

Mania Associated with Quetiapine Treatment



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SUMMARY

Presently, the use of atypical antipsychotics is getting increasingly widespread. There are several mania/hypomania cases that have been associated with atypical antipsychotic treatment that also display antimanic, antidepressive and anxiolytic effects in addition to their antipsychotic effects. In this study, a case of schizophrenia in which manic symptoms developed after increasing the dosage of quetiapine to 300mg/day, and subsequently disappeared after cessation of treatment is presented. Although the blockage of 5HT₂ receptors and the disinhibition of frontal dopamine secretion seemed to be the reasons for the development of the mania/hypomania related to atypical antipsychotics, the mechanism is not clear. During the use of atypical antipsychotics, clinicians should be cautious to patients' mood fluctuations.

Key words: mania, schizophrenia, quetiapine

INTRODUCTION

The use of atypical antipsychotics in treatment of psychiatric diseases is getting more widespread every day. These drugs are called atypical because they provide improvement not only in the positive symptoms, but also in negative symptoms. Also, they have less adverse effects on the extrapyramidal system and tardive dyskinesia, and they do not cause hyperprolactinemia (Stahl 2008). All atypical antipsychotics have higher serotonin type 2 (5HT₂) receptor / dopamine type 2 (D₂) receptor antagonism rates compared to typical antipsychotics and they are more specific for the mesolimbic system than the striatal dopamine system (Sadock and Sadock 2007). Atypical antipsychotics are indicated for additional or single treatment during the manic period of bipolar disorder, particularly in cases of schizophrenia, as mood regulators, for supplementing antidepressant treatment in cases of both psychotic and non-psychotic depression and for treatment of depressive

symptoms in the case of psychosis (Rachid et al 2004, Vieta and Goikolea 2005, Nelson and Papakostas 2009). Quetiapine is a dibenzodiazepine, which has a structure resembling clozapine and quickly separates from the D₂ receptors. They are also indicated for persistent depression and anxiety disorders as mood regulators during the manic period of bipolar disorder, the depressive period of bipolar disorder, and bipolar disorders in addition to psychotic disorders (Post and Calabrese 2004, Vieta and Goikolea 2005, Gao et al. 2006, Nelson and Papakostas 2009). The anti-depressive effects of antipsychotic agents beg the question, “do they cause a manic switch?” There are several cases associated with manic/hypomanic switch due to antipsychotics in the literature. However, it was recently suggested that antipsychotics have mood regulating effects and this makes the issue more complex. In this article, a schizophrenic patient with manic symptoms after the administration of quetiapine was discussed in light of the literature.

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CASE

The initial complaints of the 41 year old male patient, who was an unemployed high-school graduate, included seeing images, hearing voices, highly religious activities, and the feeling of being dominated by a power. The patient was hospitalized many times in the past with a diagnosis of paranoid type schizophrenia according to DSM-IV-TR (American Psychiatric Association 2005). The patient, who was unable to study in university or perform his military service, was receiving clozapine 100mg/day and chlorpromazine 400mg/day. We learned that he received electroconvulsive therapy (ECT) in the past. He had coronary artery disease and a smoking history of 3 packs/day/20 years. He received ramipril, metoprolol and acetylsalicylic acid treatment for a long period of time due to his coronary artery disease. He did not use alcohol or any other substance. He had no family history of psychiatric disease. Complete blood assay, hepatic and renal function tests, and thyroid function tests were within normal limits. He applied to the outpatient clinic to receive his usual prescription. In his mood examination he was conscious, cooperative and oriented. A limited affection was observed, reception hallucinations and aural hallucinations existed, and sleeping and appetite were normal. No suicide attempts or thoughts existed. His social and occupational functionality was poor. Internal consultation was requested due to coronary artery disease. It was recommended to the patient with a history of coronary artery disease that chlorpromazine treatment will be discontinued since it poses a risk of lengthening QT distance and causing tachycardia and orthostatic hypotension (Sadock and Sadock 2007). Chlorpromazine treatment was decreased gradually within two weeks and discontinued on September 10th, 2010. Meanwhile, severity of the reception hallucinations increased. No clozapine increase was planned in the patient since clozapine can increase the risk of metabolic syndrome. Quetiapine 100 mg/day was added to his treatment on September 14th, 2010 and the quetiapine dose was gradually titrated to 300 mg/day. While the patient did not have a manic finding until this date, upon titrating the dose of quetiapine to 300 mg/day, a euphoric mood, grandiosity, increased self care, increased spending, decreased need for sleeping, increased sexual desire, increased mobility, and an increase in speaking, which corresponded to the measures of the manic period according to DSM-IV-TR, were observed within one week (American Psychiatric Association 2005). His Young mania rating scale (YMRS) point was recorded as 29 (Karadağ et al 2001). When the history received from the patient's relative was deepened, it was found that the use of quetiapine developed similar manic findings in the past, although the dose in the past was not known. No period of manic episodes were obtained other than the period when quetiapine was used. Manic symptoms of the patient were completely subsided on day three after discontinuation of

