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Drug Class Update: Vesicular Monoamine Transporter 2 Inhibitors

Date of Review: October 2023

Date of Last Review: January 2018
Dates of Literature Search: 11/07/2017 – 06/20/2023

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
To review new evidence for the three vesicular monoamine transporter 2 (VMAT2) inhibitors, valbenazine, deutetrabenazine, and tetrabenazine, approved by the United States (U.S.) Food and Drug Administration (FDA) for the treatment of adults with tardive dyskinesia (TD) or Huntington's chorea (HC) due to Huntington's Disease (HD). Evaluate evidence for the safety and efficacy for tetrabenazine compendial supported off-label uses in people with TD or Tourette syndrome.

Plain Language Summary:
- This review looks at new evidence published since the last Pharmacy and Therapeutics Committee last reviewed the medicines used to treat tardive dyskinesia and repetitive movement disorders associated with Huntington's disease (also called chorea). Evidence for the use of these medicines for unusual muscle movement disorders such as Tourette syndrome will also be reviewed.
- People with tardive dyskinesia have unusual and uncontrolled muscle movements of the mouth, tongue, body, arms and legs. Examples of these movements are lip smacking, repeated chewing movements of the mouth and jaw, toe and finger tapping, and frequent eye blinking. Medicines used to treat nausea or mental health conditions (for example, bipolar disorder and schizophrenia) are known to cause tardive dyskinesia in some people.
- Two medicines, valbenazine (INGREZZA) and deutetrabenazine (AUSTEDO; AUSTEDO XR), are approved by the Food and Drug Administration to treat tardive dyskinesia. These medicines have been available in the United States since 2017.
- Huntington's Disease causes nerve cells in the brain to break down. This affects the body, mind and emotions. Symptoms include: trouble making decisions, memory lapses, mood swings, trouble sleeping, and fatigue. Huntington's disease is passed on in families, so if parents have the condition, their children will have a 50-50 chance of also having Huntington's disease. Genetic testing helps confirm if someone has Huntington's disease. Huntington's chorea are sudden, uncontrolled movements in the face, arms, and legs in people who have Huntington's disease. These irregular movements can make it difficult to eat, swallow, or speak.
- There are no medicines that help with all the symptoms of Huntington's disease. Two medicines, tetrabenazine (XENAZINE) and deutetrabenazine (AUSTEDO; AUSTEDO XR), are approved by the Food and Drug Administration to help treat Huntington's chorea.
- Tourette syndrome causes people to have tics. Tics are sudden twitches, movements, or sounds that people make repeatedly. Tetrabenazine (XENAZINE) has been used to manage tics associated with Tourette syndrome and tardive dyskinesia. The limited evidence supporting the use of tetrabenazine in these

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conditions is based on individual patient reports and poorly conducted studies at risk for error. Studies with better quality looked at deutetrabenazine and valbenazine for helping to lessen tics associated with Tourette syndrome, and these studies did not show benefit from either medicine, but did show an increase in side effects.

- Valbenazine, tetrabenazine and deutetrabenazine can cause dizziness and drowsiness, so people should avoid activities requiring mental alertness such as operating a motor vehicle or hazardous machinery until they know how this drug makes them feel. Deutetrabenazine and tetrabenazine can increase the risk of depression and suicidal thoughts and behavior in people with Huntington disease. Close observation of patients for the emergence or worsening of depression or unusual changes in behavior should accompany the use of these medicines.
- Providers must explain to the Oregon Health Plan (OHP) why someone needs valbenazine, deutetrabenazine or tetrabenazine before the OHP fee-for-service program will pay for it. This process is called prior authorization.

Research Questions:

1. Do the VMAT2 inhibitors, valbenazine, deutetrabenazine, and tetrabenazine, differ in efficacy when use to treat patients with TD or HC?
2. Do the VMAT2 inhibitors differ in adverse events or tolerability when used for the treatment patients with TD or HC?
3. What is the evidence for the safety and efficacy of tetrabenazine in non-FDA approved, compendial indications such as Tourette syndrome or TD?
4. Are there subgroups of patients with TD or HC based on demographic characteristics (i.e., age, gender, race, ethnicity, comorbidities, disease duration or severity) in which one VMAT2 inhibitor may be associated with reduced effectiveness or greater harm than the other VMAT2 inhibitors used to manage these conditions?

