Significant Extrapyramidal Side Effects on Low-Dose Aripiprazole

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Extrapyramidal symptoms (EPS) are a series of physical manifestations related to dopamine blockade in the nigrostriatal pathway of the brain. First-generation antipsychotics mainly cause effects by blocking dopamine D_2 receptors. The therapeutic effects of first-generation antipsychotics are postulated to be due to blocking dopamine D_2 receptors, specifically in the mesolimbic pathway. Unfortunately, dopamine receptor blockade is not limited to the mesolimbic pathway. Blockade in the mesocortical, tuberoinfundibular, and nigrostriatal pathways leads to potential worsening of negative symptoms, hyperprolactinemia, and EPS, respectively.[1] Second-generation antipsychotics were later invented with the hope of decreasing EPS and include aripiprazole among many other drugs. In comparison to first-generation antipsychotics, this class of medications also blocks dopamine D_2 receptors and additionally blocks serotonin 5-HT_{2A} receptors. The addition of serotonin 5-HT_{2A} antagonism increases dopamine release in the striatum, which reduces the overall amount of dopamine blockade, thus decreasing the risk of EPS.[2]

Case Report

Ms A is a 56-year-old Black woman with a past psychiatric history of treatment-resistant bipolar I disorder who had been started on aripiprazole 5 mg/d by her outpatient provider and was later admitted to a community hospital psychiatric unit that same day for acute mania. During that admission, aripiprazole was increased from 5 mg/d to 15 mg/d. Approximately 1 week later, Ms A went to her outpatient provider's office and spoke with staff in the lobby concerning side effects from aripiprazole. She requested to lower the dose but left the office prior to completing a full appointment with a prescriber. Later that day, she was seen in a community hospital emergency department voluntarily with complaints of "slurred speech" and "slobbering," which she attributed to aripiprazole. The on-call psychiatrist recommended decreasing the aripiprazole dose to 7.5 mg/d and starting glycopyrrolate 1 mg twice/d. Ms A was then evaluated a total of 3 additional times that week by both the emergency and crisis departments and was ultimately admitted to the hospital for further management of her medications. By this point, she had self-tapered aripiprazole to 5 mg/d but was continuing to endorse significant hypersalivation and Parkinsonian symptoms. Upon admission, aripiprazole was stopped, and she was started on benztropine 1 mg twice/d. No antipsychotics were restarted until EPS resolved. Ms A was stabilized on asenapine and benztropine prior to discharge.

Discussion

The described case emphasizes the importance of monitoring patients closely for EPS regardless of antipsychotic dose, as some patients show increased sensitivity to these medications. This sensitivity can lead to increased patient discomfort and frequent utilization of services as seen with the patient described here. Second-generation antipsychotics are generally better tolerated by patients but still can induce EPS secondary to dopamine D_2 receptor blockade.[2] Historically, aripiprazole rarely causes EPS at doses as low as 5 mg.[3] However, Ms A suffered from significant EPS, requiring numerous evaluations with minimal intervention.

Although EPS historically occurs in a dose-related pattern, it appears that some individuals may be significantly more sensitive to aripiprazole and thus experience EPS at low doses. This may be further complicated by hepatic enzymes, as aripiprazole is primarily metabolized by cytochrome P450 (CYP)3A4 and CYP2D6.[4] Patients on concomitant selective serotonin reuptake inhibitor and aripiprazole therapy are at increased risk of EPS due to increased serotonergic-mediated inhibition of the dopaminergic system.[5] Although additional research is required to provide further clarity on the possible dose-related and/or interaction-related side effects of aripiprazole, this case highlights the necessity of improving screening processes for EPS.

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