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REVIEW ARTICLE

Vesicular Monoamine Transporter Type 2 (VMAT2) Inhibitors in the Management of Tardive Dyskinesia

Lillian L Smith Mosley[1], Juan F Mosley II[1], Jessica R Fleischfresser[2] and Tiffani Reed[2]*

[1]*Associate Professor, College of Pharmacy and Pharmaceutical Sciences, Florida Agricultural and Mechanical University, USA*

[2]*PharmD Student, Florida Agricultural and Mechanical University, USA*

***Corresponding author:** *Lillian L Smith Mosley, PharmD, CPh, MBA, Associate Professor of Pharmacy Practice, College of Pharmacy and Pharmaceutical Sciences, Florida Agricultural and Mechanical University, USA, E-mail: lillian.smith@famu.edu*

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Introduction

Neuroleptic medications are prescribed for the management of mental, gastrointestinal, and neurological disorders. These disorders occur via over-excitation of dopamine in the brain. When neuroleptics are used, dopamine receptors are blocked reducing the excitation. Thus, the disorder becomes controlled. The long-term use of neuroleptics can result in a misfire of the neurons of the brain causing tardive dyskinesia (TD), an irreversible chronic condition of spontaneous movements.

Tardive dyskinesia is characterized by involuntary movements of the face and limbs. Symptoms include grimacing of the face, sucking or chewing when there is nothing in the mouth, lip-smacking, puckering, and uncontrollably sticking the tongue out. In the limbs, symptoms can include compulsory tapping and flexing.

Halliday conducted a 20-year review, in 2002, and found the prevalence of TD to be 43% [1]. Advanced age is a risk factor for TD; however, TD can occur at any age and among any race. Typically, TD occurs with the long-term use of neuroleptic medications, but schizophrenic patients can develop TD with or without the use of neuroleptics. In many cases, the neuroleptic causing TD will be discontinued or replaced with a different medication, but the benefit must outweigh the risk. Incidences where the benefit does not outweigh the risk, the use of a medication that is specific for tardive dyskinesia may be necessary. The use of vesicular monoamine transporter type 2 (VMAT2) inhibitors in TD is not a new idea, but only recently has one been FDA-approved for the treatment of TD.

This article is intended to acquaint clinicians with VMAT2 inhibitors and their use in TD. VMAT2 inhibitors role in treating TD is significant, implementing great aid to patients in clinical trials. The action of these drugs is focused on the role of dopamine in tardive dyskinesia. Treatment is based on clinical trials for recommendations regarding the effects of VMAT2 inhibitors. Prior to treatment initiation, clinicians should consider drug interactions, patient susceptibility, and adverse drug events.

The Role of Dopamine in Tardive Dyskinesia

The basal ganglia area of the brain is responsible for controlling motor functions; it does so by the use of dopamine. The basal ganglia depend on a specific amount of dopamine to perform at its best. When dopamine is lacking, it leads to uncoordinated motor functions.

Pathophysiology of TD is thought to be caused by continuous blockade of dopamine receptors in the brain [2]. Neuroleptic medications bind to dopamine receptors to prevent the action of dopamine in the

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Table 1: Dosage and Administration of VMAT2 Inhibitors.

Dosage and Administration	Valbenazine [8] (Ingrezza)	Tetrabenazine [9] (Xenazine)	Deutetrabenazine [10] (Austedo)
Strengths and Dosage Form	40 mg capsules	12.5 mg and 25 mg tablets	6 mg, 9 mg, and 12 mg tablets
Recommended Starting Dose	40 mg daily with or without food	12.5 mg daily for the first week, then 12.5 mg twice daily	6 mg daily with food
Dose Adjustments	· Dose can be increased to 80 mg daily · Patients with moderate-severe hepatic impairment: Do not exceed 40 mg/day · Poor metabolizers (PM) of CYP2D6 may need dose reductions	· Dose can be titrated by 12.5 mg intervals to a dose that reduces chorea · Patients requiring > 50 mg should be genotyped for (PM) or extensive metabolizer (EM) of CYP2D6; max daily dose for PM is 50 mg divided into 2 doses of 25 mg; max daily dose for EM is 100 mg with a single dose of no more than 37.5 mg	· Dose can be titrated by 6 mg/day to a dose that reduces chorea; max 48 mg/day (24 mg twice daily) · If switching from tetrabenazine, discontinue tetrabenazine and initiate deutetrabenazine the following day · Max dose for PM of CYP2D6 is 36 mg/day (18 mg twice daily)
Precautions	· Sedation: May impair cognitive functions · QTc prolongation: Avoid in congenital long QT syndrome and/or arrhythmias that are associated with QTc prolongation	· Do not exceed 50 mg/day (25 mg twice daily) when used with strong CYP2D6 inhibitors · Discontinue use if neuroleptic malignancy and/or extrapyramidal disorder occurs · Reduce dose or discontinue use if parkinsonism, restlessness, and agitation occurs · QTc prolongation: Not recommended to use with other QTc prolonging medications · Sedation: May impair cognitive functions	· Reduce dose or discontinue use if parkinsonism, restlessness, and agitation occurs · Discontinue use if neuroleptic malignancy occurs · Sedation: May impair cognitive functions

treatment of certain conditions. The antagonist effect on dopamine has the predisposition to cause TD, an irreversible condition.