Conclusions:

- Two high-quality systematic reviews were identified that evaluated the safety and efficacy of VMAT2 inhibitors in TD[1] or Tourette syndrome[2] since this drug class was last reviewed in January 2018. Three high-quality guidelines for management of TD associated with schizophrenia treatment[3,4] and treatment of HC[5] were identified.
- No head-to-head trials with VMAT2 inhibitors that evaluated comparative safety and efficacy in patients with TD or HC were identified. Therefore, there is insufficient evidence to broadly compare the VMAT2 inhibitors in terms of efficacy and safety in patients with TD or HC, or more specifically in populations based on age, gender, race or ethnicity.
- Evidence for the off-label use of tetrabenazine in managing tics associated with Tourette syndrome is of very low-quality from one retrospective, single-arm, open-label study in a small number of patients (n=17)[6] and another small, retrospective, open-label study (n=77).[7] Two randomized controlled trials (RCTs) evaluated the efficacy of deutetrabenazine in patients with Tourette syndrome; however, neither of these studies met the primary endpoint of change in the Yale Global Tic Severity Scale (YGTSS) from baseline over 8 to 12 weeks (see **Table 4**).[8,9]
- Currently, there are 3 FDA-approved medications to manage Tourette syndrome: pimozide, haloperidol, and aripiprazole; however, extrapyramidal side effects limit their use.[10] The 2019 American Academy of Neurology (AAN) guidance provides recommendations for treatment of tics in people with Tourette syndrome.[11] Due to insufficient evidence, no recommendations were made regarding the use of VMAT2 inhibitors in Tourette syndrome.[11] Recommendations based on moderate- to low-quality evidence were issued regarding the safety and efficacy of 2 alpha-adrenergic agonists (clonidine and guanfacine), antipsychotics, and topiramate in Tourette syndrome.[11]
- A 2018 Cochrane review evaluated evidence for therapies to treat TD.[1] This review found that the use of valbenazine may be effective in relieving the symptoms of TD.[1] One study found moderate-quality evidence of benefit for valbenazine compared with placebo (relative risk [RR] 0.63, 95% confidence interval [CI] 0.46 to 0.86, n=92).[1] However, due to the small sample size of the study, the certainty of these effects is unclear.[1]

- A 2022 meta-analysis evaluated evidence for the efficacy of VMAT2 inhibitors in treating chronic tic disorders including Tourette syndrome.[2] Five short-term RCTs compared valbenazine (n=3) or deutetrabenazine (n=2) with placebo in alleviating chronic tic disorders over 6 to 12 weeks.[2] No RCTs were identified to evaluate the safety and efficacy of tetrabenazine in chronic tic disorders. The change in tic symptom severity, as measured by the YGTSS, was not significantly different between valbenazine or deutetrabenazine and placebo (N = 583; mean difference [MD] = −0.71; 95% confidence interval [CI], −1.93 to 0.50; p=0.24; I^2 = 0%; high-quality evidence).[2] Participants taking valbenazine or deutetrabenazine were more likely to discontinue the study early for any reason than participants taking placebo (N = 626; odds ratio [OR] = 1.90; 95% CI, 1.14 to 3.18; p=0.01; I^2 = 3.2%; low-quality evidence and N = 626; OR = 2.67; 95% CI, 1.21 to 5.92; p=0.01; I^2 = 0%; moderate-quality evidence, respectively).[2]
- The American Psychiatric Association (APA) published updated guidance for schizophrenia treatment in 2020.[3] APA recommends that patients who have moderate to severe or disabling TD associated with antipsychotic therapy be treated with a VMAT2 inhibitor (strong recommendation; moderate-quality evidence).[3] In general, deutetrabenazine or valbenazine is preferred over tetrabenazine because there is more evidence to support their use.[3]
- In 2023 the Department of Veterans Affairs and the Department of Defense (VA/DoD) updated 2021 guidance for management of schizophrenia.[4] The clinical practice guideline was developed after a systematic review of recent evidence.[4] The guideline was revised to include a recommendation that suggests a trial of a VMAT 2 inhibitor for the treatment of tardive dyskinesia for individuals with schizophrenia and tardive dyskinesia (weak recommendation).[4] The Work Group's confidence in the quality of the evidence was low.[4]
- In 2019 the European Huntington's Disease Network (EHDN) commissioned an international task force to provide global evidence-based recommendations for treatment of HD.[5] Tetrabenazine is a first-line treatment for HC unless the patient suffers from poorly managed depression or suicidal thoughts (Grade A: high-quality evidence).[5]
- Valbenazine is appropriate in patients with hepatic dysfunction. Dosing adjustments for patients with moderate to severe hepatic impairment are included in the labeling.[12] In contrast, deutetrabenazine and tetrabenazine are contraindicated in patients with any hepatic impairment.[13,14] Patients who require doses of tetrabenazine greater than 50 mg per day should be first tested and genotyped to determine if they are poor metabolizers or extensive metabolizers by their ability to express the drug metabolizing enzyme, CYP2D6.[14] There is insufficient pediatric data for the use of VMAT2 inhibitors in this population, although tetrabenazine has been used off-label in children with Tourette syndrome.[15]
- A new extended-release formulation of deutetrabenazine (AUSTEDO XR) received FDA approval February 2023.[16] This formulation is taken once daily with or without food, unlike the immediate-release formulation, which must be taken twice daily with food.[16]
- In August 2023, the FDA approved an expanded indication for valbenazine (INGREZZA) to include chorea associated with HD.[12] Approval was based on results from a double-blind, placebo-controlled, phase 3 RCT (KINECT-HD) which evaluated the safety and efficacy of valbenazine in managing HC.[17] The primary endpoint was a least-squares mean (LSM) change in Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMC) score from baseline to week 12.[17] Least-squares mean changes in the UHDRS TMC score over 12 weeks were –4.6 for valbenazine and –1.4 for placebo (LSM mean difference = –3.2, 95% CI –4.4 to –2.0; p<0·0001).[17] The most commonly reported treatment-emergent adverse event was somnolence (ten [16%] with valbenazine, two [3%] with placebo).[17] No suicidal behaviour or worsening of suicidal ideation was reported in participants treated with valbenazine. [17] However due to the potential risk of depression in this population, the medication now carries a black box warning regarding the risk of depression and suicidal ideatation in HC patients treated with valbenazine.[17]

