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CASE REPORT
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Olanzapine-Induced Mania: A Case Report with New Characteristics

Mehdi Aghamohammadi[1], Mahsa Ghasemi[2*]

[1]*Department of Internal Medicine, School of Medicine, Vali-e-Asr Hospital, Zanjan University of Medical Sciences, Zanjan, Iran.*
[2]*Department of Psychiatry, School of Medicine, Shahid Beheshti Hospital, Zanjan University of Medical Sciences, Zanjan, Iran.*

Abstract

Abstract olanzapine is an atypical antipsychotic widely used for the treatment of mania as monotherapy. In this case, it paradoxically caused mania symptoms in a 40-year-old patient with intermittent explosive disorder. This case presents different characteristics from previous reports, suggesting a direct link between olanzapine and mania symptoms. The patient did not have any psychotic or mood disorder, and the symptoms rapidly disappeared during a medication-free period. Furthermore, there was no discontinuation of other medications, no prominent family history of psychiatric disorder, and no addiction to substances, all of which suggest a connection between manic symptoms and olanzapine. Possible receptor and genomic explanations for this phenomenon are also discussed.

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***Correspondence:**
Mahsa Ghasemi
Mahsa.qasemi@yahoo.com
Department of Psychiatry, School of Medicine, Shahid Beheshti Hospital, Zanjan University of Medical Sciences, Zanjan, Iran.

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Introduction

Atypical antipsychotics have been long used in the treatment of mania, with robust evidence gathered over years of research and clinical experiences. In contrast, there are case reports of olanzapine-induced mania in patients with affective disorders such as bipolar mood disorder, atypical depression, unipolar depression, or schizophrenia.[1] The case described here is unique in that the patient did not have a history of mood or psychotic illness, nor had he been prescribed any psychotropic medication before exhibiting mania symptoms.

It can be inferred that the development of mania could be a natural course of the underlying affective or psychotic disorders, or it could result from the withdrawal of a previous antipsychotic or mood stabilizer medication. These two reasons have always been an open question, raising the possibility of a potential risk between olanzapine and mania.

The following report contains a description of a patient who was free from any mood or psychotic illness and had not been prescribed any psychotropic medication for at least ten years. The patient exhibited mania symptoms after initiating olanzapine. This case is, therefore, distinctive and unprecedented in its nature.

Description of case

A 40-year-old man presented to a psychiatry clinic with irritability and verbal aggression.

He has had impulsive verbal fights and arguments since his teenage years, which were out of proportion to the provocation. The aggression lasted for about 30 minutes. These symptoms caused impairment in interpersonal functioning with his parents and later with his wife. He was diagnosed with intermittent explosive disorder based on DSM-5 criteria through clinical interviews with him, his wife, and his parents.

It was his first psychiatry visit, prompted by a conflict with his wife, who desires a divorce. He sought help to address his aggression and find a resolution.

Other diagnoses, such as bipolar mood disorder, depression disorder, atypical depression, antisocial, and borderline personality disorder, were ruled out. He had been a tramadol abuser for about ten years, between 20 to 30 years old. He also complained of decreased appetite, difficulty maintaining sleep, and frequent awakenings. His BMI was 19. Olanzapine 2.5 mg daily was prescribed to address symptoms of sleep disturbance and weight issues, as well as to manage aggression.

Two days after initiating olanzapine, the patient exhibited symptoms such as talkativeness, displaying sexually inappropriate behaviors in public, inflated self-esteem, increased goal-directed activity, and impulsive spending without any signs of psychosis. Two weeks later, he was brought to the clinic by his wife, and olanzapine was discontinued. There was no alcohol or herbal medication use, and urine toxicology was negative for illegal substances. All other investigations, such as TSH, were normal. There was no prominent family history of psychiatric disorders, and the patient was not admitted to the hospital. He was prescribed valproate sodium 200 mg twice a day but refused to take the medication due to a negative experience with olanzapine. After seven days, some symptoms, such as disinhibition and overactivity, disappeared, and talkativeness and mood swings subsided. After two weeks, he had no symptoms of mania and eventually agreed to start valproate for his chronic aggression. In a follow-up appointment after one month, he continued to be well-controlled on valproate. In the most recent visit after two months, he remained stable.