VMAT2 Inhibitors

As of today, the Food and Drug Administration (FDA) has approved one VMAT2 inhibitor in patients with TD: Valbenazine (Ingrezza, Neurocrine Biosciences). However, tetrabenazine (Xenazine, Lundbeck) and deutetrabenazine (Austedo, Teva Pharmaceuticals USA), which are approved for Huntington's Disease, are used off-label in the treatment of TD (Table 1). Valbenazine was approved in April 2017, tetrabenazine in August 2008, and deutetrabenazine was approved in April 2017 [3-5].

The vesicular monoamine transporter (VMAT) is a transmembrane protein that transports monoamine neurotransmitters dopamine, serotonin, norepinephrine, epinephrine and histamine into the synaptic vesicles from the cytosol via a vesicular H-ATPase pump by active transportation [6]. The binding of the hydrogen atom leads to a conformational change allowing dopamine to bind and load into the synaptic vesicle for release. VMAT2 specifically moves dopamine into the synaptic vesicles. VMAT2 inhibitors alter the protein and deplete the transport of dopamine, thus decreasing the release of dopamine and it's breakdown by monoamine oxidase [7]. VMAT2 inhibitors are indicated for abnormal involuntary movement disorders such as dyskinesias and chorea [8-10].

Clinical Trials

Kinect-3

The phase-3, randomized, double-blind, placebo-controlled trial was designed to determine the safety and efficacy of valbenazine 40 mg or 80 mg in 225 participants with schizophrenia, schizoaffective disorder, or a mood disorder who had moderate-severe tardive dyskinesia. The study was conducted to observe subjects change on the Abnormal Involuntary Movement Scale (AIMS). After 6 weeks of treatment, 23.8% of participants in the 40 mg/day group and 40% of participants in the 80 mg/day group had an AIMS response. There was a mean AIMS change of -1.9 (compared to -0.1 for placebo) in the 40 mg/day group, and -3.2 (compared to -0.1 for placebo) in the 80 mg/day group. Valbenazine was well tolerated in the study population. Sedation (5.1% in 80 mg/day group and 5.6% in 40 mg/day group) and xerostomia (6.9% in 40 mg/day group) were the only adverse events associated with treatment that were recorded among participants. Valbenazine significantly improved TD compared to the placebo. This study suggested valbenazine as a compelling option for those with TD. The results of this 6-week study were extended into a 42-week study to further assess the long-term effects of valbenazine in patients with TD [11].

Tolerability of tetrabenazine in the treatment of hyperkinetic movement disorders: The long-term tolerability of tetrabenazine was reviewed in 448 participants with moderate-severe hyperkinetic movement disorders including TD and other choreas from January 1997 to January 2004. Participants were studied according to a 1- to 5-point response scale (1 = reduction in hyperkinetic movements, 5 = worsening of movement disorder). Participants who had a response rating of 1 or 2 by the end of the study were 85.7% in TD and 81.4% in chorea, 77.8% in tics, 71.4% in myoclonus, and 69.5% in dystonia. 69.5% of participants experienced a 5-point response rating. Sedation (25%), Parkinsonism (15.4%), depression (7.6%), agitation and restlessness (7.6%) were the most common adverse events. Participants with TD and chorea responded more favorably than those with tics, dystonia, or myoclonus [12].

Tetrabenazine treatment in movement disorders: The efficacy of tetrabenazine was studied among 150 participants with an array of hyperkinetic movement disorders from December 1998 to December 2002. Participants were assessed according to the Clinical Global Impression of Change (CGIC) (-3 to +3). 18.6% of participants scored a +3 on the CGIC with an overall 61% improvement of conditions. The most reported side effects include sedation, weakness, lack of interest, depression, parkinsonism, agitation and restlessness. Tetrabenazine is a safe and effective option for those with hyperkinetic movement disorders such as TD [13].

