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Case Report

Remission of Aripiprazole-induced Tardive Dyskinesia with Valbenazine and Vitamin E Combination Therapy: A Case Report

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Abstract

Antipsychotic medications comprise a cornerstone for the management of multiple psychopathologies, but their use is associated with significant side effects. Tardive dyskinesia (TD) is one such effect that is particularly troublesome. TD is clinically distressing, hard to treat, and poorly understood by the medical community. Due to these challenges, second-generation antipsychotics, such as aripiprazole, tend to be favored for their reduced risk of TD; however, rare cases of aripiprazole-induced TD have been documented. This report presents a novel case of TD secondary to aripiprazole monotherapy, managed successfully with Valbenazine and Vitamin E. A 39-year-old woman with schizophrenia was treated with aripiprazole, titrated to 30 mg daily. Though her psychotic symptoms improved significantly, she developed clinically distressing moderate-severe TD symptoms after one year of treatment. Her dose of aripiprazole dose was reduced, and a combination of Valbenazine 40 mg and Vitamin E 400 mg daily was initiated. This intervention led to substantial improvement, allowing the patient to achieve remission of TD symptoms and improvement in her psychiatric symptoms. This improvement persisted for over a year, even after the patient independently elected to discontinue Valbenazine therapy. Although recent case reports display clozapine as therapeutic for Aripiprazole-induced TD, the risks associated with clozapine necessitate alternative strategies for management of TD symptoms. The successful use of Valbenazine and Vitamin E in this case suggests a potentially safer and more accessible treatment option. This case study also supports the oxidative stress hypothesis of TD pathogenesis, and highlights the need for early screening, recognition, and intervention in TD to improve patient outcomes.

Keywords

Aripiprazole, Tardive Dyskinesia, Valbenazine, Vitamin E, Antipsychotics, Extrapyramidal Symptoms

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1. Introduction

Antipsychotic medications are fundamental for the management of many pathologies. Although most commonly used for schizophrenia, these agents are frequently used on and off-label for conditions including bipolar disorder, autism spectrum disorder, treatment-resistant major depressive disorder, and more [1-3]. While robust literature supports that these medications are highly effective, their efficacy must be carefully balanced with their extensive side effect profile [4]. Such effects include, anticholinergic/antihistaminergic effects, sedation, epileptogenic effects, QTc prolongation, and increased risk of mortality [1]. A unique set of adverse reactions associated with this class of medications are the extra-pyramidal symptoms (EPS): a group of motor disorders caused by Dopamine 2 (D2) dopamine receptor antagonism classified as akathisia, dystonia, parkinsonism, and tardive dyskinesia (TD) [1]. TD is a particularly challenging side effect for clinicians and patients alike. This side effect is clinically distressing for patients, often persists despite cessation of the causative drug, and remains to be poorly understood by the medical community [5, 6]. In light of these challenges, many clinicians prefer second generation antipsychotics (SGA's), particularly aripiprazole, over first generation antipsychotics (FGA's) due to the decreased risk for patients to develop TD [7].

The comparative reduction in TD risk of SGA's vs FGA's is due to differences in each class's pharmacologic mechanism of action. Positive symptoms of schizophrenia (i.e., delusions, hallucinations) are suspected to be caused by excess dopaminergic signaling throughout the mesolimbic pathway [8]. FGA's show robust reduction in positive symptoms by antagonizing D2 receptors. However, this receptor antagonism occurs diffusely throughout the brain. It is theorized that D2 blockage in the nigrostriatal pathway can lead to the development of EPS, such as TD [9]. Rather than receptor antagonism, SGA's employ various mechanisms to decrease dopamine signal transduction. Aripiprazole is one such SGA with a particularly interesting mechanism; the drug displays partial 5-HT1A agonism, 5-HT2A antagonism, and dynamic D2 receptor modulation [10]. The effects on these receptors allow for functional antagonistic effects in signaling pathways with excess dopamine, and agonistic effects in pathways with deficient dopamine, yielding a stabilization of dopaminergic activity [10]. Aripiprazole's mechanism allows for a reduction in schizophrenia symptomatology with less of a detrimental effect on homeostatic dopamine signaling [10].