Discussion

There is a continued concern with AA-induced mania or hypomania.

The most recent review in 2023 investigates whether there is a risk for manic to be triggered by AA treatment in mood disorders[2] showed that AA protects against the development of TEM (treatment-emergent mania). However, the review only included patients who had a previous history of mood disorders, whereas our patients did not have any history of mood disorders or a family history of such disorders.

One of the recent reviews only included clinical studies and case reports published between 2004 and 2010, with all of the studies including patients suffering from schizophrenia spectrum disorders or, bipolar disorder or atypical depression.[1] Once again, our case report stands out as the patient did not have any history of psychotic or mood disorders.

In Michalopoulou's 2006 study,[3] out of individuals receiving olanzapine treatment, six were identified with schizophrenia, three with schizoaffective disorder (one of whom had the bipolar type), one with bipolar disorder I, and one with recurrent major depressive disorder. The remaining three patients were diagnosed with delusional disorder (paranoid type), psychotic disorder NOS, and pervasive developmental disorder with mood instability and aggressive behavior, respectively.

In this review, all the patients experienced mood or psychotic disorders except the last one, who had autism spectrum disorder and aggression. Aggression behavior is like in our case. This 16-year-old case had previous risperidone treatment. The symptoms of mania could potentially be explained by discontinuing risperidone. It is possible that the abrupt discontinuation of risperidone may have led to a rebound effect, resulting in the emergence of manic symptoms.[4]

The key pharmacological feature of atypical antipsychotic medications is their stronger activity as antagonists of the 5-HT2A serotonin receptors compared to the D2 dopamine receptors. Lane and colleagues have proposed that risperidone-induced mania may be linked to the dosage administered. Lower doses could block 5-HT2A receptors without affecting D2 receptors. Blocking 5-HT2A receptors

might then trigger increased frontal dopamine release, potentially leading to the onset of manic episodes. It would be valuable to investigate if a comparable mechanism plays a role in the effects of olanzapine.[5] At low doses of an atypical antipsychotic, there is a higher level of 5-HT2 activity compared to D2 activity in terms of receptor occupancy ratio.[6,7]

A new theory suggests that atypical antipsychotics trigger frontal dopamine release through a combined blockade of 5-HT2A and D2 receptors, enhancing the impact of 5-HT1A receptor stimulation on dopamine release in the frontal region. Therefore, the functioning of the serotonin system plays a crucial role in how these medications affect frontal dopamine release.[8,9]

At lower doses, risperidone is linked to increased 5HT-2A receptor occupancy, which can lead to heightened forebrain dopaminergic activity by removing inhibition from the dopaminergic system, affecting mood. On the other hand, at higher doses, the saturation of 5HT-2A receptors and the rise in D2 occupancy work against this effect of heightened 5HT-2A activity.[7]

Chantal Henry's case report in 2002,[10] olanzapine's effects may vary depending on the levels of natural neurotransmitter release. Changes in neurotransmitter release could influence how a partial agonist behaves, acting as an agonist when neurotransmitter release is low and as an antagonist when release is high. During manic episodes, the balance between dopamine and serotonin activity may be disrupted, leading to altered occupancy of 5-HT2A and D2 receptors. This could result in differences in the effects of mixed drugs, as suggested by Lane *et al*. The combined blockade of 5HT-2A and D2 receptors by second-generation antipsychotics may increase dopamine release in the prefrontal cortex, potentially through 5HT-1A receptor activation, regardless of the drug's intrinsic 5HT-1A affinity.[8]

Some argue that mania is part of the natural course of underlying affective or psychotic disorder. In two of the cases in Michalopoulou's review,[3] the discontinuation of olanzapine alone was efficient in controlling the manic/hypomanic symptoms. In three cases, three different types of medications were included to manage manic symptoms: Haloperidol, chlorpromazine, valproate, and benzodiazepines. In our case, after discontinuing olanzapine, mania symptoms subsided and there was no need for other medication. So, it can be concluded that it was not related to the natural course of a new onset or previous underlying illness.

