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Clozapine & Valbenazine for Treatment of Tardive Cervical Dystonia: A Case Report

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Abstract

Cervical dystonia is a subtype of tardive dyskinesia characterized by smooth, sustained muscle contractions affecting the head, neck, and shoulders. This condition can be caused by antipsychotic medication exposure. It has a significant impact on the patient's quality of life and represents a treatment challenge for providers. We present the case of a 29-year-old male with a history of schizophrenia treated with antipsychotic medications who presented with on and off smooth twisting movements of his neck and hand tremors. He was initially treated with benztropine and a decrease in the dose of his antipsychotic medications. However, when his symptoms continued to worsen, he was cross tapered to clozapine and valbenazine. Valbenazine is a VMAT2 inhibitor FDA approved for treatment of tardive dyskinesia, but there is little data regarding its use for tardive dystonia. The cervical dystonia impact profile-58 (CDIP-58) was administered to monitor the patient's symptoms. Overall, there was a reduction in cervical dystonia symptoms within a 10-week period. This case illustrates the potential for clozapine plus valbenazine to treat tardive cervical dystonia.

Keywords: Tardive Cervical Dystonia Valbenazine Case

1. Introduction and patient information

Tardive dyskinesia is a neuroleptic induced movement disorder characterized by repetitive, involuntary movements which may include chewing, tongue protrusions, lip smacking and rapid eye blinking (1). Recent meta-analyses have estimated the global mean tardive dyskinesia prevalence to be 25.3%. The overall prevalence with current second-generation treatment was 20.7% versus 30.0% with current first-generation treatment (2).

Tardive dystonia is a subtype of tardive dyskinesia, characterized by sustained, involuntary twisting movements of the face, neck, limbs and/or trunk (3). Its prevalence has not been well characterized. Although tardive dystonia may present with dystonia in any distribution, craniocervical types are the most common. In fact, it has been suggested that tardive dystonia, particularly when occurring in the cervical distribution, may be clinically identical to primary adult-onset dystonia. Thus, the diagnosis appears to rest solely on history of exposure to dopamine antagonist medications (4). Subtypes of tardive dystonia include cervical dystonia, blepharospasm, Meige syndrome, upper or lower limb dystonia, truncal dystonia, hemidystonia, multifocal dystonia and generalized

dystonia. Cervical dystonia, which is typically localized to the neck region, has the potential to migrate to generalized dystonia in roughly 13% of cases (5). Current treatments for cervical dystonia are limited, but include stopping the offending drug, medical symptom control, botulism toxin injections and deep brain stimulation for severe cases (6).

Tardive dystonia can be difficult to treat. Oral medications are often limited due to their side effect profiles and a combination of medications is usually necessary for adequate symptom control (7). Botulinum toxin injections have proven effective for both idiopathic dystonia and tardive dystonia (4). However, the beneficial effects wear off in 3 to 4 months and treatment must be repeated (6). About 30% of the patients receiving botulinum toxin discontinue the treatment due to reasons such as logistic difficulties, adverse events, or lack of response to treatment (8). Here, we contribute to the literature by presenting a case of cervical dystonia caused by second generation antipsychotics.

In this case report we present a 29-year-old African American male with a history of paranoid schizophrenia who developed tardive cervical dystonia after exposure to second generation antipsychotics. He was responsive to a combination treatment of clozapine and valbenazine, a VMAT2 inhibitor approved for tardive dyskinesia. We argue that this can be a viable treatment option for patients requiring continued antipsychotic treatment in the setting of cervical dystonia with severe and distressing symptoms.

2. Objectives for case reporting

The objectives for this case report are to highlight the possibility of valbenazine as a treatment option for patients with tardive cervical dystonia experiencing refractory symptoms after other treatments.

3. Case report

Mr. A, is a 29-year-old African American male with a history of paranoid schizophrenia. The patient's early clinical course and medication compliance was complicated by poor follow up, incarcerations and multiple psychiatric inpatient admissions. When the patient presented to our clinic, he was recently discharged from an inpatient psychiatric facility and prescribed benztropine and quetiapine. Here we present the longitudinal course of his symptoms and medications.

Under our care, the patient continued quetiapine for a year at which time he was cross tapered from quetiapine to both oral and injectable paliperidone to control his psychosis and aggression. At that time, he was also enrolled in the Assertive Community Treatment team. The Assertive Community Treatment team is a multidisciplinary team that treats patients with severe mental illness who are noncompliant with outpatient treatment and provides individualized services to each client by going into the community or the client's home.