The impetus for the use of aripiprazole can be partially explained by the relative risk-reduction of EPS, particularly TD, compared to other antipsychotic medications [11]. In addition to selecting this drug with the goal of preventing TD, research shows that patients who develop TD can achieve reduction or remission of symptoms by switching to aripiprazole [12-14]. However, despite its more favorable profile, aripiprazole itself has been shown to cause TD [15]. Literature regarding the treatment of TD that develops in patients taking aripiprazole is limited, with most cases necessitating clozapine to induce remission of symptoms [16, 17]. These limitations underscore the need for alternative therapeutic strategies. This report details a novel case of TD secondary to aripiprazole therapy, where remission was achieved using a combination of Valbenazine and Vitamin E. The findings add to the growing body of evidence surrounding the management of TD, particularly in cases where aripiprazole is implicated as the causative agent.

The Abnormal Involuntary Movement Scale (AIMS) is a rating scale used to assess TD in patients taking psychiatric medications [18]. It is one of the most widely used tools for the objective clinical evaluation of TD [18, 19], and is available in the public domain, allowing for unrestricted use and reproduction. The scale has demonstrated validity and high inter-rater reliability, particularly among experienced raters [20, 21]. Clinical trials suggest that a decrease in AIMS score of 2 or more points on the AIMS indicates a clinically significant improvement in symptoms [22].

The AIMS assessment consists of two phases: (1) an examination phase, where patient is instructed to follow several simple commands, followed by (2) a scoring phase, where the clinician evaluates the presence of involuntary movements throughout the preceding maneuvers [18]. The scale consists of 12 total items - the first seven assessing dyskinesias in the patient's face, jaw, tongue, extremities, and trunk, while the remaining five items holistically evaluate the significance of these dyskinesias [18]. Each item is scored on a scale of 0-4 (0 = no abnormal movements, 4 = severe dyskinesia) [18].

In this case report, the authors used the sum of the first 7 items, generating a total severity score ranging from 0 to 28. This sum total was used to monitor for changes in the patient's dyskinesias over time. In this case report, the authors used the sum of the first 7 items, generating a total severity score ranging from 0 to 28. This sum total was used to monitor for changes in the patient's dyskinesias over time.

2. Case Presentation

A 39-year-old woman with a medical history of hypertension and obesity, but no prior psychiatric diagnoses, presented to an outpatient psychiatry clinic due to a three-year history of auditory hallucinations and paranoid delusions without significant mood disturbances. The patient was provisionally diagnosed with schizophrenia, and Aripiprazole 10 mg daily was initiated to mitigate her symptoms of psychosis while minimizing the risk of extrapyramidal side effects.

Over the next several months, the patient's Aripiprazole was gradually increased to 30 mg daily, which correlated with a marked reduction in her psychotic symptoms and improved sociability. To establish a baseline for potential extrapyramidal symptoms, an Abnormal Involuntary Movement Scale

(AIMS) assessment was conducted; the assessment yielded a score of 0, indicating no observable TD at that time.

Shortly thereafter, the patient reported a possible manifestation of early TD in the form of new- intermittent episodes of shakiness. At the next appointment, although her psychotic symptoms were well-controlled, the patient expressed growing concern about newly observed involuntary lip, tongue, and jaw movements. An AIMS evaluation resulted in a score of 10, indicating the presence of moderate TD. This finding prompted immediate intervention - the patient's Aripiprazole dosage was reduced to 25 mg, and she was initiated on Valbenazine 40 mg and Vitamin E 400 mg daily to address her new motor symptoms. These adjustments to the medication regimen allowed her to maintain control of her hallucinations and delusions, while experiencing increased comfort and functionality in daily activities secondary to a reduction in TD symptoms, as evidenced by a gradual reduction in AIMS scores back to 0.

With her psychotic symptoms remaining well-controlled for months and no signs of TD present, the patient's Aripiprazole dosage was reduced from 25 mg to 10 mg in an effort to limit the patient's total exposure to the medication. Unfortunately, the dose reduction coincided with an exacerbation of psychotic symptoms. After a thorough discussion of potential therapeutic options, and a failed attempt at alternative pharmacotherapy due to denial by the patient's insurance, the clinician and the patient engaged in shared decision-making, and the patient elected to gradually increase her dose of Aripiprazole once more.

At the clinicians next follow up visit with the patient, she disclosed that she had independently discontinued Valbenazine therapy, citing personal preference. However, she reported satisfactory control of her psychotic symptoms without experiencing any re-emergence of TD on a regimen of only Aripiprazole 20 mg and Vitamin E 400 mg daily. Both the patient and clinician agreed on periodic follow-ups to monitor for any emerging motor symptoms and ensure sustained efficacy of her treatment plan. As of her most recent visit nearly one year after discontinuing Valbenazine, the patient maintains adequate control of psychiatric symptoms while maintaining consistent AIMS scores of 0.

