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Treatment of Tardive Dyskinesia with High-Dose Vitamin B6 Associated with Depression

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ABSTRACT

Tardive dyskinesia (TD) is a movement disorder associated with dopamine receptor blocking medications. Recommended treatments for TD include discontinuing the causative agent, adding vesicular monoamine transporter 2 (VMAT2) inhibitors, or adding vitamin B6. We present a 66-year-old Caucasian male with bipolar I disorder who developed TD while on lithium and quetiapine, having been euthymic on this regimen for three years. He was initially treated with 1200 mg B6 daily, which failed to improve his TD and was associated with a depressive episode. He switched to valbenazine 40 mg daily, which improved his TD and concurrently his mood, but months later, the TD symptoms worsened again. Our case adds to the literature by demonstrating that some patients with TD will not respond to vitamin B6. To our knowledge, ours is the first case suggesting the association of high-dose vitamin B6 with depression. This case also demonstrates that response to valbenazine may not last, and further studies are needed.

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KEYWORDS

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INTRODUCTION

Tardive dyskinesia (TD) is a movement disorder that may be severe and can involve the mouth, tongue, jaw, trunk, and extremities. It is most commonly caused by dopamine receptor blocking medications.[1] The annual incidence of TD is 3.9% overall for patients on long-term, second-generation antipsychotics.[2] Common treatments for TD include discontinuing the offending agent or adding dopamine-depleting VMAT2 inhibitors such as valbenazine.[3] More recently, high-dose pyridoxine (vitamin B6) has also been studied as a treatment for TD.[4] Vitamin B6 is metabolized to Pyridoxyl-5-PO4, which is a coenzyme that participates in the process of synthesizing dopamine, epinephrine, norepinephrine, serotonin, melatonin, and GABA, the latter of which has been shown to correlate with measured levels in the brain as a function of TD symptoms.[5,6]

A study by Lerner et al. showed vitamin B6 400 mg daily reduced TD symptoms by 68.6% per the Extrapyramidal Symptoms Rating Scale (ESRS) after four weeks compared to baseline.[7] A double-blind, placebo-controlled crossover study also by Lerner et al. showed statistically significant improvement of TD symptoms in patients with schizophrenia and schizoaffective disorder on vitamin B6 1200 mg daily.[8] Several similar studies reviewed by Umar et al. showed varying responses to vitamin B6, from having no significant changes to a 77% reduction in symptoms.[9]

We present a case of a patient with bipolar I disorder and TD who did not respond to high-dose vitamin B6 therapy but did develop an episode of depression during the B6 treatment period. To our knowledge, ours is the first case suggesting a possible association of high-dose vitamin B6 with depression. This suggests the need for further studies into factors that might predict a positive response to high-dose vitamin B6 and caution to follow mood symptoms

in patients receiving this treatment. For historical clarification, our patient was not approved by insurance for the use of valbenazine at the onset of TD symptoms, hence why vitamin B6 was trialed first. Upon obtaining valbenazine some months later, the patient initially responded to the VMAT2 inhibitor with an improvement of TD symptoms; however, symptoms worsened on the same regimen after several months. Therefore, this case also suggests that longer-term studies are needed on the efficacy of valbenazine.

CASE PRESENTATION

A 66-year-old Caucasian male with bipolar I disorder (whose most recent depressive episode and alcohol use disorder were in full remission) and tardive dyskinesia was referred to our clinic. The patient's bipolar disorder had been stable for over three years on lithium 300 mg twice daily and quetiapine 200 mg nightly.

At his first visit, he reported a history of depressive and manic episodes with hallucinations and alcohol use at the time of his diagnosis in his thirties. He had several psychiatric hospitalizations in the past but had been euthymic for over 3 years and sober for 30 years. He also had mild tremors of both hands and dyskinesias of the face and mouth, which he was aware of but were not bothersome. He continued treatment with lithium 300 mg bid and quetiapine 200 mg qhs. Lithium levels were monitored regularly and ranged from 0.5-0.7 mEq/L throughout treatment, never showing toxicity or variation from his established sufficient levels.

At the next three-month appointment, he reported an increasing right arm tremor. His oral, facial, and lingual manifestations were also noted to be increased. The patient did not wish to alter medication as his mood was stable, and the tremors were not bothersome. His Abnormal Involuntary Movement Scale (AIMS) score was 11, with an overall severity of 2 (mild).

Six months into treatment, the patient reported a significantly increased tremor and dyskinetic oral movements, having shattered nine of his teeth. He required a bite guard to prevent further damage and was prescribed pain medication and antibiotics. His AIMS score was 9, with an overall severity of 3 (moderate). Despite his worsening physical condition, the patient reported a stable mood. He was started on vitamin B6 1200 mg daily as a substitute to treat his TD.

Three months after starting vitamin B6, the patient returned to the clinic with a significantly depressed mood. He stated the onset of depressive symptoms coincided with starting the vitamin B6 supplement and did not change after completing the course of antibiotics and pain medication prescribed by dentistry. He did not disclose the addition of any other supplements or medications. He reported decreased energy, decreased interest in hobbies, increased sleep, decreased appetite, and lower self-worth. He denied suicidal ideations. No other changes in social history or life stressors were noted. In addition, there was no improvement in his TD from the B6 therapy. His AIMS score was 9, with an overall severity of 3 (moderate). The patient was instructed to discontinue vitamin B6 at that time and start valbenazine 40 mg daily.