A complicating factor in linking the reported mood elevation to atypical antipsychotics is the concurrent use of other medications that could contribute to inducing mania or hypomania.[1]

Comedication was in almost the majority of previous cases. But our case did not have any comedication to questionable the link between olanzapine and its induction mania.

The discontinuation of the mood stabilizer before the prescription of risperidone could have resulted in the induction of manic symptomatology. Stopping lithium treatment is linked to a significant risk of manic relapse in patients with bipolar disorder and schizoaffective disorder.[11] which has occurred in some cases of previous literature. Despite our case, who did not use any medication.

Michalopoulou proposed that the rapid remission of the manic/hypomanic symptoms that were observed in three risperidone-treated cases, in one olanzapine and in one ziprasidone after discontinuation of the atypical APs, could indicate that these symptoms are directly influenced by the medications.[3]

It is essential to underscore that underlying mood instability in intermittent explosive disorder could be considered a susceptibility to presenting manic symptoms. This highlights the complexity of the individual's clinical presentation.

It is interesting to note that the impact of several genetic factors on the therapeutic profile of the atypical APs is being investigated. For instance, studies have shown that the impact of olanzapine on dopamine-dependent prefrontal cortical function in individuals with schizophrenia is affected by the genotype of catechol O-methyltransferase (COMT), an enzyme that metabolizes dopamine released in the prefrontal cortex.[12] More investigation is needed to determine the effect of genomes in olanzapine-induced mania.

Conclusion

Olanzapine, an atypical antipsychotic widely used for monotherapy in the treatment of mania, para-

doxically caused mania symptoms in a 40-year-old patient with intermittent explosive disorder. The patient had no history of psychotic or mood disorders, which, in similar previous cases, was better explained as a natural course of the illness. The rapid disappearance of symptoms during a medication-free period confirmed that it was the usual progression of the illness.

There was no medication discontinuation, such as mood stabilizers or other antipsychotics, which, in some former similar cases, were better explained.

Additionally, the patient does not have a prominent family history of psychiatric disorders. Although he abused tramadol, which is reported to cause mania in some case reports, for several years, he ceased using it ten years before the onset of mania symptoms. He was not addicted to any potential substances that could cause mania. We obtained a detailed collateral history of the patient through his wife, who was apparently reliable.

A connection between manic/hypomanic symptoms and atypical antipsychotic treatment seems to exist. It seems that the possible reason for this phenomenon is related to the higher potency of 5-HT2A serotonin receptor antagonists than as D2 dopamine receptor antagonists, particularly in low doses of olanzapine. At lower doses, olanzapine is linked to increased 5HT-2A receptor occupancy, potentially leading to heightened forebrain dopaminergic activity through the disinhibition of the dopaminergic system, which can impact mood. Conversely, at higher doses, the saturation of 5HT-2A receptors and the rising D2 receptor occupancy work against this effect of heightened 5HT-2A activity.

Another possible explanation is that the combined 5HT-2A and D2 receptor blockade of the SDAs increases dopamine release in the prefrontal cortex. Also, it has been shown that genetic factors have an impact on the therapeutic profile of atypical Aps., considering all aspects, it can be concluded that a connection between manic/hypomanic symptoms and atypical antipsychotic treatment seems to exist.

Alternative explanations, such as underlying mood instability and neurobiological vulnerability, can explain this presentation.

Even though he was followed up for three months, longitudinal data remains crucial for evaluating the persistence of symptoms, treatment response, and the potential recurrence of manic episodes.

From a practical point of view, clinicians should be mindful of the potential for mood-altering effects of these medications in vulnerable individuals, even if they are diagnosed with no mood or psychotic disorder. Clinicians should thoroughly consider the potential advantages of antipsychotic treatment in comparison to the likelihood of mood and behavioral side effects in individual patients. However, attributing the onset of mania to the prescription of olanzapine can be difficult to determine and establishing causality between prescribing olanzapine and induction mania is challenging and additional investigation will be needed to understand the mechanisms underlying their paradoxical effects.

Author Contributions

All the authors have contributed significantly to this article

Mehdi Aghamohammadi – First author. Conceptualization and writing of the original draft.

Mahsa Ghasemi – corresponding author. Conceptualization, supervision, editing and approval of the final version to be published.

Conflict of interest

None to declare.

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