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

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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

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...
Dystonia. It also inhibits transmission at gamma neurons in muscle can be used to reduce muscular over activity, including dyskinesia or junction thereby inducing weakness in striated muscles. Therefore, it inhibiting transmission of alpha motor neurons at the neuromuscular treatment of TD. One example is Botulinum, which works by acetyl cholinergic blockade can also cause worsening of abnormal basal ganglia pathways [6]. Some research suggests that long-term exposure to neuroleptics results in D2 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 dose 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.

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