Annals of Depression and Anxiety

Open Access

Austin Publishing Group

Special Article - Depression Treatment

Aripiprazole-Induced Tardive Dyskinesia: A Case Report and Update of Treatment

Shaikh S*, Meyer J, Syed MA and Schwartz TL
Department of Psychiatry, SUNY Upstate Medical University, USA

***Corresponding author:** Shaikh S, Department of Psychiatry, SUNY Upstate Medical University, USA

Received: September 18, 2019; **Accepted:** October 14, 2019; **Published:** October 21, 2019

Abstract

Tardive dyskinesia (TD) is a side effect seen in patients taking antipsychotic medications. Symptoms of TD are reversible in some patients, but widely the symptoms are believed to be irreversible with limited off label medication options available until recently. FDA recently approved Valbenazine and deutetrabenazine for treatment of TD. Below we present a case of aripiprazole-induced (TD) which was successfully treated by valbenazine. However, the patient developed side effects, suggesting even these medications may have drawbacks. We aim to review the causes and treatment options for TD through the below review.

Keywords: Tardive dyskinesia; Valbenazine; Aripiprazole; Depression

Abbreviations

AIMS: Abnormal Involuntary Movement Scale; D_2,D_3: Dopamine 2 receptor and Dopamine 3 receptor; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; EPS: Extrapyramidal Symptoms; ESRD: End-Stage Renal Disease; FDA: Food and Drug Administration; FGA: First-Generation Antipsychotic; GABA: Gamma-Aminobutyric Acid; MAO: Monoamine Oxidase, MDD: Major Depressive Disorder; SGA: Second-Generation Antipsychotic; TD: Tardive Dyskinesia; VMAT-2: Vesicular Monoamine Transporter 2

Introduction

The advent of antipsychotics in the 1950 has revolutionized the field of psychiatry. However, their association with irreversible extrapyramidal symptoms (EPS) and tardive dyskinesia (TD) gave patients and providers great concern. Tardive dyskinesia (TD) is a disorder characterized by hyperkinetic athetoid, choreic movements involving face, tongue or extremities associated mostly with the long-term use of antipsychotics i.e. dopamine-2 receptor blocking agents. TD is most commonly caused by first-generation antipsychotics (FGA), but it is also associated with some second-generation antipsychotics (SGA) as well [1]. Until recently there was no bonafide treatment available for TD. However, the FDA recently approved valbenazine and deutetrabenazine for this indication.

Case Report

Mr. J is a 67- year-old man who presented with major depressive disorder (MDD) and tardive dyskinesia (TD) from long-standing aripiprazole augmentation. A psychiatrist in different practice with Bipolar 1 disorder initially diagnosed Mr. J in 1980. At that time, he reported a history of alcohol and tobacco use disorder, with "changes in mood" when under influence of alcohol. However, he denied ever suffering from any other symptoms of mania, such as grandiosity, decreased need for sleep, pressured speech, and flight of ideas, distractibility or increased activity when he was sober. His wife also corroborated this. Furthermore, he and his wife reported he had been sober since 1980. In 1980, he was started on trifluoperazine a first-generation antipsychotic with poor effect. At that time, his outpatient psychiatrist switched him to lithium with good effect. He was successfully treated with lithium for about 30 years. However, he eventually developed End-Stage Renal Disease (ESRD) and required a kidney transplant in 2010. After lithium, he was switched to valproic acid for one year based upon his presumptive bipolar diagnosis, but his next developed pancreatitis.

In 2011, he was started on aripiprazole for mood stabilization. He denied having any symptoms suggestive of mania or depression for 7 years. Unfortunately, in 2018, he developed progressive slurring of speech, drooling, became fidgety, developed involuntary myoclonic jerks and tremors about one every minute. These symptoms persisted despite taper of aripiprazole. The patient became depressed reporting anhedonia, low energy, poor sleep, hopelessness, difficulty concentrating and ultimately required psychiatric hospitalization. At that time, he was tapered off and discontinued aripiprazole and was started on lamotrigine. It was later titrated to 50 mg nightly for his depressed mood and propranolol 20mg twice daily, off label for his TD. However, the patient's mood and movement symptoms failed to improve. He was seen by neurology and diagnosed with TD due to previous use of long-standing aripiprazole use. Neurology recommended a trial of trihexyphenidyl 1mg twice daily and discontinuation of propranolol which had caused mild bradycardia and "low energy." The patient was discharged, but he represented to the emergency department within a week with newly developed orofacial involuntary movements and no improvement in his overall symptoms. He was again seen by neurology and switched to clonazepam 0.5mg twice daily. The patient failed to improve despite this switch and so neurology recommended that the clonazepam be discontinued and conservative waiting without TD treatment was warranted.