Recommendations:

- After review of clinical evidence, no changes are recommended to the Preferred Drug List (PDL).
- Revise prior authorization criteria (PA) to include use of valbenazine in patients with HC and add a trial, contraindication, or hypersensitivity to alpha-adrenergic blockers, antipsychotics or topiramate before approving tetrabenazine to alleviate tics in people with Tourette syndrome.

- After discussion, the committee recommended removing the requirement for prescribing by a specialist and modifying the renewal criteria to state the patient has experienced clinical improvement in AIMS score reduction.
- Review costs in the executive session.

Summary of Prior Reviews and Current Policy:

- The VMAT2 inhibitors were reviewed at the January 2018 Pharmacy and Therapeutics (P & T) committee meeting. Evidence for 2 new VMAT2 inhibitors, valbenazine and deutetrabenazine, which had recently received FDA approval for TD and management of HC, was presented.[18] Recommendations were based on low-quality quality evidence from small, short-term studies primarily funded by industry.[18] Prior to the approval of valbenazine and deutetrabenazine, the only FDA-approved VMAT2 inhibitor was tetrabenazine, which entered the market in 2008 for the use in patients with HC.[14]
- There was insufficient direct comparative evidence between VMAT2 inhibitors for efficacy outcomes in people with TD and HC or for treatment of dyskinesia associated with other conditions in adults (e.g., Parkinson's disease and Tourette syndrome).[18] There was insufficient evidence to evaluate long-term efficacy or safety of VMAT2 inhibitors and long-term data in larger populations were not available to determine the significance of harms observed in the short-term phase 3 trials.[18]
- After review of the evidence, the P & T Committee approved recommendations to create a new PDL class for VMAT2 inhibitors. Prior authorization criteria were implemented for valbenazine, deutetrabenazine, and tetrabenazine to ensure appropriate use (**Appendix 5**). All 3 medications are non-preferred (**Appendix 1**) on the Practitioner-Managed Prescription Drug Plan (PMPDP).
- A comparison of all FDA-approved VMAT2 inhibitors is presented in **Table 1**. In the first quarter of 2023, there was no utilization of valbenazine or deutetrabenazine in the Oregon Health Plan (OHP) Fee-for-Service (FFS) program. One OHP FFS member who had a claim for tetrabenazine.

Table 1. Vesicular Monoamine Transporter 2 Inhibitors

Generic Name (BRAND NAME)	FDA-Approved Indication(s)	Dosing Frequency	Drug Interactions/Dosing Recommendations	Warnings/Precautions
Valbenazine (INGREZZA)[12]	• TD in adults • HC in adults	Once daily with or without food	Concomitant CYP2D6 and CYP3A4 inhibitors: Maximum recommended dose is 40 mg once daily.	• Avoid co-administration with MAOIs and strong CYP3A4 inducers • Avoid use in congenital long QT syndrome or arrhythmias associated with prolonged QT interval • **Black Box Warning:** Depression and suicidality in people with HC
Deutetrabenazine (AUSTEDO, AUSTEDO XR)[13,16]	• TD in adults • HC in adults	IR: Two times daily with food XR: Once daily with or without food	Concomitant CYP2D6 inhibitors: Maximum recommended dose is 36 mg per day.	• Hepatic impairment • Avoid use in congenital long QT syndrome or arrhythmias associated with prolonged QT interval • Avoid co-administration with MAOIs or reserpine • **Black Box Warning:** Depression and suicidality in people with HC

Tetrabenazine (XENAZINE)[14]	• HC in adults **Off-label uses cited in Micromedex: Tardive dyskinesia and Tourette syndrome*	Three times daily with or without food	Concomitant CYP2D6 inhibitors: Maximum recommended dose is 50 mg per day.	• Hepatic impairment • Avoid co-administration with MAOIs or reserpine • Avoid use in congenital long QT syndrome or arrhythmias associated with prolonged QT interval • **Black Box Warning:** Depression and suicidality in people with HC
Abbreviations: FDA = Food and Drug Administration; HD = Huntington's chorea; IR = immediate release; MAOIs = monoamine oxidase inhibitors; TD = Tardive dyskinesia; XR = extended release				

Background:

Tardive Dyskinesia

Tardive dyskinesia is a delayed-onset, involuntary movement disorder which occurs in patients treated with dopamine receptor blocking agents (DRBAs), including anti-psychotic drugs (e.g., haloperidol, fluphenazine, risperidone), certain tricyclic antidepressants (e.g., amoxapine, amitriptyline), and some antiemetics (e.g., metoclopramide, prochlorperazine, promethazine).[19] Symptoms of TD include spontaneous, repetitive motions that commonly affect the muscles of the lower face and jaw and occur in an involuntary jerking or writhing fashion; patients may also have difficulty in walking, breathing and using their hands.[20] Tardive dyskinesia is one of many disorders thought to arise from dopamine receptor blockade, but it is distinct from other movement disorders such as Parkinson's disease, Tourette syndrome, and Huntington's chorea.[19] Genetic testing, neuroimaging, and other diagnostic work-ups may be necessary to rule out other causes of dyskinesia.[19] The Diagnostic and Statistical Manual of Mental Disorders definition for DRBA-induced TD requires exposure to a DRBA for at least 3 months (or 1 month in patients ≥ 60 years of age), presentation of symptoms within 4 weeks after withdrawal of an oral medication (or within 8 weeks of a depot medication), and persistence of symptoms for 1 month after discontinuation of offending agent.[21] Sudden withdrawal of a DRBA is suspected of triggering the development of TD, therefore, it is safer to taper the dosage of a DRBA before stopping it.[22]

The yearly rate of TD development in patients treated with DRBAs is approximately 2 to 5% with a 5-year incidence of approximately 20% to 25%.[23] It is estimated that 20 to 50% of patients treated with a DRBA will develop TD.[21] Neuroleptic-induced TD is higher in women, especially those middle-aged and elderly, where incidence rates may reach as much as 30% after 1 year of cumulative exposure.[19] TD may persist for years even after discontinuation of the DRBA, and in many cases, may not be reversible.[24] The debilitating effects of TD lead to increased mortality, decreased physical functioning, medication nonadherence, and a lower quality of life.[24]

Nonmodifiable patient-related and illness-related risk factors for TD include older age, female sex, White or Black race/ethnicity, longer illness duration, intellectual disability and brain damage, negative symptoms in schizophrenia, presence of mood disorders, cognitive symptoms in mood disorders, and genetic polymorphisms involving antipsychotic metabolism.[25] Modifiable comorbidity-related and treatment-related factors include diabetes, smoking, and alcohol and substance abuse, first generation antipsychotic versus second generation antipsychotic treatment, higher cumulative and current antipsychotic dose or antipsychotic plasma levels, early parkinsonian side effects, anticholinergic (e.g. benztropine) co-treatment, akathisia, and emergent dyskinesia.[25] If patients require continued treatment, then every effort should be made to switch to medication with lower risk of TD.[23] In the cases of antipsychotics, switching to clozapine or quetiapine may be considered because they have lower dopamine receptor affinity and relatively low risk of TD.[23] In cases of antiemetics, those without dopamine receptor blocking activity (e.g., ondansetron and trimethobenzamide) should be considered first-line.[23]

Tardive Dyskinesia Treatments: Valbenazine and Deutetrabenazine

Two VMAT2 inhibitors, valbenazine and deutetrabenazine, are FDA-approved treatments for TD.[12,13] The VMAT2 inhibitors interfere with dopamine uptake and storage in presynaptic vesicles, resulting in decreased dopamine available for release in the synapse, which opposes the increased dopaminergic activity caused by prolonged DRBA use.[20] Several characteristics differentiate these 2 medications, including drug interaction potential, dosing in special populations, and frequency of administration. Valbenazine metabolism can be affected by co-administration with strong CYP3A4 inhibitors, CYP3A4 inducers, and CYP2D6 inhibitors.[12] Drug interactions with deutetrabenazine have been identified only when co-administered with CYP2D6 inhibitors.[13] Patients with CYP2D6 genetic polymorphisms may demonstrate alterations in metabolism necessitating dose adjustments for both medications.[12,13] Another difference between these medications are recommendations for use in hepatic impairment. Valbenazine is appropriate in patients with hepatic dysfunction and dosing adjustments for patients with moderate to severe hepatic impairment are included in the labeling.[12] In contrast, deutetrabenazine is contraindicated in patients with any degree of hepatic impairment.[13] Electrocardiogram (ECG) monitoring is recommended for both agents in patients at risk for QT prolongation (i.e. congenital long QT syndrome or history of cardiac arrhythmias).[12,13] Finally, valbenazine is dosed once daily versus immediate-release deutetrabenazine, which is dosed twice daily.[12,13] A new, extended-release formulation of deutetrabenazine (AUSTEDO XR) received FDA approval February 2023.[16] This formulation is taken once daily with or without food, unlike the immediate-release formulation, which must be taken twice daily with food.[16]

