Worsening Mania Associated With Slow Increase of Quetiapine Dose

To the Editor: Atypical antipsychotics are widely prescribed for bipolar disorder.[1,2] Quetiapine is the only antipsychotic medication approved as monotherapy in the treatment of bipolar depression, largely as the result of two controlled trials.[1] Both trials indicated that quetiapine is more effective than placebo without increasing the risk of switching into mania.[1] In a large, double-blind, placebo-controlled trial with quetiapine as monotherapy for bipolar mania, patients' withdrawal due to disease deterioration was less in the quetiapine group as compared with placebo.[3] We report a case in which slow increase in the dosage of quetiapine was associated with worsening of manic symptoms.

Case Report

A 66-year-old man with a history of bipolar disorder was admitted after a week of agitation. He was diagnosed with bipolar disorder at age 28 and had a history of multiple psychiatric hospitalizations. He was alert and cognitively intact, and his medical history was notable for chronic hepatitis C. His physical and neurological examinations were unremarkable. Laboratory tests and a head CT scan showed no abnormalities. His previous medication regimen, consisting of lithium, 900 mg/day (serum level=1.0 mmol/liter), and quetiapine, immediate release 200 mg/day, was continued after admission. Over the next 10 days, quetiapine was slowly increased in 25 mg/day increments to address his agitation. However, his manic symptoms worsened as evidenced by loud singing, intrusiveness, disinhibition, provocativeness, irritability, insomnia, and increasing hostility. Organic pathology and medication side effects were excluded. His liver function tests remained within normal limits throughout the hospitalization. At the dose of 400 mg of quetiapine, he exhibited grandiose delusions; he believed that he should be the mayor of New York City. Quetiapine was discontinued and his manic symptoms remitted within 24 hours. This improvement was sustained while lithium was maintained at the same dosage. The patient was discharged in a normothymic state 5 days after discontinuation of quetiapine.

Discussion

To our knowledge, this is the first reported case of worsening mania associated with a gradual increase of quetiapine dose. The patient's manic symptoms worsened significantly as the quetiapine dose was raised slowly from 200 mg to 400 mg while the patient's serum lithium levels were within the therapeutic range. When quetiapine was discontinued, the patient's grandiosity and irritability rapidly improved. The temporal relationship between the slow increase of quetiapine and worsening symptomatology, as well as the rapid improvement of manic symptoms once quetiapine was discontinued, argue against the natural course of the illness of a manic episode.

The mechanism of antidepressant action of quetiapine is unclear. However, it has been suggested that its antidepressant activity is mediated by its metabolite *N*-Desalkylquetiapine, which leads to norepinephrine reuptake transporter inhibition and partial serotonin 1A agonism.[4] A speculation may be that slow clearance of the metabolites as an age effect or genetic trait in this case led to very high levels of *N*-Desalkylquetiapine potentiating quetiapine's antidepressant effect and leading to worsening of mania. Moreover, a positron emission tomography (PET) study using quetiapine 750 mg or 450 mg/day found that there was no D_2 receptor occupancy at the low dose of quetiapine, while $5HT_{2A}$ receptor occupancy was consistently high.[5] Despite the normal head CT scan, brain-aging related neurotransmitter changes and therefore different medication effects could be considered. Calabrese et al.[1] reported an incidence of treatment-emergent mania 2.2% with 600 mg/day of quetiapine and 3.9% with 300 mg/day of quetiapine. The absence of dopaminergic receptors blockade and the high affinity for serotonergic receptors at lower doses, may explain quetiapine's antidepressant activity and worsening mania in case of slow titration in manic patients. In this case, geriatrician treatment practice of "start low and go slow" raised questions.

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