Seventeen months after enrollment in the Assertive Community Treatment team, we noticed the beginning of abnormal head and neck movements. He presented with a tracking movement of the head and inability to focus on objects. We ruled out ophthalmic causes and the only significant abnormal lab value at this time was an elevated prolactin level of 62.2ng/ml (reference range 4-25 ng/ml).

Within a month, he also began having mild tremors of his hands and head. At this time, the patient's benztropine was increased and oral paliperidone was decreased. He was continued on injectable paliperidone.

Within a month of these treatments, his hand movements improved, but his head movements became more prominent. The decision was made to reduce his antipsychotic dose

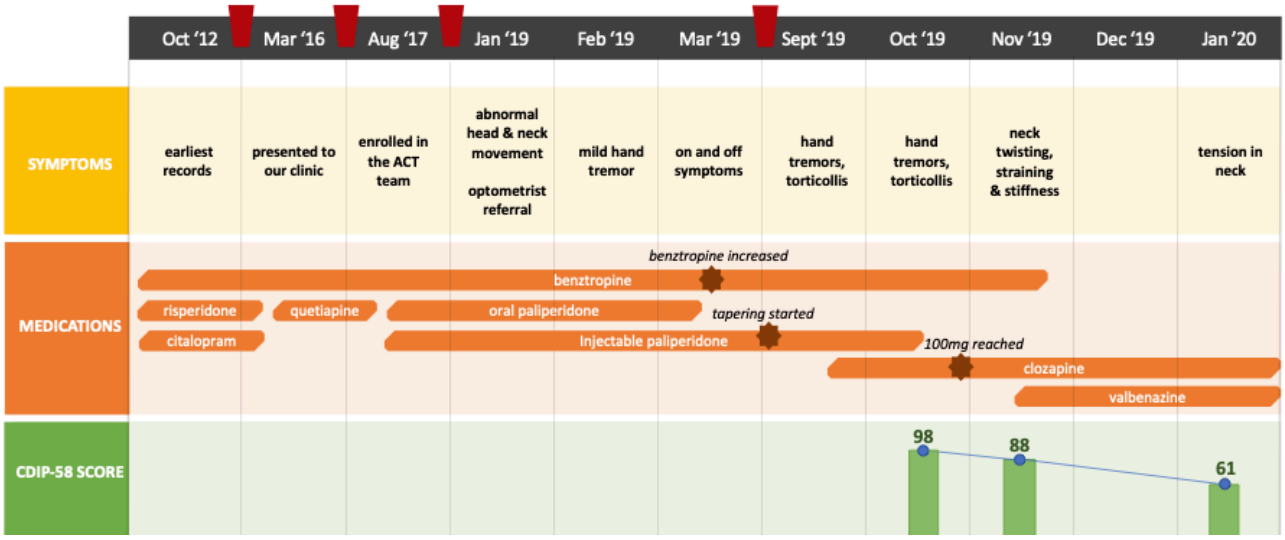

Figure 1. A timeline of the patient's symptoms (in yellow, top row), medications (in orange, middle row), and CDIP scores (in green, bottom row). Sx: symptom.

further. His oral paliperidone was discontinued and his injectable paliperidone was decreased.

The patient was maintained on this regimen for about 7 months. During this time, he continued to have waxing and waning dystonic symptoms. The delay in discontinuing his antipsychotics was based on the patient's history of severe psychosis, aggressive behavior, and history of oral medication noncompliance. However, in September 2019, it was decided he should be started on clozapine with close monitoring and support by the Assertive Community Treatment team.

Shortly after starting clozapine, at the patient's worst symptoms, he was administered the first CDIP-58 questionnaire. The CDIP-58 is a validated scale to assess the day-to-day impact of cervical dystonia. The possible scores range from 58 to 290. He first received a score of 98.

The clozapine was slowly up-titrated due to significant dizziness and sedation. At this time a neurology consultation was also obtained. Neurology recommended botulinum injections and clozapine on two separate occasions. Patient refused botulism injection but was willing to remain on clozapine. After 1.5 months of being on clozapine with continued distressing symptoms, the patient was started on 40mg of valbenazine and up titrated to 80mg to target and hasten symptom resolution. See **Figure 1**.

He was maintained on clozapine and valbenazine for 10 weeks. At the end of 10 weeks his CDIP-58 score was 61. This is 37 points (38%) lower than his initial score. Specifically, there was a 61% decrease in head and neck symptom severity and a 33% decrease in the symptoms related to daily activities such as cooking, cleaning. Over one year later on both clozapine and valbenazine, the patient has continued resolution of his symptoms without recurrence. He was maintained on both drugs at the time the case report was written with close monitoring.