Deutetrabenazine for tardive dyskinesias: The phase II/III, randomized, double-blind, placebo-controlled trial was designed to determine the efficacy and safety of 12 mg/day (6 mg twice daily) deutetrabenazine in 117 participants with moderate-severe TD. The study was conducted to observe subjects' primary endpoint change in AIMS scores and secondary endpoint change on the CGIC. After 12 weeks of treatment, 3% of participants had a reduced AIMS score compared to placebo (1.6%) and 48.2% experienced success based on CGIC compared to placebo (40.4%). Common side effects reported were sedation (13.8%), headache (6.9%), psychosis (1.7%), and suicidal ideation (1.7%). Deutetrabenazine is an effective and safe treatment option for those suffering from involuntary movement disorders [14].

Pharmacokinetics

Valbenazine: The absolute bioavailability of valbenazine 40 mg capsule, given under fasting conditions, is approximately 49%. Valbenazine is present at the maximum concentration in serum (Tmax) from 0.5 to 1 hour. The mean peak plasma concentration (Cmax) of valbenazine is decreased by 47% when taken with food. The Cmax and AUC of valbenazine's active metabolite are unaffected. Valbenazine is more than 99% protein bound, with a volume of distribution averaging 92 L. Following oral administration, valbenazine is metabolized extensively by hydrolysis and oxidation (CYP3A4/5). Approximately 60% of absorbed valbenazine is eliminated renally and 30% by fecal route. It also has a plasma elimination half-life of 15 to 22 hours. Furthermore, less than 2% is excreted unchanged in the urine or feces, with a total plasma clearance of 7.2 L/hr [8].

Tetrabenazine: At least 75% of tetrabenazine is absorbed following oral administration, with an elimination half-life ranging from 2 to 10 hours depending on a patient's state of hepatic impairment. *In vitro*, tetrabenazine is 82% to 85% protein-bound, while the active metabolite alpha-dihydrotetrabenazine (α-HTBZ) is protein-bound at a range of 60% to 68% and beta-dihydrotetrabenazine (β-HTBZ) is 69% to 63%. Tetrabenazine is rapidly and extensively metabolized, primarily by cytochrome P450 (CYP) 2D6. Approximately 75% of the orally administered dose is excreted renally as unchanged; 7% to 16% is excreted by fecal route. Following intravenous (IV) administration, only 3% of tetrabenazine is excreted fecally [9].

Deutetrabenazine: Following oral administration, deutetrabenazine is metabolized to the active deuterated dihydro-metabolites (HTBZ), α-HTBZ and β-HTBZ, with a Tmax of 3 to 4 hours post-dose. Food has no effect on the AUC of deuterated dihydro-metabolites; however, there is a 50% increase in Cmax. At least 80% of deutetrabenazine is absorbed post-oral dose. The metabolite, α-HTBZ, is 60% to 68% bound to human plasma proteins, with a volume of distribution of 500 L. On the other hand, protein binding of β-HTBZ is 59% to 63% and the volume of distribution is 730 L. Deutetrabenazine is metabolized in the liver by CYP2D6. The total body clearance of deuterated dihydro-metabolites is 47 L/hr. and 70 L/hr. respectively, with a half-life of 9 to 10 hours. The mean total recovery of deutetrabenazine in the urine is 75% to 86% and 8% to 11% is excreted in the feces [10].

Drug Interactions

MAOIs

When monoamine oxidase inhibitors (MAOIs) are co-administered with valbenazine, the concentration of monoamine neurotransmitters can increase, leading to an increased risk of serotonin syndrome. To avoid this reaction, MAOIs should not be given with valbenazine. In patients taking MAOIs, tetrabenazine and deutetrabenazine are contraindicated. Tetrabenazine and deutetrabenazine should not be used with MAOIs or within 14 days of discontinuing MAOI therapy. The combined use of tetrabenazine or deutetrabenazine with MAOIs may potentiate the elevation of catecholamine levels, leading to hypertensive crisis [8-10].

Strong CYP2D6 inhibitors

Active metabolites of tetrabenazine and deutetrabenazine, α-HTBZ and β-HTBZ, are substrates for CYP2D6. Combined use of these two medications with

strong CYP2D6 inhibitors can increase metabolite exposure almost 3-fold. No more than 50 mg/day (25 mg twice daily) of tetrabenazine should be used and no more than 36 mg/day (18 mg twice daily) of deutetrabenazine should be used in patients already taking strong CYP2D6 inhibitors (e.g. paroxetine, fluoxetine). Reducing the valbenazine dose, based on tolerability, should also be considered when administered with strong CYP2D6 inhibitors [8-10].

Reserpine

Reserpine irreversibly binds to both VMAT1 and VMAT2 with a long duration of action (days). At least 20 days should pass before starting tetrabenazine or deutetrabenazine to reduce the risk of overdose or deficiency in serotonin and/or norepinephrine in the central nervous system [8-10].