Despite some improvement in the patient's motor symptoms, his mood worsened, and he started feeling more hopeless, depressed and developed suicidal thoughts prompting psychiatric hospitalization, now with our service. During this hospitalization, his history was

Citation: Shaikh S, Meyer J, Syed MA and Schwartz TL. Aripiprazole-Induced Tardive Dyskinesia: A Case Report and Update of Treatment. Ann Depress Anxiety. 2019; 6(1): 1099.

carefully reviewed, and given the limited evidence of not enough prior manic DSM-5 symptoms, we removed the bipolar diagnosis, which we felt was likely in error. He was started on escitalopram an SSRI for depression and titrated to 10mg daily. He was also started on trazodone, titrated to 75mg at night, off label for insomnia, with good effects. Neurology was again consulted; they reported that the patient continued to have signs and symptoms consistent with TD, including orofacial movements, tremors, and myoclonic jerks, but these had improved slightly. However, the patient remained disturbed by his TD, so he elected to try valbenazine a VMAT-2 inhibitor that was titrated to 40 mg, daily for TD. He reported excellent effect, with significant reduction in tics, involuntary movements, grimaces, and stiffness. His AIMS score decreased from 27 to 6 within a period of three days during his inpatient stay. Mr. J reported steady improvement in his mood particularly with improvement in psychical symptoms. The patient's depressive symptoms improved, and he was discharged home. Two weeks following discharge home, Mr. J reported complete resolution of his TD. However, he reported feeling increasingly drowsy, making it hard to complete his activities of daily living at times. He, therefore, discontinued the medication and consulted with his outpatient psychiatrist and neurologist. He again started experiencing symptoms of TD and was restarted on valbenazine by his outpatient providers.

Discussion

The pathophysiology of TD is not completely understood, it undoubtedly involves the basal ganglia. The basal ganglia facilitates voluntary movements via the direct motor pathway to the thalamus and inhibits extraneous movements via the indirect pathway [2]. Therefore, disruption in these circuits may result in movement disorders such as TD and EPS [3]. The most prominent theory about the pathophysiology of TD is that the antipsychotics which antagonize D_2 and D_3 dopamine receptors disrupt this loop and cause dyskinesia [4] Another prominent theory suggests that long-standing exposure to neuroleptics results in D_2 receptor upregulation and postsynaptic dopamine receptor super sensitivity [5]. Alternatively, animal studies found that antipsychotics might damage GABA containing neurons disturbing the balance of the direct and indirect basal ganglia pathways [6]. Some research suggests that long-term use of antipsychotic drugs causes oxidative stress-producing toxic free radicals [7]. Some experiments in the past have also shown that acetyl cholinergic blockade can also cause worsening of abnormal movements in TD [8].

Many off-label medications have been used as an adjunct for treatment of TD. One example is Botulinum, which works by inhibiting transmission of alpha motor neurons at the neuromuscular junction thereby inducing weakness in striated muscles. Therefore, it can be used to reduce muscular over activity, including dyskinesia or dystonia. It also inhibits transmission at gamma neurons in muscle spindles, thereby altering reflex over activity [9]. However, its use is limited in that the movements must be limited to one specific muscle group. Trihexyphenidyl, an anticholinergic drug in moderate to high doses has shown to be useful in treating dystonia but not tardive dyskinesia. It blocks muscarinic acetylcholine receptors and decreases cholinergic nerve activity thus correcting the imbalance between acetylcholine and dopamine in the striatum and alleviate the symptoms of tardive dystonia [10]. However, as seen in this case, this pharmacodynamic property is often noted to make TD worse. Other medications like levetiracetam, dextromethorphan and ginkgo biloba have also shown to be helpful at times, but the mechanism of these medications is unclear, and the evidence is limited [11-13].

Historically, tetrabenazine was the first VMAT-2 inhibitor used off label for TD. Unfortunately, tetrabenazine's adverse effect profile including drowsiness, insomnia, depression, anxiety, akathisia, frequent dosing, plasma fluctuations, worsening mood and increase in suicidal ideations had limited its use [14,15]. Benzodiazepines may also be used to treat TD. Studies have shown that low dose clonazepam may be useful in reducing dyskinesia. Benzodiazepines are believed to act on gamma-aminobutyric acid A ($GABA_A$) receptors, balancing the direct and indirect pathways, in order to alleviate the symptoms of TD. However, given their propensity for addiction and withdrawal, these are at times avoided [6].

Valbenazine and deutetrabenazine were recently FDA approved for the treatment of TD. They act by inhibiting vesicular monoamine transporter type 2 (VMAT- 2) a presynaptic protein. VMAT-2 helps in transporting dopamine, serotonin, and norepinephrine, for neurotransmission and storage. VMAT-2 inhibition increases levels of neuronal cytosolic dopamine and decreases release of synaptic dopamine. As a result, dopamine concentrations are lowered as MAO enzymes now can more effectively degrade dopamine. This decreases dopamine in the synapse and lowers stimulation of postsynaptic receptor, and thus improves dyskinesia [15,16]. Several phase two and phase three trials demonstrated the safety and efficacy of these medications by reducing patients Abnormal Involuntary Movement Scale (AIMS) score significantly. The most common adverse effects noted with valbenazine were fatigue (10.9%), headache (3.4%), somnolence (10.9%), dry mouth (5.4%), akathisia (2.7%), fall (4.1%) and insignificant QTc prolongation. Notably, it did not significantly worsen psychosis or mood. Similar adverse effects were noted in those receiving deutetrabenazine treatment including somnolence, insomnia, fatigue, akathisia, and diarrhea. Deutetrabenazine carries a black box warning for increased suicidal ideation, changes in mood and risk of depression in patients with Huntington's disease [17].