Table 1. *Significant Developments in the Presented Case. When administered, Items 1-7 of AIMS were summed to generate a single value representative of the patient's TD symptoms. (ARIP = Aripiprazole; VBZ = Valbenazine; Vit. E = Vitamin E).*

Date	Clinical Summary	AIMS Score	Pharmacologic Management
01/2021	Marked psychotic symptoms, excess sleep, social isolation	N/A	Start ARIP 10 mg, gradually increase dose over subsequent visits
03/2022	Clinical improvement achieved (Reduced psychotic symptoms, improved sociability and participation in household activities)	0	Continue ARIP 30 mg
06/2022	New onset involuntary lip, tongue, jaw movements	10	Decrease ARIP to 25 mg Start VBZ 40 mg Start Vit. E 400 mg
03/2023	TD symptoms resolve, continued control of psychiatric symptoms	0	-
03/2024	Clinically well-appearing, clinician desires to mitigate total exposure to antipsychotic medication	N/A	Decrease ARIP to 10 mg
04/2024	Recurrence of psychotic symptoms occurs	0	Increase ARIP to 15 mg
06/2024	Decrease in psychotic symptoms, patient desires dose increase	2	Increase ARIP to 20 mg
08/2024	Patient independently discontinues VBZ, psychotic symptoms well controlled	1	Discontinue VBZ per patient request Continue ARIP 20 mg and Vit. E 400 mg
10/2024	Clinically stable, no significant changes	0	-
01/2025	As above	0	-
04/2025	Most recent appointment, patient maintains adequate control of psychiatric symptoms without reemergence of TD	0	Continue ARIP 20 mg and Vit. E 400 mg

3. Discussion

Tardive dyskinesia (TD) is a multifaceted and poorly understood disorder, most commonly associated with the prolonged use of antipsychotic medications [23]. Its clinical relevance lies in its potential to significantly impair quality of life and complicate the long-term management of psychiatric disorders. When antipsychotic therapy is indicated, aripiprazole is often chosen by clinicians due to its relatively decreased incidence of TD [24, 25]. However, it is vital to consider that all antipsychotic medications, including aripiprazole, can lead to the development of TD [7]. As such, the regular screening of patients on antipsychotic medications for TD symptoms is warranted.

When considering the management of the patient who develops TD, in moderate to severe cases, the standard of care typically includes vesicular monoamine transporter 2 (VMAT2) inhibitors, such as Valbenazine, which reduce dopaminergic signaling by inhibiting dopamine transport into presynaptic vesicles [26]. Additionally, de-escalating or discontinuing the offending antipsychotic medication may be considered, though this approach risks exacerbating the underlying psychiatric condition [26, 27]. While these treatments address the symptoms of TD, they do not target its underlying pathophysiology. Furthermore, the use of VMAT2 inhibitors may cause additive side effects such as somnolence, nausea, and parkinsonism [15, 28, 29]. Emerging evidence suggests that transitioning to Aripiprazole may reduce or even remit TD symptoms induced by other antipsychotics [11, 30-33]. However, data remains limited, particularly regarding the medication's efficacy across diverse patient populations and in cases where Aripiprazole itself is the causative agent.

Recent case reports have highlighted clozapine as a potential therapeutic option for Aripiprazole-induced TD [16, 17, 34]. However, clozapine use is associated with significant drawbacks, including the risk of agranulocytosis and the need for intensive hematologic monitoring, which may limit its feasibility in certain patient populations [35-37]. This case report introduces an alternative approach using a combination of Valbenazine and Vitamin E, offering a potentially safer and more accessible treatment option for Aripiprazole-induced TD.

Valbenazine, a VMAT2 inhibitor, is well-established as a standard treatment for TD of varying etiologies [34, 38-42]. This case adds to the existing evidence by demonstrating its efficacy in addressing TD symptoms specifically associated with Aripiprazole therapy. The justification for VMAT2 inhibitor therapy lies in one of the theorized mechanisms for TD pathogenesis - chronic blockade of dopamine receptors by antipsychotic agents promotes "super-sensitivity" of the receptors, causing a net increase in dopamine signaling in particular neurologic regions (i.e., the basal ganglia), evoking movement symptoms [43-47]. By decreasing the transport of monoamines (such as dopamine) into presynaptic vesicles, less dopamine is released by presynaptic neurons, causing a decrease in the total dopaminergic signaling and reducing the movement symptoms of TD [43-47]. In this case, we expand upon this literature to show that VMAT2 inhibitors are effective when TD occurs due to aripiprazole therapy. The use of Valbenazine rather than clozapine avoids the need for frequent laboratory testing and avoids the risk of agranulocytosis, myocarditis, and cardiomyopathy, and decreases the risk of seizure [23]. In contrast to Clozapine, Valbenazine can also be used in patients with comorbidities or a history of cardiac pathologies, epilepsy, and myelosuppression [23, 37]. By allowing for a safer, less cumbersome course of therapy for the patient, Valbenazine is an attractive choice for the treatment of TD secondary to Aripiprazole therapy.

