Successful Treatment of Severe Tardive Dyskinesia with Valbenazine, Including a Patient’s Perspective

Richard C. Josiassen
Dawn M. Filmyer
Jack Gillean
Syed Sikandar Shah
Tyler E. Dietterich
Rita A. Shaughnessy

Background: Tardive dyskinesia (TD) is a chronic involuntary movement disorder frequently induced by dopamine receptor blockers, particularly first-generation antipsychotics. Until recently, management of TD was restricted to lowering the dose of the current medication, switching to another medication, or using off-label treatments with insufficient evidence of efficacy. Valbenazine, a vesicular monoamine transporter-2 (VMAT2) inhibitor, became the first drug to be approved by the FDA specifically for the treatment of TD.

Case Report: We describe the case of a 49-year-old African-American woman who was diagnosed with bipolar disorder at the age of 34 and treated with lithium carbonate (900 mg daily) and citalopram (10 mg daily). She also received low doses of second-generation antipsychotics for weeks at a time, but these were always discontinued due to severe sedation. Over a decade later, at the age of 45, she experienced rapid onset of severe TD symptoms. She enrolled in a phase III double-blind clinical trial and received valbenazine 80 mg, with encouraging results.

Conclusions: Once-daily dosing of valbenazine (80 mg) was effective and safe over a long period, even in this atypical case of severe and rapid-onset TD.
Tardive dyskinesia (TD) is a disorder characterized by a wide range of involuntary choreathetoid movements [1]. The clinical picture is often a mixture of facial grimacing, flicks of the tongue, and smacking of the lips. Additionally, there may be rapid jerking movements or slow writhing movement in the extremities. Although TD most commonly occurs in patients treated long-term with dopaminergic antagonist medications, TD-like movements were reported as de novo cases long before the development of the first-generation antipsychotic (FGA) agents. People with schizophrenia, bipolar disorder, and other neuropsychiatric disorders are especially vulnerable to the development of TD due to their exposure to first- and second-generation antipsychotics, anticholinergics, toxins, and substance abuse. Until recently, management of this condition was suboptimal and restricted to drug discontinuation (when clinically possible), switching to less potent dopamine antagonists, or off-label treatments with insufficient evidence of efficacy, such as clonazepam and amantadine, or vitamin A, vitamin E, or ginkgo biloba [2].

Recently, the emergence of a new vesicular monoamine transporter-2 (VMAT2) inhibitor has generated enthusiasm as a treatment for TD. Valbenazine was the first VMAT2 inhibitor (NBI-98854) approved by the US Food and Drug Administration (FDA) for the treatment for TD [3,4]. It is a novel, highly selective VMAT2 inhibitor. Normally, VMATs facilitate the transport of dopamine (and other monoamines) into synaptic vesicles for future release into the synaptic cleft (“exocytosis”). In contrast, VMAT2 inhibitors block the loading of dopamine into synaptic vesicles, thus reducing dopamine release and depleting dopamine levels throughout the brain [5]. The approval of valbenazine has been followed by the very recent FDA approval (August 30, 2017) of a second VMAT2 inhibitor, known as deutetrabenazine (SD-809), for the treatment of TD [6,7].

We present the case of “Ms. K”, a 49-year-old African-American woman who took part in KINECT 3, the phase 3 pivotal trial of valbenazine [4]. At the age of 34, she was diagnosed with bipolar disorder and then at the age of 45 symptoms of TD emerged. In 2013, prior to enrollment in KINET 3, she consulted a movement disorder specialist who gave her an Abnormal Involuntary Movement Scale (AIMS) [8] total score (sum of items 1–7) of 28, and described her as “the worst case of TD I have ever seen”. Following that evaluation (in 2013), she was referred to our site for possible enrollment into the KINECT 3 study.

**History**

Ms. K was raised by her maternal grandmother and several aunts and remembers a stable, nurturing early childhood. At the age of 9, she met her biological mother for the first time and moved with her from the Midwest to the Northeast. From that point, her home life was marked by verbal and physical abuse and neglect. Despite a chaotic home life, the patient excelled academically, attending private elementary and secondary schools, and entered college on a full scholarship intending to go into medicine.