Two months after starting valbenazine, the patient reported up to a 50% decrease in bruxism and arm movements. He also reported an improvement in his mood and no longer felt depressed. His AIMS score was reduced to 7 with an overall severity of 2 (mild).

At the next visit, he reported worsening hand tremors and oral dyskinesia. At this time, his AIMS score was 11, with overall severity of 3 (moderate). He did not want to stop the valbenazine despite the relapse of TD, and his bipolar depression remained in remission.

DISCUSSION

This case is presented due to the relapse of depression our patient exhibited while on high-dose vitamin B6. The dosage of B6 1200 mg was chosen based on the study by Lerner et al. published in 2007, in which 50 hospitalized patients with schizophrenia or schizoaffective disorder with TD were given daily doses of 1200 mg and compared with a placebo.8 They saw statistically significant improvements in ESRS scores of the patients treated with the vitamin

vs. the placebo group. They also noted the study revealed no side effects in patients on the high dose of B6. Lerner and his group have published several studies on vitamin B6 and tardive dyskinesia; however, they conclude that while efficacious in their small, specific patient samples, the mechanism of action has yet to be determined.[8]

In looking at other studies of vitamin B6 or its metabolically active form, pyridoxal 5' phosphate, it is proposed that antioxidant properties may improve TD if the pathogenesis is due to free radical formation.[5] Other studies have shown that low levels of folate or pyridoxine in the brain correlate with depression, giving rise to more evidence that major depressive disorder or bipolar disorder patients may benefit from vitamin B6.[10] However, a Cochrane review of literature on using pyridoxal 5' phosphate to treat neuroleptic-induced TD in patients with schizophrenia found little quality evidence to support the drug. They cited small samples, limited follow-up periods, and few studies, with a need for more future research.[4]

While clinical trials for patients are hard to come by, Jeanclos et al. published an interesting experiment in Molecular Basis of Disease in January 2019, which showed that increasing the level of pyridoxal 5' phosphate in the CNS of mice did not affect dopamine, serotonin, epinephrine, or glutamate. Instead, the level of GABA was increased by 20% or more. This led to improved spatial learning and memory but decreased motor performance and induced anxiety within the mice.[11] It has been shown that GABA plays a prominent role in movement disorders, but its ability to be modulated by the gene for pyridoxal phosphatase is a novel finding.[12]

Several connections and contradictions to our case are noted in the literature. In the Lerner et al. trials, patients showed statistically significant improvement of TD without any side effects reported. Not only did our patient not benefit from vitamin B6, but he also developed a depressive episode after 3 years of euthymia while on consistent lithium dosing and levels obtained during treatment. Our patient also had the diagnosis of bipolar I disorder versus schizophrenia or schizoaffective disorder. Another speculation is that our patient's mood disorder predisposed him to have a depressive episode upon the disruption of vitamin B6 levels, or his depression was coincidental and independent of treatment changes.

Tardive dyskinesia is a challenging and objective phenomenon to measure. While using the ESRS or AIMS, points may be assigned differently between physicians and their observations. This was notably the case with our patient, as he was seen by multiple psychiatry residents who performed the AIMS separately. Although AIMS was created by the National Institute of Mental Health (NIMH), this method has inconsistencies among different raters and leads to difficulty interpreting the efficacy of treatments.[13]

While our case provides an example of differing interpretations by physicians, we cannot discredit the subjective experience reported by the patient. On the trial of vitamin B6, our patient did not report improvements of his TD, but after 2 months on valbenazine, he reported a 30-50% decrease in bruxism and tremors. However, five months later, he reported worsening symptoms on the same medication that previously helped. The Food and Drug Administration approved the VMAT2 inhibitor valbenazine based on 3 placebo-controlled, 6-week clinical trials.[14] However, as demonstrated with our patient, TD often requires a treatment period longer than 6 weeks. Published in 2019, KINECT 4 was a phase 3 study on valbenazine, which followed patients through week 48 of treatment.[15] Neurocrine Biosciences reported that 53.7% of patients taking 40 mg of valbenazine daily through the end of the study had continuous improvements of TD. While this number is a majority, the sample size of participants at week 48 was n=20, meaning this statistic accounted for only about 11 patients.[16] This failure of valbenazine to consistently provide symptom management for our patient, as well as more recent studies with limited power, suggests the need for continued studies on the response of TD to valbenazine.

Overall, our case report contributes to the literature by raising the possibility that high-dose vitamin B6 treatment of TD can be associated with the onset of depression in a patient with bipolar disorder. While many studies have reported improvements in dyskinetic movements treated with vitamin B6,

our case suggests the need for further research on the etiology and treatment of TD, the mechanism of action of vitamin B6 in the brain, and other methods of treatment for neuroleptic-induced TD. Finally, we provide an example of a patient who initially appeared to improve on valbenazine but later had a relapse of TD symptoms. Further studies of valbenazine are needed to understand the long-term outcomes of this treatment.

CONCLUSION

The presented case adds to the limited literature regarding the use of vitamin B6 to treat antipsychotic-induced tardive dyskinesia and reveals inefficacy and associated depression relapse. This study also suggests the need for further research on the long-term use of VMAT2 inhibitors in treating tardive dyskinesia.

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