). These two cases have been presented in order to draw attention to the rare but important risk of manic shift when bupropion is preferred for bipolar depression treatment. Given the possible risk of manic/hypomanic shift, importance of frequent clinical follow-up is emphasized when choosing antidepressants for patients with bipolar depressive episodes, even if the risk is said to be low.

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