Unfortunately, in her freshman year she began having episodes of hypomania, irritability, depressed moods, sleeplessness, and impulsive behavior, including a suicide attempt. She began to abuse alcohol and marijuana. In her sophomore year, she became pregnant, dropped out of school, and began working full-time at a bank, where she was rapidly promoted. Soon she “…had a good salary…was living the good life…spending tons of money on very expensive clothes, shoes, and a whole lot of jewelry”. In her early 30’s, she began using cocaine, and, as her career flourished, so did her cocaine and crack consumption. During one of several admissions for treatment of drug abuse, a psychiatrist “…suggested that I needed to get treated for bipolar disorder if I ever wanted to get well”. In response, “I bluntly informed that psychiatrist that I’m not crazy and that I just need to get my cocaine use under control. In no time, I had been hospitalized 10 times for episodes of mania or depression”. Her treatment included mood stabilizers, antidepressants, and an occasional low dose of second-generation antipsychotics. She gained a considerable amount of weight, and was noncompliant with her medications when discharged from the hospital. Her highly successful career soon came to an abrupt end and she found herself working odd jobs and needing public assistance to survive. As she celebrated her 40th birthday, she began to realize that “my life was totally out of control”.

**Psychiatric intervention**

Now, with 3 children and few financial or personal resources, she joined Narcotics Anonymous, stopped using cocaine, and initiated psychiatric treatment. Her medications consisted of a mood stabilizer (lithium carbonate 900 mg daily) and an antidepressant (citalopram 10 mg daily), with occasional low doses of second-generation antipsychotics (SGAs) added for sleep (usually risperidone or quetiapine, although she was also briefly on aripiprazole and ziprasidone). Her SGA treatments were intermittent, at times only 2–3 weeks. She was never treated with a first-generation antipsychotic (FGA). Even at the lowest doses, SGAs caused excessive drowsiness and were regularly
discontinued. Her bipolar symptoms were progressively brought under control. She regularly exercised, worked part-time in a community hospital, and enrolled part-time at a local college. She commented that this was a time when “I felt the most normal and healthy that I can remember”.

Onset of movement disorder

In 2011, she began to notice minor involuntary movements in her fingers and hands, but attributed them to anxiety. Initially, the movements did not seem to be a cause for concern. Soon, lip puckering appeared and “...my lower jaw started jerking back and forth...people began to stare at me”. When a family member commented on the movements, “I decided to check it out with my family doctor, who immediately referred me to a movement disorder clinic at one of the local medical schools. That was when I was formally diagnosed with TD. I had no idea what those words would mean for my life”. At that time, the patient was again being treated with risperidone (4 mg daily) for sleep, and the consulting neurologist recommended she be switched to quetiapine (400 mg daily). The movements worsened, involving the entire body, and the quetiapine was discontinued. Balance and gait disturbances became very obvious (with occasional falls in public) and she began biting the inside of her mouth. Symptoms of dystonia developed. The movements were now so obvious that her employer fired her “for being drunk on the job”. On several occasions, a professor in one of her college classes publically “told me to please sit still or leave the room”, and “people just stared at me wherever I went”.

It was at this point, in 2013, that Ms. K returned to the movement disorder specialist she had seen previously, and he described her as “the worst case of TD I have ever seen”. He contacted our group, hoping the patient would be eligible for the valbenazine project. In October 2014, she signed an informed consent, and screening commenced.

Screening and enrollment into KINECT 3

The abrupt onset and severity of her symptoms were unusual; in less than 2 years she had gone from being symptom-free to the “worst case of TD I have ever seen”. More than a decade had passed between her initial exposure to antipsychotics and the onset of TD. This raised several questions. Was this neuroleptic-induced TD, a spontaneous dyskinesia, or some other neurologic condition? Moreover, during screening, the patient began to search for her estranged biological father and learned that he had recently died in an institution with a diagnosis of unspecified dementia and motor disturbance. Further complicating the picture was her history of intermittent cocaine and crack use for a dozen years or more. These drugs block the dopamine transporter and have been associated with a variety of movement disorders [8]. Therefore, as part of screening, a brain MRI was ordered to rule-out structural lesions. Genetic testing was ordered to rule-out Huntington’s disease. Another consultation was requested at the university-based movement disorders clinic to confirm their original TD diagnosis. The results from the brain MRI and Huntington’s disease test returned negative.

Her medical history included hypertension, mitral valve prolapse, cutaneous lupus erythematosus, an episode of viral meningitis, and chronic constipation. She was being treated with lithium carbonate for her mood disorder, citalopram for depression, clonazepam and Ativan for movement disorder, and lisinopril for high blood pressure. The clonazepam and Ativan had little to no effect on the severity of her TD symptom. With inclusion and exclusion criteria satisfied, the patient was randomized to one of the 3 blinded-treatment arms.