Assessment of Tardive Dyskinesia

The assessment of TD is challenging due to the variability in research criteria and different rating scales.[26] An accepted standard has been the 12-item Abnormal Involuntary Movement Scale (AIMS), developed by the U.S. National Institute of Mental Health.[27] The current standard in research is for the AIMS to be used by remote video raters who are experts in movement disorders.[28] The first 7 items of the AIMS rate dyskinetic movements in 7 different muscle groups or body areas using a 5-point scale (0 = none, 1 = minimal/extreme normal, 2 = mild, 3 = moderate, 4 = severe), with a total score ranging from 0 to 28.[27] Four of the items measure facial, lip, jaw, and tongue movements, one item is assigned to the upper extremities, one item is assigned to the lower extremities, and one item is assigned to the trunk.[27] The last 5 items assess the patient's awareness of their abnormal movements, functional impact, and severity of symptoms (global impression) and dental health status.[27] Higher scores indicate increased severity of TD symptoms.[27] The AIMS evaluation is suggested at least every 6 months for people taking antipsychotics.[29] However, there is not a well-established guideline for interpretation of AIMS scores, and there is criticism that it lacks sensitivity due to its limited range and non-specificity for movement frequency.[29] There is no minimal clinically effective difference (MCID) established and evidence has not demonstrated that improvement in the AIMs score translates into improved function or quality of life for patients with TD.[29] However, the first 7 items of the AIMS assessment were used as the primary outcome measure for the VMAT2 inhibitors approved by the FDA for the management of TD.[28] A 2-point decrease in AIMs severity score maybe considered clinically important, based on data analysis of the pivotal phase 3 RCTs that led to FDA approval of valbenazine and deutetrabenazine.[30,31]

<u>Huntington's Disease</u>

Huntington's Disease is a rare, incurable, inherited neurodegenerative disorder characterized by progressive motor, cognitive, and psychiatric dysfunction.[32,33] Symptoms of HD usually appear in middle-aged adults. The average duration of survival after clinical onset of symptoms ranges from 10 to 20 years.[33] One of the most recognized motor signs is chorea, characterized by unwanted muscle contractions that progress over time and interfere with activities of daily living.[34] Huntington's disease results from a gene abnormality of an exon 1 CAG (cytosine-adenine-guanine) amino acid sequence trinucleotide expansion in the huntingtin (HTT) gene on chromosome 4.[32] The mutant huntingtin accumulates within brain cells, causing cell toxicity and neuron dysfunction throughout

the brain as the disease progresses.[34] Early stages of HD are often characterized by deficiencies in voluntary motor function while mid-stages are associated with more of an impact on motor coordination and function.[32] Optimization of quality of life is the focus of HD treatment through symptom management since there is no cure or treatment to slow progression for this disease.[32] The estimated incidence of HD is 3 to 7 per 100,000 people in western European populations.[35] This condition is less common in Japan, China, Finland and Africa.[35] In the OHP population (FFS and Coordinated Care Organizations), 148 people had claims for Huntington's disease from October 2021 to November 2022.

Management of Huntington's Chorea: Tetrabenazine and Deutetrabenazine

Tetrabenazine received FDA approval in 2008 for use in treating symptoms of chorea associated with HD and has been used off-label for severe TD; however, mixed efficacy and numerous safety concerns have limited its widespread use.[11] The use of tetrabenazine is limited by variable CYP2D6 metabolism which often results in dosing 3 times a day.[36] Tolerability is also an issue with tetrabenazine due to adverse effects such as sedation, fatigue, akathisia, anxiety and nausea.[36] In the pivotal phase 3 trial of tetrabenazine in patients with HC, the tetrabenazine group experienced more adverse effects compared to the placebo group, with 90% of patients reporting a TEAE compared to 70% in the placebo group.[37] Tetrabenazine labeling has a black box warning due to risk of suicide and depression associated with its use in patients with HD.[14] Prior to the approval of deutetrabenazine in 2017, the only treatment approved for chorea symptoms associated with HD was tetrabenazine. Deutetrabenazine is an isomer of tetrabenazine. The substitution of deuterium for hydrogen in the tetrabenazine molecule produces a longer drug half-life, less frequent daily dosing, and reduced metabolism variability of deutetrabenazine. Deutetrabenazine labeling also has a black box warning due to risk of suicide and depression associated with its use in patients with HD.[13] There are no head to head trials of tetrabenazine and deutetrabenazine to evaluate comparative safety and efficacy in patients with HC.

Symptom Assessment of Huntington's Disease

The severity of HC and functional impact is measured by the Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMS) and is the main endpoint used in many trials.[38] The UHDRS-TMS motor scale uses 106 questions to measure chorea, Parkinsonism, dystonia, eye movements, and other signs of HD.[39] There are 31 items that are graded 0 (not affected) to 4 (most severely affected).[39] There is limited evidence that a 1-point increase in the UHDRS-TMS, in patients in the early stages of HD, correlates with an approximately 10% loss of the likelihood of being able to work, manage finances, drive and supervise children.[39] In studies of patients with a diagnosis of HD, the mean annual change in patients UHDRS-TMS was 3.8 points.[39] The American Academy of Neurology (AAN) guidelines define the change in subscores of less than 1-point decrease in UHDRS as unimportant, 1 to less than 2-point decrease as modestly important, 2 to less than 3-point decrease as moderately important and more than a 3-point decrease as very important.[39]