quetiapine treatment. His YMRS point was recorded as 4. The patient was observed for the last eighteen months and no manic finding was determined.

DISCUSSION

The cause of the manic symptoms was considered to be from the use of quetiapine in our patient. The rapid occurrence of manic symptoms within one week upon titration of quetiapine to 300 mg/day, the development of manic findings in the past due to the use of quetiapine, and the disappearance of manic findings after discontinuation of quetiapine without any other treatment support, in our opinion, suggested that the manic symptoms were associated with quetiapine. An alternative conclusion could be that the discontinuation of chlorpromazine caused the manic symptoms. However, there are no cases of mania triggered by discontinuation of chlorpromazine in the literature. In addition, these symptoms also occurred in the past after the addition of quetiapine to the chlorpromazine treatment of the patient and this supports the idea that the mania was associated with quetiapine treatment. The patient received clozapine 100 mg/day regularly for the past ten years without any titration. These findings led us to think that the manic symptoms were not associated with clozapine. There is no case of mania associated with clozapine in the literature. In addition, the patient received the same cardiac drugs for a long period of time and there was no recent change in his drugs and/or their doses. There are no cases of mania associated with metoprolol, ramipril and acetylsalicylic acid in the literature. No pharmacokinetic and pharmacodynamic interaction that may cause changes in drug levels were observed among the drugs used by the patient. Therefore, we believe that the manic symptoms were associated with quetiapine. Administering quetiapine again was not attempted considering that it may have triggered a new manic attack. Aubry et al (2000) suggests the use of a guide with 8 items to assess events associated with the drugs. When assessed according to the guide, including the symptoms and diagnosis before administration, diagnostic assessment during adverse event, time to administration, dose, drugs used until administration of suspicious treatment, concomitant drugs, result and the re-administered agents, it may be concluded that quetiapine is significantly associated with the mania findings in this case.

The literature reports mania/hypomania cases associated with atypical antipsychotics, which are also reported as having anti-manic, antidepressant, and anxiolytic effects in addition to its antipsychotic effects. Aubry et al (2000) reported the development of manic/hypomanic symptoms in sixteen cases associated with the use of risperidone and ten cases associated with the use of olanzapine between 1966-1999. Rachid et al (2004) updated this review in 2003 and reported 6 new

hypomania/mania cases with risperidon, 5 new hypomania/mania cases with olanzapine, 5 new hypomania/mania cases with quetiapine, 11 new hypomania/mania cases with ziprasidone, 6 new hypomania/mania cases with flupentixol and one new hypomania/mania case with amisulpride between 1999 and 2003. Finally, in 2006, Michalopoulou and Lykouras (2006) reported manic/hypomanic switches associated with atypical antipsychotics in a total of 53 cases, including 22 cases with risperidon, 14 cases with olanzapin, 5 cases with quetiapine, 11 cases with ziprasidon and one case with amisulpride, between 1994 and 2005. The literature review was updated using the terms antipsychotics, mania, hypomania and 3 new manic switch cases with quetiapine were found between 2005 and 2011 (Erberk-Ozen N 2008, Nicolato et al 2009). In addition, mania/hypomania cases triggered with aripiprazole and paliperidone were reported (Donohue A 2010, Hsieh and Liou 2010). However, no mania/hypomania case was found associated with clozapine and sertindole, even though they have significant antidepressant effects and they resemble quetiapine and typical antipsychotics other than flupentixol, which is considered as partially atypical in the literature and has antidepressant effects (Aubry et al 2000).

