Olanzapine-Induced Mania in Bipolar Spectrum Disorder: A Case Report

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Objective: To report the case of a 46-year old male with major depressive disorder, who represented manic symptoms, when olanzapine was added to his treatment.
Method: A 46-year old female, with a diagnosis of treatment resistant depression was referred to the authors. He had past history of depression for more than 20 years. The symptoms were present nearly every day since 1981, without any distinct period of remission, nor any noticeable fluctuation. His irritability had been disruptive to his family all these years. His doctor had prescribed maprotiline 25 mg/day, and lorazepam, 2mg/day, in addition to fluoxetine for the last 5 months. He is also a father of two children with methylphenidate-resistant and sodium valproate-responsive attention-deficit hyperactivity disorder. Considering the antidepressant effects of olanzapine and its positive effects on irritability, the authors added olanzapine, to the patient's previous medications.
Results: After one week, he showed new problems such as talkativeness and beginning to smoke for the first time in his life, elevated mood, grandiosity about his intelligence and abilities, talkativeness, and shopping sprees. The score on the mania rating scale was 14. Fluoxetine was discontinued and sodium valproate, were prescribed. It took around 2 months to completely control the manic symptoms.
Conclusions: In the patients with depression who show bipolar spectrum disorder features, adding mood stabilizers may be preferred to the drugs as olanzapine which could induce mania.
Key words:
Attention deficit disorder with hyperactivity, Bipolar disorder, olanzapine,Depression

Iran J Psychiatry 2006; 1: 128-130

Paradoxical effects of psychiatric medications have been a subject of debate, one of which is the effect of atypical antipsychotics on manic episodes. Efficacy of olanzapine, an atypical antipsychotic, in acute mania has been established based on various clinical trials(1, 2). However, affective side effects of different antipsychotics have been reported.
Typical antipsychotics can cause switching to depression in bipolar patients (3). On the other hand, there are several reports of atypical antipsychotic-induced mania. Also, in recent years, there have been at least 11 case reports of mania following the administration of olanzapine, most of which were in patients with a primary psychotic disorder (4, 5). However, many of these accounts lack precision of information on the use of other psychotropic medications shortly before olanzapine was administered, and the use of concomitant medications, which renders the conclusions on a causal relationship between olanzapine administration and start of mania doubtful (6, 7). Yet, some reports are highly suggestive of such causal association (8, 9).

Rachid et al. (1), in a recent review of literature on atypical antipsychotic- induced mania, between January 1999 to December 2003, found five cases of olanzapine-induced mania: two patients with schizophrenia, one with delusional disorder, one with bipolar I disorder (BID), and one with recurrent major depressive disorder (MDD). The MDD case in this review, was similar to Fahy and Fahy's observation (6). However, with reference to the latter article, we found a manic episode in the patient's history that indicated to a diagnosis of BID To the best of our knowledge, this paper is the first report of acute mania after administration of olanzapine in a patient with chronic and treatment-resistant MDD. Also, as there were some clues of a bipolar spectrum disorder in our patient, it warrants a discussion of the clinical implications (10).

Case report

The patient was a 46-year-old married man who had been referred to the authors for evaluation and treatment of depressive symptoms in December 2004. He stated that he had been depressed as long as he could

remember. The depression had exacerbated in 1981 after experiencing a major life event. Since then, he had had depressed mood, irritability, loss of interest, early insomnia and broken sleep, low body energy and fatigue, poor concentration, low sexual desire and excessive thoughts of death. He did not report hypersomnia, psychomotor retardation, prominent anxiety and obsession during this period. According to the patient and his wife, the symptoms were present nearly every day since 1981, without any distinct period of remission, nor any noticeable fluctuation. His irritability had been disruptive to his family all these years. He had referred to a psychiatrist irregularly for four years, and had taken fluoxetine 20 to 60 mg/day. His doctor had prescribed maprotiline 25 mg/day, and lorazepam 2mg/day, in addition to fluoxetine for the last 5 months. The patient's compliance was good and the drugs had caused a little improvement of the symptoms.