The UHDRS total chorea score (UHDRS-TCS) is a subscore which rates facial, bucco-oral-lingual, trunk and extremity chorea. Standardized assessment of chorea based on the UHDRS-TCS subscore is determined by frequency and severity of chorea in 7 areas of the body by a scale of 0 to 28, with a higher number indicating worse disease.[39] This subscoring portion represents 23% of the overall UHDRS-TMS and is recommended for determining the impact of chorea symptoms over using the UHDRS-TMS.[38] The clinically important change for this endpoint has not been determined.[40]

Symptom Assessment Used for Both Tardive Dyskinesia and Huntington's disease

The patient's global impression of change (PGIC) is used to determine the patient's perspective on overall improvement in movement dysfunction.[41] This is a 1 to 7-point Likert scale with a score of 1 representing "very much improved" and a score of 7 suggesting "very much worse".[41] The clinical global impression of change (CGIC) is a clinician perspective of the severity of the patient's symptoms utilizing the same scale as the PGIC.[41] Limitations to the CGIC is the reliance on provider recall of patient symptoms.[41] The CGI-TD score is used to rate the overall change in tardive dyskinesia symptoms on a scale from 1 ("very much

improved") to 7 ("very much worse").[41] The 36-question short form (SF-36) quality of life assessment is also used with a higher score indicating an improved quality of life. A summary of outcome assessments for TD and HD are presented in **Appendix 3**.

Symptom Assessment of Tic Severity: Yale Global Tic Severity Scale

The YGTSS is a clinician-rated scale that measures tic severity and is commonly used as a primary outcome measure in RCTs.[42] The motor and phonic (i.e., coughing, throat clearing, grunting, blowing, squeaking) tics are rated separately on a 0 (none) to 5 (severe) scale across 5 dimensions: number, frequency, intensity, complexity, and interference.[42] The scores from each dimension (number, frequency, intensity, complexity, and interference) are summed to produce the Total Motor Tic score (range 0–25), the Total Phonic Tic score (range 0–25), and the combined Total Tic score (range 0–50).[42] The scale also includes a separate Impairment scale that reflects overall tic-related impairment (range 0–50).[42] Higher scores indicate more severe tics.[43] In 2021, a study evaluated 706 children and adolescents with Tourette syndrome to study the reliability of the YGTSS, and found that the YGTSS correlates well with the Clinical Global Impression Scale for tics.[44] The YGTSS may be insensitive to clinically meaningful tic reduction in patients with frequent severe symptoms while fluctuating excessively in response to small changes in the symptoms of those with mild phonic tics.[2] Tic severity is only captured during the past 7 days and tic-related impairment is not incorporated into the Total Tic Score and requires separate assessment.[2] Despite these limitations, the YGTSS remains the gold standard for assessing tics and has reliably demonstrated the efficacy of other pharmacological agents typically used in the treatment of TS, including FDA-approved medications.[2]

Off-label Uses for Tetrabenazine: Tardive Dyskinesia and Tourette Syndrome

Tardive Dyskinesia

Tetrabenazine is only FDA-approved for management of HC, but it has been used off-label to manage TD.[14],[15] Low-quality evidence from a limited number of patients enrolled in 2 single-arm, open-label trials suggests that tetrabenazine may decrease the frequency and severity of movements in adults with TD.[45,46] The first study, published in 1999, included 20 patients with refractory TD and assessed AIMS as an outcome measure.[45] In addition to TD, 45% of patients also showed mild evidence of parkinsonism, and 25% had akathisia at baseline.[45] Participants in this study were diagnosed with a psychiatric disorder or symptoms (unspecified psychosis, schizophrenia, bipolar disorder, agitation), gastrointestinal disorder, or organic brain disorder.[45] Use of the DRBA was stopped in all cases. Cessation of antipsychotic medications is often not practical in patients with chronic psychotic disorders due to the risk of relapse, and it may have confounded treatment results due to unmasking or worsening of existing TD.[45] The mean dose of tetrabenazine was 60 mg daily with a mean treatment duration of 20 weeks.[45] TD severity was assessed by a single-blinded investigator who rated videos using the standardized AIMS, both at baseline and at approximately 3 months after starting treatment.[45] Improvement on the motor section of the AIMS was demonstrated at the end of treatment versus baseline values ($p < 0.001$) and no patient had unchanged or worsened TD.[45] Eleven patients rated themselves as markedly improved, 6 as moderately improved, and 2 as mildly improved.[45] The most common adverse events were sedation and parkinsonism observed in 25% of patients enrolled in the study.[45]

The second study was a 1988 publication of case series that included 23 patients with TD who were treated with tetrabenazine.[46] The mean total dose of tetrabenazine was 91 mg daily; however, duration of therapy was not reported.[45] Severity of involuntary movements was evaluated in three regions (face/mouth/tongue, trunk, limbs) using a 5-point involuntary movement scale (0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe) and video recordings were made for each patient before and during treatment.[46] At baseline, 83% of patients has a severity score of 3 or 4 (moderate/severe).[46] After treatment with tetrabenazine 87% of patients noted improved involuntary movement scores of 1 or 2 (none/minimal).[46] Side effects were minimal and the most common events were drooling (9%) and parkinsonism with tremor (4%).[46]

