The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this case gave informed consent for publication of the column.

Atypical antipsychotics, dystonia, and psychotic depression: old solutions for new problems

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An 18-year-old man with no psychiatric history presented to the emergency department with depressed mood and psychotic symptoms. The patient smoked cannabis daily in the preceding month but had no history of stimulant use. In the days before he arrived at hospital, he had been increasingly paranoid, stating that cameras had been planted in his home, that snipers were on the roof targeting him, and that he was being sent threatening messages through his phone. As the patient was naïve to psychotropic medications, he was started on a low dose of quetiapine (25 mg twice daily) with a plan to titrate upwards over the course of an admission. After receiving 3 doses, he developed an acute dystonic reaction (affecting his hands and arms) and akathisia. The medication was abruptly discontinued, and the patient was given a single dose of benztropine (2 mg orally). By the next morning, his dystonic symptoms and akathisia had completely resolved.

The patient then opted to undergo electroconvulsive therapy (ECT) rather than risk again developing extrapyramidal symptoms (EPS) by switching to another antipsychotic medication. He underwent a series of 12 ECT treatments and achieved remission of his psychotic symptoms and low mood toward the end of the treatment course. He was discharged with a prescription for an antidepressant.

Among patients with a major depressive disorder, 14%–18.5% also have psychotic features.[1,2] This subset of patients is harder to manage and has worse long-term outcomes than those without psychotic features.[3] Treating psychotic depression with an antidepressant and an antipsychotic achieves better remission of symptoms than treatment using either option alone.[4]

Antipsychotics impart their effects via dopamine receptor blockade in the brain. Although this action reduces psychotic symptoms, it can also produce akathisia, dystonia and other EPS by increasing cholinergic output in the striatum. This occurs as acetylcholine is released when dopaminergic D_2 receptors found on striatal cholinergic interneurons become bound by an antipsychotic. This increase in acetylcholine alters the activity of striatal projection neurons, which can provoke motor problems/EPS.[5] Individual antipsychotics, however, differ in their propensity to cause these effects. Second-generation antipsychotics, also known as atypicals (e.g., quetiapine), are less likely to cause such reactions than first-generation antipsychotics.[6] While the risk of EPS is reduced by atypical antipsychotics, any antipsychotic that targets dopamine receptors has the potential to trigger EPS.[7]

Although intrinsic antipsychotic activity is related to dopaminergic D_2 receptor blockage (and in some cases, blockage of other D_2-like receptors), atypicals also antagonize $5HT_{2A}$ receptors. These $5HT_{2A}$ receptors, found on glutamatergic pyramidal neurons, are targeted by serotonin, which stimulates glutamate release. Consequently, GABAergic neurons become activated and release γ-aminobutyric acid (GABA), which inhibits dopamine release from dopaminergic neurons. When $5HT_{2A}$ receptors are bound by atypical antipsychotics, dopamine release is no longer disrupted. There is an increase in striatal dopamine that competes with the dopamine receptor antagonists. This results in enough reduction of antipsychotic binding to D_2 receptors to decrease the likelihood of developing EPS.[8] An alternate theory proposes that atypical antipsychotics bind to D_2 receptors with a lower affinity than first-generation antipsychotics. This causes more rapid dissociation of the antipsychotic from the receptor, which lowers overall D_2 occupancy, again mitigating the risk of EPS.[9] Aripiprazole and brexpiprazole, sometimes called third-generation antipsychotics, are also less likely to cause EPS on account of them being partial agonists of D_2 receptors, which results in reduced dopamine binding to the site but still some weak stimulation of the receptor.[10]

Dystonia generally occurs within days of starting a neuroleptic. Male sex, adolescent age, previous episodes of acute dystonia, cocaine use and treatment with high-potency antipsychotics also place a patient at greater risk of developing this complication.[11] Quetiapine, being a low-potency atypical antipsychotic, is among the antipsychotics that pose the smallest risk of such reactions. In fact, EPS occurs at similar frequencies with quetiapine as with placebo.[12] There have been few case reports describing dystonic reactions triggered by quetiapine, and these patients have often also been prescribed other medications that may themselves have increased the risk of dystonia.[13–17] Nevertheless, our patient still developed this relatively uncommon adverse effect but responded well to benztropine, an anticholinergic medication whose action restored proper balance of striatal dopamine and acetylcholine.

For patients presenting with psychotic features who are at an increased risk of developing dystonic reactions owing to the presence of risk factors or

a previous history of dystonia secondary to antipsychotics, ECT should be considered. In fact, ECT is a first-line treatment recommendation for psychotic depression and should be proposed as an option to patients presenting with these symptoms.[18] It is highly effective in these individuals, achieving remission in up to 95% of cases.[19] Unfortunately, patients and often physicians are sometimes hesitant to try ECT owing to stigma and concerns about possible adverse effects, including retrograde and anterograde amnesia.[20] The data, however, show that life-threatening events from ECT are rare and that memory issues are largely transitory.[18] Our patient's negative experience with quetiapine and robust response to ECT highlights the importance of using an individualized approach to the management of psychotic depression and of providing patients with information about all effective treatment options.

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