Conclusion

Disfiguring TD may cause either social anxiety or depression in patients, as they have to deal with a new chronic illness/disorder that is disfiguring oftentimes. As in this case, treating TD may improve mood. While the patient's TD was successfully treated with valbenazine, he later developed somnolence and fatigue forcing him to discontinue the medication. Given the need for long term dosing to keep TD symptoms at bay and given their side effect profile long term use of VMAT-2 inhibitors may be complicated. This case study provides a good starting point for discussion and further research highlighting long-term use of VMAT-2 inhibitors on quality of life.

References

1. Waln O, Jankovic J. An update on tardive dyskinesia: from phenomenology to treatment. Tremor Other Hyperkinet Mov (NY). 2013; 12: 3.

2. Byrne JH, Dafny N. (eds.), Neuroscience Online: An Electronic Textbook for the Neurosciences, Department of Neurobiology and Anatomy, the University of Texas Medical School at Houston. 1997.

3. Mink JW. The Basal Ganglia and Involuntary Movements: Impaired Inhibition of Competing Motor Patterns. Arch Neurol. 2003; 60: 1365-1368.

4. Seeman P. Dopamine D2 receptors as treatment targets in schizophrenia. Clinical Schizophrenia Related Psychoses. 2010; 4: 56-73.

5. Teo JT, Edwards MJ, Bhatia K. Tardive dyskinesia is caused by maladaptive synaptic plasticity: a hypothesis. Mov Disord. 2012; 27: 1205-1215.

6. Gunne L, Häggström J, Sjöquist B. Association with persistent neuroleptic-induced dyskinesia of regional changes in brain GABA synthesis. Nature. 1984; 309: 347-349.

7. Shireen E. Experimental treatment of antipsychotic-induced movement disorders. J Exp Pharmacol. 2016; 8: 1-10.

8. Cornett EM, Novitch M, Kaye AD, Kata V, Kaye AM. Medication-Induced Tardive Dyskinesia: A Review and Update. Ochsner J. 2017; 17: 162-174.

9. Nigam PK, Anjana Nigam. "Botulinum toxin" Indian Journal of Dermatology. 2010; 55: 8-14.

10. Burke RE, Fahn S, Jankovic J, Marsden CD, Lang AE, Gollomp S, et al. Tardive dystonia: Late onset and persistent dystonia caused by antipsychotic drugs. Neurology. 1982; 32: 1335-1346.

11. Zhang WF, Tan YL, Zhang XY, Chan RC, Wu HR, Zhou DL, et al. Extract of Ginkgo biloba treatment for tardive dyskinesia in schizophrenia: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2011; 72: 6.

12. Woods SW, Saksa JR, Baker CB, Cohen SJ, Tek C. Effects of levetiracetam on tardive dyskinesia: a randomized,double-blind, placebo-controlled study. J Clin Psychiatry. 2008; 69: 546-554.

13. Cloud, Leslie J, Factor SA. "Tardive dyskinesia: therapeutic options for an increasingly common disorder" Neurotherapeutics: the journal of the American Society for Experimental Neuro Therapeutics. 2013; 11: 166-176.

14. German CL, Baladi MG, McFadden LM, Hanson GR. Regulation of the dopamine and vesicular monoamine transporters: pharmacological targets and implications for disease. Pharmacol Rev. 2015; 67: 1005-1024.

15. Solmi M, Pigato G, Kane JM, Correll CU. Treatment of tardive dyskinesia with VMAT-2 inhibitors: a systematic review and meta-analysis of randomized controlled trials. Drug Des Devel Ther. 2018; 12: 1215-1238.

16. Citrome L. Valbenazine for tardive dyskinesia: A systematic review of the efficacy and safety profile for this newly approved novel medication-What is the number needed to treat, number needed to harm and likelihood to be helped or harmed. Int J Clin Pract. 2017; 71.

17. Touma, Katie TB, Jonathan R Scarff. "Valbenazine and Deutetrabenazine for Tardive Dyskinesia" Innovations in clinical neuroscience. 2018; 15: 13-16.

Ann Depress Anxiety - Volume 6 Issue 1 - 2019
ISSN : 2381-8883 | www.austinpublishinggroup.com

Citation: Shaikh S, Meyer J, Syed MA and Schwartz TL. Aripiprazole-Induced Tardive Dyskinesia: A Case Report and Update of Treatment. Ann Depress Anxiety. 2019; 6(1): 1099.