4. Discussion

We have described a case of what we believe to be second generation antipsychotic induced tardive cervical dystonia successfully treated with the combination of clozapine and valbenazine.

Tardive cervical dystonia affects the neck muscles producing repetitive, patterned movements and spasmodic muscle contractions. Other clinical features include extra-cervical involvement, retrotorticollis and spasmodic head movements. Tardive cervical dystonia is most often distinguished from idiopathic cervical dystonia by exposure to dopamine antagonist medications and neck pain is usually found to precede its onset. We believe our patient had tardive cervical dystonia. He had hand tremors (extra-cervical involvement), spasmodic head movements, exposure to antipsychotics and no family history of dystonia or movement disorders (4).

Current pharmacological options for treatment of tardive cervical dystonia include anticholinergics, baclofen and clonazepam (9). Open clinical trials and case reports have suggested clozapine may also be effective in treating dystonia (10). Meta analyses of D2 receptor occupancy with positron emission tomography (PET) and single photon emission computed tomography in patients taking clozapine, have suggested relatively lower D2 receptor occupancy, and relatively higher D1 receptor occupancy compared to other atypical antipsychotics (11).

The uniqueness of clozapine's receptor binding profile and lower affinity for D2 receptors than other antipsychotics may contribute its amelioration of tardive dystonia. This is in line with the prevailing theory of dopamine receptor super-sensitivity in tardive dystonia. It is thought that chronic blockade of D2 receptors with dopamine receptor blocking agents within the dorsal striatum leads to upregulation of D2 receptors and hypersensitization of the motor cortex (12).

It is not uncommon for clozapine to take weeks if not months to offer relief from dystonia symptoms. The reason for this is largely unknown but we speculate it may have to do with recalibration of the D1 and D2 receptor profile in the brain.

Our patient experienced symptoms of tardive dystonia that were not responsive to anticholinergic medications, nor a decrease in antipsychotic medications, suggesting a severe and pervasive disruption in his dopaminergic pathways. We chose to add valbenazine in addition to clozapine to this patient's medications as there were significant concerns for a prolong, retracted course of tardive dystonia given his duration and severity of symptoms.

Valbenazine was FDA approved in 2018 to treat adults with tardive dyskinesia (13). Valbenazine works by reversibly inhibiting vesicular monoamine transporter 2 (VMAT2), thereby decreasing synaptic dopamine release and post synaptic receptor stimulation (14). VMAT2 radiotracers used in human PET scans have shown that valbenazine has a predilection for the basal ganglia. Valbenazine's action in the basal ganglia and its dopamine depleting action in the synapse may contribute to the resolution of dysfunction in the cortico-striatal-thalamic cortical circuit and the extrapyramidal systems in patients with tardive dystonia (15). By decreasing the amount of dopamine available in the striatum with a VMAT2 inhibitor we decrease the amount of dopamine available without blocking the "stop signal" indirect dopamine pathway receptors (critical for preventing unwanted muscle movement) (16).

VMAT2 inhibitors oppose the increased dopaminergic activity associated with long term antipsychotic use. They have the strongest evidence for efficacy in tardive dyskinesia (12) and based on our case findings, include tardive dystonia as well.

We measured our patient's symptom resolution in this patient with the CDIP-58 scoring tool. The CDIP-58 is comprised of 58 questions assessing symptoms of spasmodic torticollis. The total score can range from 58-290. A score of 58 signifies that symptoms have no effect on the patient's life and a score of 290 represents symptoms having severe effect on the patient's life (17). A CDIP score was unable to be obtained before starting clozapine. This is a limitation of the case report and should be performed in further research. Nevertheless, we saw significant symptom resolution clinically and objectively using the CDIP-58.

In this case, the patient was treated with both clozapine and valbenazine. It is possible that symptom resolution was entirely caused by clozapine. This limits our ability to see the sole effect of valbenazine on tardive cervical dystonia. However, we have demonstrated that the combination of clozapine and valbenazine can be effective.

5. Conclusion

Our case serves as a reminder that cervical dystonia can present in a variety of ways and the symptoms may wax and wane over many months. We propose that patients with severe and disabling symptoms, ongoing psychosis, and inability to receive botulism toxin injection, as in this case, should be switched to clozapine. We also propose that adding valbenazine may benefit patients suffering from continued symptoms. Further research is needed to develop strong, evidence-based protocols for effectively managing moderate to severe tardive cervical dystonia.

Conflicts of Interest:

Authors declare no conflicts of interest

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