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COMMENTARY

Are Hypomanic/Manic Episodes "Induced by" or "Associated with" Quetiapine Initiation?

Rami Bou Khalil[1,2]

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Introduction

An increasing number of case reports are concerned with hypomanic/manic symptoms induced by some atypical antipsychotic drugs, especially quetiapine [1]. In the current volume of *Drug Safety—Case Reports*, the case series published by Rovera et al. [2] demonstrates that quetiapine-related hypomania is an interesting event that is worth being appropriately diagnosed and managed in patients with bipolar disorder. Quetiapine is a second-generation dibenzothiazepine antipsychotic drug approved for the treatment of schizophrenia, major depression, bipolar disorder, bipolar depression, and mania. Several randomized, double-blind, placebo-controlled studies with quetiapine in bipolar depression included treatment-induced hypomania/mania as a secondary outcome, although the incidence of treatment-induced hypomania/mania with quetiapine at a dose of 300 or 600 mg/day seems no higher than that with placebo [3–5].

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✉ Rami Bou Khalil
ramiboukhalil@hotmail.com

[1] Hotel Dieu de France Hospital, A. Naccache Boulevard, Achrafieh, P.O. box: 166830, Beirut, Lebanon

[2] Department of Psychiatry, Saint Joseph University, Beirut, Lebanon

Possible Pharmacologic Reasons Behind Quetiapine-Related Hypomania/Mania

Quetiapine is characterized by a greater affinity to 5-hydroxytryptamine-2 (5-HT_2) receptors than with dopamine-2 (D_2) receptors [6]. At low doses (up to 300 mg/day), it shows a consistently higher degree of occupancy of 5-HT_{2A} receptors than of D_2 receptors; the degree of occupancy of both receptors is dose dependent [7]. The 5-HT_2 antagonistic action of quetiapine may disinhibit the dopaminergic system and enhance dopaminergic activity at the level of the forebrain and influences the mood state [8]. Quetiapine has relatively low D_2 antagonism, which may reflect its capacity to bind loosely to the D_2 receptor and to dissociate rapidly from it, allowing attenuated physiological dopamine transmission to continue, despite the occupancy of D_2 receptors. Quetiapine is also a partial agonist of the 5-HT_{1A} receptors. Accordingly, the enhancement of frontal dopamine release when quetiapine is first administered could be attributed, at least partly, to 5-HT_{1A} receptor activation, which is produced by simultaneous blockade of 5-HT_{2A}/D_2 receptors and the 5-HT_{1A} agonist property of quetiapine itself [9]. Another possible explanation for the manic/hypomanic induction potency of quetiapine is that patients experiencing quetiapine-induced mania/hypomania might have a polymorphism of the gene responsible for the pharmacokinetic properties of the cytochrome P450 (CYP450) enzyme. This category of patients may have little or no activity in any subgroup of this enzyme. Since quetiapine is extensively metabolized by the CYP450-3A4 isoenzyme, the hypomanic/manic symptoms related to quetiapine treatment could be explained by a deficiency in the metabolism of the drug. Accordingly, when these patients receive an antipsychotic drug with mood-stabilizing properties, they will not benefit from its effects unless

higher doses are reached [10]. Finally, as Rovera et al. [2] discuss, norquetiapine, the most important active metabolite of quetiapine, has also been implicated in this induction of hypomania/mania. In fact, norquetiapine has been shown to be associated with antidepressant and anxiolytic effects in humans through its effect on dopamine release in the prefrontal cortex as well as dopamine reuptake inhibition. Moreover, norquetiapine potentiates serotoninergic and noradrenergic transmission through its high affinity for serotoninergic receptors and through noradrenalin reuptake inhibition [2].

Is Quetiapine-Related Hypomania/Mania "Induced by" or "Associated with" Quetiapine?

According to the Naranjo algorithm, an adverse drug reaction can be considered when there are previous conclusive reports on the reaction and the adverse event has occurred after initiation of the suspected drug [11]. In the majority of case reports of hypomania/mania described in the literature, this reaction appeared shortly after quetiapine initiation but the condition improved either when the drug dosage was increased or when another mood stabilizer was added to the patient's treatment. These facts are in line with what can be considered an adverse drug reaction due to quetiapine. However, some important concerns must be addressed in future studies before confirming that these described hypomania/mania episodes are adverse drug effects directly related to quetiapine intake. First, patients must be rechallenged with quetiapine and the hypomanic/manic episode must recur. Second, the hypomanic/manic episode should not reappear when a placebo is given to the same category of patients who develop hypomanic/manic episodes after receiving quetiapine. Third, in some conditions, the drug or its active metabolite might need to be detected in body fluids in toxic concentrations or in concentrations higher than those found in individuals who did not develop the adverse drug reaction in order to consider it responsible for the reaction. Most importantly, the hypomanic/manic episode should not be explained by alternative causes [11]. In this regard, there may be several alternative explanations as to why a patient with a bipolar disorder experiences a hypomanic/manic episode after an atypical antipsychotic drug such as quetiapine is initiated.

Other Possible Reasons for Quetiapine-Related Hypomania/Mania

There may be several reasons why a patient may develop quetiapine-related hypomania/mania regardless of the pharmacologic properties of the medication. The first reason is the natural course of the disease itself. Bipolar disorder is a disease characterized by a chronic course with a high incidence of relapse. A significant proportion of patients with bipolar disorder experience a rapid cycling form of the disease (lifetime prevalence ranges between 25.8 and 43%), especially those with a long course of illness, a history of drug and alcohol misuse, and thyroid function problems [12]. Rapid cycling bipolar disorder is characterized by at least four mood episodes occurring in the same year. Another important risk factor for developing rapid cycling bipolar disorder is related to the history of antidepressant drug intake. Patients with bipolar disorder who are prescribed quetiapine for bipolar depression might be at a higher risk of developing a rapid cycling form of the disease because of a stronger tendency than other patients with bipolar disorder to have been prescribed antidepressant agents in their past. Accordingly, a few weeks after quetiapine initiation, these patients will develop a hypomanic/manic episode related to the natural course of their rapid cycling bipolar disorder rather than to an adverse drug reaction due to quetiapine administration.

The second explanation for the occurrence of hypomanic/manic episodes is related to the impact on mood stability of withdrawal from previous drugs. Since low doses of quetiapine do not have a potent antagonistic effect on dopamine receptors, the withdrawal of a high-potency dopamine antagonist and the initiation of quetiapine may stimulate dopamine receptors until a high dose of the newly prescribed antipsychotic drug is reached. From this perspective, the occurrence of a hypomanic/manic episode is regarded as a result of the switch between two antipsychotics rather than an adverse effect of quetiapine.

The third explanation can relate to an indirect effect of quetiapine on mood and cognitive functions. Quetiapine has a moderate anticholinergic effect that may affect cognitive functions and lead to delirium in at-risk individuals [13]. In addition, quetiapine may induce hypothyroidism, which can clinically manifest as a hypomanic/manic episode in some patients [14, 15].

Conclusion

No placebo-controlled studies have assessed the specific population of patients with bipolar disorder who develop hypomanic/manic episodes after receiving quetiapine. Accordingly, it is still difficult to answer all the questions raised by this drug-related reaction. Consequently, whether hypomania/mania is an adverse drug reaction or simply associated with the prescription of quetiapine is as yet unclear. Regardless, there seems to be a consensus that clinicians must be aware of this possible adverse event and

that they should manage it by increasing the dosage of quetiapine.

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Compliance with Ethical Standards

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