The patient was the fourth of 7 siblings. In the family, only his mother had suffered from a mood disorder (diagnosed as MDD) for which she took tricyclic antidepressants until her death. Although she had never experienced a distinct episode of (hypo)mania, the patient remembered that his mother had very short episodes of elation and sudden mood changes. There was no available valid information on the second and third degree family members.

The patient was married for 20 years and had two sons, 18 and 15 years old. Both sons had had irritability, hyperactivity and poor concentration since early childhood and were on methylphenidate for a diagnosis of attention-deficit hyperactivity disorder (ADHD) made by the authors. Children had benefited from methylphenidate in regard with symptoms of poor concentration and hyperactivity, but there was no improvement in their irritable mood. Subsequently, we augmented methylphenidate with sodium valproate, which resulted in significant improvement of their irritability.

The patient's physical examination and laboratory tests, including thyroid function tests, were normal.

Olanzapine Trial

Considering the antidepressant effects of olanzapine and its positive effects on irritability, the authors added olanzapine 1.25mg/day, to the patient's previous medications and increased it gradually up to 5mg/day. After one week, his wife called the clinic complaining of her husband's new problems such as talkativeness and beginning to smoke for the first time in his life. When the patient was visited, he had elevated mood, grandiosity about his intelligence and abilities, talkativeness, and shopping sprees. The score on the Mania Rating Scale was 14 (11). Fluoxetine was discontinued and sodium valproate 600 mg/day, olanzapine 5 mg/day, and lorazepam 2 mg/day, were prescribed. It took around 2 months to completely control the manic symptoms. After the acute symptoms of mania subsided, olanzapine and lorazepam were tapered and the treatment with sodium valproate was continued. The patient was followed for 10 months and there was no relapse during this period.

Discussion

As alluded to above, the patient was a case of MDD and had a major depressive episode as long as at least two years so that we can say there was *chronic* specifier according to the Fourth Edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (12). Because his depressive symptoms did not respond to the long-term administration of fluoxetine and the combination of fluoxetine and maprotiline, we could assume it as treatment-resistant depression (TRD)—a diagnostic indicator of bipolar spectrum disorder (BSD) (13, 14).

Recently the possibility of a relationship between ADHD and bipolar disorder has attracted growing interest (15). This patient has two children with methylphenidate-resistant ADHD and both of which had a favorable therapeutic response to sodium valproate, which is also an effective treatment for manic episodes (16). This familial aggregation associated with favorable therapeutic response to a mood stabilizer in the offsprings of the index patient can hint the probability of a familial predisposition for bipolar disorder. Thus, the presented patient could have had some bipolar spectrum features before the manic episode: TRD and probable bipolar diagnosis for both his children.

In prior reports of olanzapine-induced mania, the patients had received different doses of olanzapine, from 2.5 to 10 mg/day, before the development of mania (1). In the present study the dose of olanzapine was 5 mg/day. It has already been suggested that atypical antipsychotics induce obsessive-compulsive symptoms via 5-HT_{2a} antagonism, and that the obsessive-compulsive symptoms are related to low drug doses and would remit by increasing the dose (17). However, no such dose related pattern can be concluded for the manic symptoms. Therefore, more studies are needed to explore the mechanism for olanzapine (and other atypical antipsychotics), which probably is different from the mechanism of antidepressant-induced mania. It should be noted that long-term administration of a specific serotonergic drug (fluoxetine) and even inclusion of a relatively specific noradrenergic drug (maprotiline) did not probably result in switching to mania in this patient, but adding low dose olanzapine caused a full-blown manic episode in a short period. In this regard, future investigations will create new views about pathophysiology of mania.

Regarding the existence of bipolar spectrum features and given that there were some indicators of bipolar susceptibility and the probability of switching to mania before the introduction of olanzapine in this patient, it is advisable that adding mood stabilizers such as lithium would be preferred to the drugs as olanzapine which could induce mania.

Acknowledgement
The authors thank Nahaleh Moshtagh PhD and Negar Sharif PhD for editing the article.

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