Treatment response

The AIMS ratings used in this study were the mean of consensus scores from 2 blinded centralized raters. The average baseline AIMS rating for KINECT 3 study participants (n=227) was 10.0 (SD=4.0), and the baseline AIMS for this case was 14. Figure 1 displays Ms. K’s change from baseline in AIMS ratings superimposed on the mean change from baseline in AIMS ratings of the intent-to-treat (ITT) population from the 6-week KINECT 3 study. By week 6, her AIMS total score was reduced by 50% from baseline, which is considered by many to be a robust treatment response.

Upon completion of the 6-week study, Ms. K elected to continue in the subsequent 42-week, double-blind extension study. She continued on 80 mg of valbenazine and her TD symptoms continued to improve, but did not completely resolve. The AIMS total score is an overall picture of symptom reduction, but does not provide any specific information regarding individual symptoms. A review of her actual AIMS video record showed symptom reduction across all body regions. Importantly, her choreiform dyskinesia showed more improvement than did her dystonia, although both showed meaningful reduction. It appeared that stress and anxiety were at times associated with a worsening of her movement symptoms. As her TD symptoms diminished, Ms. K began to socialize and re-establish relationships with her estranged family and slowly began to return to more normal activities of daily living. Her cardiac condition and psychiatric status remained stable throughout the study.

Regarding adverse effects, the patient experienced marked sedation when taking 80 mg of valbenazine and often slept most of the afternoon and into the evening. This resulted in her occasionally missing her BID and TID doses of psychiatric medications. She did not want to reduce the valbenazine dose, and within 2–3 weeks the sedation subsided. She had
other adverse effects, including an episode of drooling, nasal congestion, a very brief episode of mania, and a foot fracture from falling when walking on ice. These were transient, mild-to-moderate in severity, and judged by the investigator as unrelated, or unlikely to be related, to the study drug. The brief episode of mania took place when she was experiencing drug-related sedation and had been inconsistent in taking her mood stabilizer in the afternoon and evening for more than a week.

At the conclusion of the KINECT 3 extension phase, the patient underwent a mandatory 4-week “wash-out” to formally end the study (November 2015), and then another 4 months because the study drug was unavailable. Without the study drug, her TD symptoms returned to the previous baseline level of severity. This is an important observation for Ms. K, as well as the other study participants, in who TD symptoms returned to baseline levels with discontinuation of the study drug [3,4,6,7]. This suggests that the underlying pathophysiology of TD may be irreversible and that long-term treatment is required. In March 2016, Ms. K resumed valbenazine treatment and now, with FDA approval (April 11, 2017), she is able to receive valbenazine through a specialized pharmacy. As before, the drug was effective in treating her symptoms, and now, after 2 years of treatment, the clinical improvement appears to be very stable, and Ms. K now often says “... I feel hopeful for the future”. (See Video 1 for short clips at baseline and week 6).

**Discussion**

Recent progress with selective VMAT2 inhibitors has opened up a new and encouraging avenue for the treatment of TD. It is a striking development that raises several interesting questions. Will reducing the availability of dopamine throughout the brain have a therapeutic effect on any psychiatric symptoms? Does long-term VMAT treatment repair the underlying...
pathophysiology of TD? Is valbenazine effective in iatrogenic and non-iatrogenic causes of dyskinesia? Will early intervention with VMAT2 inhibitors prevent or delay the onset of TD? As with the introduction of any new medication, important questions arise, and only future studies will elucidate the full potential of the medication. Nonetheless, the findings that VMAT2 inhibitors are effective and safe over a long period of time, even in cases with severe symptoms, is very welcome news for psychiatric medicine.

Conclusions

This is a case report regarding the positive experience of one individual with severe TD who took valbenazine. Although the case is somewhat atypical and complex, it is also illustrative and encouraging. The personal narrative and video provided by Ms. K demonstrates the profound negative consequences TD can have on one’s life, and the potential restorative impact of successful treatment.

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Statement

The subject of this case report took part in a clinical trial known as KINECT 3 (ClinicalTrials.gov identifier: NCT 02274558) sponsored by Neurocrine Bioscience, Inc. It was a 6-week, randomized, double-blind, placebo-controlled trial of valbenazine developed for the treatment of tardive dyskinesia. Participants subsequently entered a 42-week extension period of valbenazine treatment. Richard C. Josiassen, PhD served as a Principal Investigator for this study. Jack Gillean, MD and Syed Sikandar Shah, MD were Chief Residents in Psychiatry at Drexel University College of Medicine when they were involved in this clinical trial. The authors thank Ann Marie Donohue, PhD for her assistance in subject recruitment.

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