It is reported that 54% of the cases of mania associated with the use of atypical antipsychotics were diagnosed as schizophrenia (Michalopoulou and Lykouras 2006). Various demographic and clinical parameters, such as sex, age, schizophrenia subtype, and duration of disease, which may be risk factors for schizophrenia patients with secondary mania/hypomania associated with antipsychotics were studied but no significant risk factor could be determined (Aubry et al 2000, Rachid et al 2004). Five of eight mania/hypomania cases triggered with quetiapine were diagnosed with schizophrenia, as in our case. It was seen that the manic/hypomanic symptoms associated with quetiapine started from two days to three weeks and the dose of quetiapine used changed between 100 mg and 600mg. Our case also began quetiapine at a dose of 100 mg/day and this dose was titrated to 300mg/day in two weeks and the manic symptoms occurred within one week after titration to 300 mg. In the literature, for the treatment of mania/hypomania cases triggered by quetiapine, the dose of quetiapine was decreased, stopped, and another antipsychotic, benzodiazepine, and mood regulator were added and the mania/hypomania symptoms disappeared within one to ten days (Rachid et al 2004). In our case, the manic symptoms disappeared upon discontinuation of quetiapine treatment without the need for an additional treatment. This supports the idea that mania is caused by the use of quetiapine rather than the discontinuation of the use of chlorpromazine.

The basic mechanism suggested for manic/hypomanic switch associated with atypical antipsychotics is that risperidon and olanzapine block receptors 5HT_{2A}, but not low doses of D₂ receptors, and this prevents an increase in the release of

frontal dopamine and manic symptoms. Quetiapine has a low rate of 5HT_{2A}/D₂ binding rate, but its affinity for receptors 5HT_{2A} are higher compared to D₂ receptors at lower doses and it is considered to play a role in the development of mania/hypomania. At higher doses, the dopaminergic blockade effect may eliminate suppression of dopamine. However, medium and high doses rather than lower doses were used in the cases reported in the literature and this suggests that other mechanisms than antagonism of receptor 5HT_{2A} may play a role in the development of mania/hypomania associated with antipsychotics. It was shown that quetiapine could not rise to the sufficient concentrations in the plasma to increase the level of norepinephrine in healthy individuals, although it has an affinity for norepinephrine reuptake transport (Jensen et al 2008, Nelson and Papakostas 2009, Çetin M 2010). Ziprasidone that is reported to cause manic/hypomanic switch at a significantly high rate has a high affinity for the 5HT_{2A} and 5HT_{2A}/D₂ binding rate. High agonist affinity for 5HT_{1A} may be responsible for noradrenergic and serotonergic reuptake inhibiting antidepressant effects and therefore for manic/hypomanic switch. Also, amisulpride, which does not have an affinity for 5HT_{2A}, increases dopamine transfer into the prefrontal cortex through presynaptic D₂ and D₃ autoreceptor activity, causes antidepressant effects and causes the development of mania. In mania/hypomania cases triggered with aripiprazole, it was suggested that an increase in the release of frontal dopamine through partial agonism of receptors D₂ and 5HT₁ may be responsible for this effect (Rachid et al 2004, Donohue 2010).

Recently, publications suggest that quetiapine is effective in the maintenance of treatment of bipolar disorders alone or combined with conventional mood regulators. Even if the mechanism of action of quetiapine is in the maintenance treatment of bipolar disorders, it is suggested that this action is achieved over glutamate receptors. Most of the mania cases triggered by quetiapine and antipsychotics occur in schizophrenia patients already considered to be hypoglutamatergic and this is an interesting area that should be studied (Mundo et al 2006).

Nowadays the use of atypical antipsychotics is getting more widespread day by day. The literature reports a few mania/hypomania cases associated with atypical antipsychotic treatment, which is also reported as having anti-manic, antidepressant, and anxiolytic effects in addition to its antipsychotic effects. During atypical antipsychotic use, attention should be paid to mood fluctuations of patients. Scanning depression or hypomania/mania in patients diagnosed as schizophrenic with standard measures on a daily basis may prevent ruling out depression or mania/hypomania manifestations below the threshold. Further studies are needed to elucidate the mechanism of manic/hypomanic switch associated with atypical antipsychotics.

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