Tourette Syndrome

The primary clinical features of Tourette syndrome are tics, which vary in their severity.[43] Tics are involuntary or semi-involuntary, sudden, brief, intermittent, repetitive movements (motor) or sounds (phonic) and often stereotypical.[43] Behavioral therapy is considered first-line therapy for Tourette syndrome.[43] Currently, there are 3 FDA-approved medications to manage this condition: pimozide, haloperidol and aripiprazole; however, extrapyramidal side effects limit their use.[10] Tetrabenazine has been studied in several low-quality studies as an alternative to conventional neuroleptics because it does not cause tardive dyskinesia. In a retrospective, open-label, single-arm study, of 217 patients with movement disorders, 17 adults with Tourette syndrome received tetrabenazine at a dose of 81 mg daily (range 37.5 to 100 mg).[6] All of these patients had responded poorly to prior treatment with haloperidol or developed therapy-limiting adverse effects.[6] Tetrabenazine showed moderate reduction in abnormal movements in 4 patients (6%) and fair response in 11 patients (65%).[6] The most frequently reported adverse events in all patients (n=217) were parkinsonism, depression and anxiety, but were not classified by type of movement disorder. In another retrospective, open-label study, 77 patients with Tourette syndrome (75.3% male), and a median age of 14 years, were treated with tetrabenazine for an average of 2 years.[7] The median dose of tetrabenazine was 50 mg daily (range: 6 to 125 mg).[7] Tetrabenazine showed a moderate to marked improvement in Tourette syndrome-related symptoms and functional improvement in 83% of patients.[7] Adverse events included drowsiness or fatigue (36%), nausea (10%), depression (9%), insomnia (8%), and parkinsonism (6.5%).[7] No RCTs have evaluated the safety and efficacy of tetrabenazine in Tourette syndrome. Two RCTs have been published which evaluate the efficacy of deutetrabenazine in patients with Tourette syndrome (see **Table 4**).[8,9] Neither of these studies met the primary endpoint of change in the YGTSS total tic severity score from baseline over 8 to 12 weeks.[8,9]

In 2019 the American Academy of Neurology (AAN) published practice guidance for treatment of tics in people with Tourette syndrome and chronic tic disorders.[11] Due to insufficient evidence, no recommendations were issued with respect to the use of VMAT2 inhibitors in managing tics associated with Tourette's syndrome. However, recommendations for the safety and efficacy of alpha-adrenergic agonists (clonidine and guanfacine), antipsychotics and topiramate were provided in the guidance.[11] The recommendations and supporting evidence are summarized below.

- *Physicians should prescribe alpha-adrenergic agonists for the treatment of tics when the benefits of treatment outweigh the risks (Level B recommendation).*[11]
  People with tics receiving clonidine are probably more likely than those receiving placebo to have reduced tic severity, and people with tics receiving guanfacine are possibly more likely than those receiving placebo to have reduced tic severity, with the majority of trials conducted in children.[11] In children with tics and comorbid attention-deficient/hyperactivity disorder (ADHD), clonidine and guanfacine have demonstrated beneficial effects on both tics and ADHD symptoms.[11] The effect size of clonidine and guanfacine on tics appears larger in children with tics and ADHD compared with individuals with tics without a comorbid diagnosis of ADHD.[11] Relative to placebo, clonidine is probably associated with higher rates of sedation, and guanfacine is probably associated with higher rates of drowsiness.[11]

- *Physicians may prescribe antipsychotics for the treatment of tics when the benefits of treatment outweigh the risks (Level C recommendation).*[11]
  Haloperidol, risperidone, and aripiprazole are probably more likely than placebo to reduce tic severity, and pimozide, ziprasidone, and metoclopramide are possibly more likely than placebo to reduce tic severity.[11] There is insufficient evidence to determine the relative efficacy of these drugs.[11] Relative to placebo, the evidence demonstrates a higher risk of drug-induced movement disorders with haloperidol, pimozide, and risperidone, a higher risk of weight gain with risperidone and aripiprazole, a higher risk of somnolence with risperidone, aripiprazole, and tiapride, a higher risk of QT prolongation with pimozide, and a higher risk of elevated prolactin with haloperidol, pimozide, and metoclopramide.[11] Systematic reviews of trials and cohort studies demonstrate a higher risk of drug-induced movement disorders (including tardive dyskinesa, drug-induced parkinsonism, akathisia, acute dystonia, and tardive dystonia), weight gain, adverse metabolic side effects, prolactin increase, and QT prolongation with both first- and second-generation

antipsychotics across psychiatric and neurologic conditions.[11] The long-term use of metoclopramide is associated with tardive dyskinesia, resulting in a black box warning from the FDA.[11]