Alcohol

Alcohol use with sedating drugs has an additive effect and can worsen sedation [8-10].

QTc prolongation

Both tetrabenazine and deutetrabenazine increase QTc interval (about 8 msec). In the event these are co-administered with other QTc prolonging drugs (e.g., antipsychotic medication, antibiotics, Class 1a/III antiarrhythmic medications), there would be an expected increase in prolongation of the QT interval. Valbenazine may prolong the QT interval, but it is only clinically significant when patients are taking strong CYP2D6 or CYP3A4 inhibitors or those who are CYP2D6 poor metabolizers. For those patients, a dose reduction to 40 mg once daily may be needed. Valbenazine should be avoided in patients with congenital long QT syndrome and arrhythmias that are associated with QT prolongation [8-10].

Neuroleptic drugs

Interactions of tetrabenazine or deutetrabenazine with dopamine antagonists or antipsychotic agents increases the risk for neuroleptic malignant syndrome (NMS), parkinsonism, and akathisia adverse events [9,10].

CYP3A4 inhibitors and inducers

Interactions of valbenazine with strong inhibitors of CYP3A4 can increase valbenazine metabolite exposure and strong CYP3A4 inducers may decrease valbenazine metabolite exposure. When valbenazine is administered with strong CYP3A4 inhibitors, consider dose reduction; when administered with strong CYP3A4 inducers, consider increasing the dose [8].

Digoxin

Digoxin concentrations may increase due to the inhibition of P-glycoprotein (P-gp) when digoxin and valbenazine are administered concomitantly [8].

Adverse Events Associated with VMAT2 Inhibitors

In clinical studies of valbenazine, tetrabenazine and deutetrabenazine, the most common side effects were sedation, and akathisia [11-14]. Warnings and precautions for VMAT2 inhibitors include somnolence, QTc prolongation, and akathisia (Table 2) [8-10]. The labeling for valbenazine includes additional warnings and precautions for anticholinergic effects (e.g. xerostomia, urinary retention, constipation) and muscle pain [8]. The labeling for tetrabenazine and deutetrabenazine includes additional warnings for depression, suicidality, NMS, parkinsonism, hyperprolactinemia, and binding to melanin-containing tissues [9,10]. Additional warnings for tetrabenazine includes difficulty swallowing and orthostatic hypotension [9].

Monitoring Parameters

It is recommended that QT interval be monitored prior to initiation and during treatment with any VMAT2 inhibitor because of the leading risk of prolonged QT interval. Increased monitoring of CYP2D6 is recommended when initiating a dose of tetrabenazine higher than 50 mg/day and deutetrabenazine higher than

Table 2: Warnings and Precautions Associated with VMAT2 Inhibitors [8-10].

Warning/Precaution	Valbenazine	Tetrabenazine	Deutetrabenazine
Sedation/Somnolence	x	x	x
Akathisia	x	x	x
QTc Prolongation	x	x	x
Anticholinergic Effects (e.g. xerostomia, urinary retention, constipation, blurred vision)	x		
Muscle Pain	x		
Depression and Suicidality		x	x
NMS		x	x
Parkinsonism		x	x
Hyperprolactinemia		x	x
Binding to Melanin-Containing Tissue		x	x
Dysphagia		x	
Orthostatic Hypotension		x	

x: Represents the medication mentioned for that particular columnar cause the particular side effect listed for that row.

36 mg/day. Regular monitoring of akathisia, new or worsening changes in mental behavior, and NMS upon discontinuation or initiation of tetrabenazine and duetetrabenazine is recommended. If an episode of NMS occurs, treatment should be discontinued. If parkinsonism occurs, the dose of tetrabenazine or deutetrabenazine should be reduced or discontinued altogether. Continuous monitoring of blood pressure is essential when taking tetrabenazine due to a risk of hypotension while standing. Monitor for dysphagia in patients receiving tetrabenazine. Sedation and somnolence is a common side effect of VMAT2 inhibitors which can impair cognitive functions [8-10].

Conclusion

The VMAT2 inhibitors valbenazine, tetrabenazine, and deutetrabenazine are compelling treatment options for patients that suffer from tardive dyskinesia when the benefit of discontinuing the neuroleptic medication that is causing TD does not outweigh the risk. The ability of these drugs to block VMAT2 and decrease the breakdown of dopamine in the brain allows clinicians to treat tardive dyskinesia without causing detrimental repercussions to a patient's underlying condition.

Various clinical trials have shown that VMAT2 inhibitors can help patients reduce their symptoms of TD. This is important in helping patients increase the dopamine levels in the basal ganglia and reduce the amount of uncoordinated involuntary movements.

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