The efficacy of VMAT2 inhibitors in TD management is supported by the dopamine receptor super-sensitivity hypothesis [45]. In contrast, Vitamin E targets a different proposed mechanism of TD pathogenesis: oxidative stress-induced neurodegeneration [48-53]. A well-known antioxidant, Vitamin E has demonstrated cytoprotective effects against oxidative damage [49-60] and may help mitigate neurodegeneration associated with chronic antipsychotic use, potentially conferring a neuroprotective effect in TD [49]. Presently, there is no existing research assessing the efficacy of Vitamin E in conjunction with other TD treatments, such as VMAT2 inhibitors. However, the authors believe that given the safety of Vitamin E at appropriate doses, the low cost of the compound, and the tendency for patients to view natural substances such as vitamins in a positive light, Vitamin E may represent a viable adjunctive therapy for TD [59, 61-68]. Vitamin E may be especially beneficial early in TD pathogenesis, potentially delaying or reducing the need for VMAT 2 therapy.

This case underscores the importance of maintaining a high index of suspicion for TD in patients taking antipsychotic medications. The recent expansion of indications for antipsychotics have increased the number of patients at risk of developing TD [2, 69]. Evidence suggests that early detection and prompt intervention can significantly enhance the reversibility of TD symptoms and prevent symptom progression [31, 70]. In the subject of this report, the timely initiation of Valbenazine and Vitamin E therapy contributed to the successful remission of her symptoms. Therefore, the authors suggest that regularly screening this patient population for TD with a tool such as the AIMS may facilitate earlier diagnosis and improve clinical outcomes.

This report highlights the potential of combining Valbenazine and Vitamin E as a treatment for Aripiprazole-induced TD. However, further research, including randomized controlled trials, is needed to validate this approach and establish its generalizability across diverse patient populations. Additionally, the timing of the intervention coincided with a small reduction in the dosage of Aripiprazole, further limiting the ability to attribute remission of symptoms to the intervention.

The findings from this case study add to the growing base of literature to help better understand the phenomenon of TD.

The case bolsters the notion that VMAT2 inhibitors are effective for TD and posits that augmenting with Vitamin E may further improve patient outcomes. The pharmacologic intervention employed in this report poses an alternative to clozapine therapy for patients who develop TD secondary to Aripiprazole therapy. The case also emphasizes the importance of early detection and intervention for TD symptoms, suggesting that routine screening can improve patient outcomes. If a patient experiences TD, in particular if symptoms occur secondar to Aripiprazole therapy, clinicians may consider the use of Vitamin E and Valbenazine as a means to alleviate motor symptoms without necessarily discontinuing Aripiprazole.

4. Conclusions

This case highlights the critical need for early recognition and intervention in TD to improve patient outcomes. The AIMS scale, which can be quickly and easily administered by clinicians, may serve as a practical means to detect early manifestations of TD. The observed remission of aripiprazole-induced TD with valbenazine and vitamin E suggests a more easily accessible therapeutic approach for this population than prior literature has reported. Furthermore, the sustained remission of TD symptoms with vitamin E monotherapy supports the hypothesis that oxidative stress contributes to TD pathogenesis. Given vitamin E's safety and accessibility, clinicians may consider its use early in the course of TD. Further research is required to validate these findings and explore their applicability to broader patient populations.

Abbreviations

TD	Tardive Dyskinesia
EPS	Extra-pyramidal Symptoms
SGA's	Second Generation Antipsychotics
FGA's	First Generation Antipsychotics
D2	Dopamine 2 (as in, Dopamine 2 Receptor)
AIMS	Abnormal Involuntary Movement Scale
ARIP	Aripiprazole
VBZ	Valbenazine
Vit. E	Vitamin E
VMAT2	Vesicular Monoamine Transporter 2

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Conflicts of Interest

The authors declare no conflicts of interest.

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