Mirtazapine-Induced Transient Dyskinesia

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Mirtazapine is an atypical antidepressant with a unique pharmacologic profile, antagonizing central α_2 receptors, 5-HT_2 and 5-HT_3 receptors, and H_1 receptors. Mirtazapine's shared affinity with the atypical antipsychotics for the 5-HT_2 receptors but lack of effect at the D_2 receptor may explain its efficacy in treating the negative symptoms of schizophrenia[1] with a low incidence of extrapyramidal symptoms (EPS).

Tardive dyskinesia, a syndrome of stereotyped hyperkinetic movements, occurs following months to years of treatment with antipsychotics or antiemetics. While potentially permanent, tardive dyskinesia has shown variable reversibility of 1% to 62%.[2] Remission generally takes months to years, but brief courses have been documented and termed *transient dyskinesia*. A MEDLINE search pairing the terms *dystonia*, *akathisia*, *dyskinesia*, and *tardive dyskinesia* with *mirtazapine* revealed several case reports of mirtazapine-associated dystonia[3–5] and akathisia[6–9] but no cases associating mirtazapine with transient dyskinesia. Here, we report a case of transient dyskinesia that developed after initiation of mirtazapine therapy for depression.

Case Report

Ms A is a 51-year-old woman who experienced orofacial dyskinesia with tongue protrusion and lateral tongue sweeping after initiation of mirtazapine for depression on 2 separate occasions. On each occasion, cessation of mirtazapine led to symptom resolution within a short period. This symptom resolution occurred despite her taking a higher dose of mirtazapine a third time and not experiencing similar symptoms. Of significance, Ms A had a history of transient dyskinesia while taking risperidone and olanzapine as augmentation therapy to duloxetine for recurrent major depressive disorder. Her other psychiatric illness was panic disorder. Her medical history was significant for restless legs syndrome, type 1 diabetes mellitus complicated by below-knee right-leg amputation, heart failure with preserved ejection fraction, hypertension, and recurrent pulmonary emboli. Her scheduled medications included insulin degludec and aspart, gabapentin, losartan, atorvastatin, rivaroxaban, and pramipexole. As-needed medications included propranolol and lorazepam, which were each prescribed up to 3 times daily for anxiety. Her family history was significant for depression in her mother and sister. She had 1-time use of methamphetamines in the remote past.

Prior to initiating mirtazapine, she took duloxetine 30 mg, risperidone 1.5 mg, and olanzapine 2.5 mg daily for 4 months for her depression. Risperidone and olanzapine were discontinued when she developed involuntary tongue-thrusting and lateral tongue-sweeping movements. These symptoms remitted within days of risperidone and olanzapine cessation, consistent with a diagnosis of transient dyskinesia. Five months after stopping risperidone and olanzapine, she was started on mirtazapine 15 mg once nightly for depression. After taking her first dose of mirtazapine, she developed similar orofacial dyskinesia with involuntary tongue protrusion and lateral tongue-sweeping movements. Mirtazapine was stopped, and her dyskinesias remitted shortly thereafter. One month after this trial, she was again prescribed mirtazapine 15 mg once nightly at a different facility. She experienced the same symptoms of orofacial dyskinesia with tongue protrusion. Symptoms again resolved after mirtazapine discontinuation. Prior to our encounter during a hospital admission, she had been put on mirtazapine for 2 days at a higher dose of 30 mg once nightly. She developed no orofacial dyskinesias on this higher dose of mirtazapine.

Discussion

We believe that mirtazapine incited transient dyskinesia in our patient who was susceptible to hyperkinetic movement disorders, as demonstrated by her personal history of restless legs syndrome and development of transient dyskinesia on low-dose risperidone and olanzapine therapy. Several mechanisms may be responsible for this phenomenon. While mirtazapine has been suggested as a therapeutic agent in the treatment of akathisia by antagonism of the 5-HT_2 receptors,[10] the pathogeneses of akathisia and tardive dyskinesia are thought to be distinct.[11] Mirtazapine antagonism of the 5-HT_{2C} receptor results in downstream dopaminergic excess,[12] supporting the supersensitivity hypothesis that suggests receptor upregulation following prolonged dopamine blockade is responsible for the hyperkinesis observed in tardive dyskinesia. Problematically, receptor downregulation occurs in the weeks following antipsychotic cessation, but our patient did not experience mirtazapine-incited transient dyskinesia until several months after discontinuing risperidone and olanzapine. Alternatively, antagonism of the

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α_2 receptor may be responsible for the observed event, as supported by reports of α_2 activation with clonidine therapy resulting in decreased symptoms in patients with tardive dyskinesia.[13] We suggest that mirtazapine results in a state of noradrenergic-dopaminergic imbalance, which is responsible for inciting the remitted transient dyskinesia in a susceptible patient. Recently, a case report[14] described induction of tardive dyskinesia following long-term bupropion therapy, supporting our hypothesis that both the norepinephrine and dopamine axes are involved in the pathogenesis of tardive dyskinesia. We cannot rule out concurrent pramipexole therapy as having significant impact on the dopamine axis, but we believe that pramipexole therapy alone was not responsible for this patient's symptoms due to her ongoing therapy throughout both incidences of mirtazapine initiation and discontinuation. The only drug interaction between mirtazapine and pramipexole is additive sedative effects of the 2 medications. While rare, mirtazapine may incite tardive dyskinesia in patients who have demonstrated susceptibility for tardive dyskinesia on antipsychotic therapy. Thus, we recommend caution when starting mirtazapine in patients who have experienced extrapyramidal symptoms on relatively low-dose antipsychotic therapy.

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