- *Physicians should prescribe topiramate for the treatment of tics when the benefits of treatment outweigh the risks (Level B recommendation).*[11] Topiramate is possibly more likely than placebo to reduce tic severity.[11] In patients with mild but troublesome tics who are not obtaining a satisfactory response or experience adverse effects from other treatments, topiramate may be a useful alternative. While generally well-tolerated at low doses (25–150 mg/day) it may cause adverse effects, including cognitive and language problems, somnolence, and weight loss, and may increase the risk of renal stones.[11]

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.
The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
Cochrane: Miscellaneous Treatments for Antipsychotic-Induced Tardive Dyskinesia
A 2018 Cochrane review updated previously published Cochrane reports with new evidence for therapies to treat TD.[1] Literature was searched through April 2017 for the efficacy of the many different types of medications used to treat TD; only one VAMT-2 inhibitor, valbenazine was included in the literature search.[1] Thirty-one RCTs of 24 interventions with 1278 participants met inclusion criteria; 22 of these trials provided new evidence for the 2018 update.[1] All participants were adults with chronic psychiatric disorders, (mostly schizophrenia) and antipsychotic-induced TD.[1] Studies were primarily of short duration (3 to 6 weeks) with small sample sizes (10 to 157 participants), and most studies (61%) were published prior to the year 2000.[1] Studies published after the year 2000 assessed melatonin, valbenazine, levetiracetam, and ginkgo biloba.[1] The Cochrane authors reported the overall risk of bias in these studies was unclear, mainly due to poor reporting of allocation concealment, generation of the sequence, and blinding.[1]

One study found moderate-quality evidence of a benefit for valbenazine in TD compared with placebo (RR 0.63, 95% CI 0.46 to 0.86, 1 RCT, n=92).[1] However, due to the small sample size, additional data from ongoing trials are needed to confirm these results.[1] Results for the remaining therapeutic interventions provided insufficient data due to low- to very low-quality of evidence in small studies.[1]

Efficacy and Tolerability of VMAT2 Inhibitors in the Treatment of Tic Disorders
A 2022 meta-analysis evaluated evidence for the efficacy of VMAT2 inhibitors in treating chronic tic disorders including Tourette syndrome.[2] Studies were included in the meta-analysis if they reported on a double-blinded RCT of VMAT2 inhibitors (valbenazine, deutetrabenazine, tetrabenazine) against placebo for the acute treatment (up to 12 weeks) of tic disorders in patients with Tourette syndrome as determined by formal diagnostic criteria.[2] No restrictions were made regarding age (children/adolescents or adults) or dosing design (fixed-dose or flexible-dose studies).[2] Literature was searched through October 2021 and 5

double blinded RCTs involving 8 comparisons of VMAT2 inhibitors against placebo met inclusion criteria.[2] The primary efficacy outcomes assessed change from baseline in tic symptom severity scores on the YGTSS.[2] Other outcomes in the systematic review included acceptability as measured by total study withdrawal and tolerability as measured by the number of study withdrawals due to adverse effects.[2]

Only one RCT was conducted in adults (age range, 18 to 64 years).[2] This study involved 124 participants with a mean age of 35 years. Of these, 80 were men (67%), and 107 self-identified as White (89%).[2] The study tested fixed doses of valbenazine against placebo for 8 weeks.[2] This study was rated at high risk of bias (RoB).[2] The other 4 RCTs were conducted in children/adolescents (age range, 6–17 years).[2] These pediatric studies involved 502 participants with a mean age of 11.9 years (2.6 year standard deviation); 81% (n=398) were male, and 87% (n=426) identified as White.[2] Two studies tested valbenazine and 2 studies evaluated deutetrabenazine against placebo in both fixed-dose and flexible-dose designs—one study of each dosing design for each of the two medications—for a median duration of 10 weeks (range, 6–12 weeks).[2] Three of the 4 trials were rated as low RoB and the other one as high RoB.[2] Only 2 RCTs were published. Data for the other 3 RCTs was obtained from clinicaltrials.gov. No RCTs were identified that evaluated the safety and efficacy of tetrabenazine in Tourette syndrome.

Change in tic symptom severity, as measured by the YGTSS, did not differ between valbenazine or deutetrabenazine and placebo (n = 583; 5 RCTs; MD = −0.71; 95% CI, −1.93 to 0.50; p=0.24; I^2 = 0%; high-quality evidence).[2] Subgroup testing did not identify differences between children/adolescents and adults (p = 0.37) nor between valbenazine and deutetrabenazine (p = 0.42).[2] Participants taking valbenazine and deutetrabenazine were more likely to dropout than those on placebo (n = 626; OR = 1.90; 95% CI, 1.14 to 3.18; p=0.01; I^2 = 3.2%; low-quality evidence).[2] Participants taking VMAT2 inhibitors were more likely to drop out as a result of adverse effects than those on placebo (N = 626; OR = 2.67; 95% CI, 1.21 to 5.92; p=0.01; I^2 = 0%; moderate-quality evidence).[2] This analysis suggests that valbenazine and deutetrabenazine are not associated with a clinically meaningful effect in the treatment of Tourette syndrome.[2] This study also demonstrates increased total dropout rates with valbenazine or deutetrabenazine versus placebo.[2] However, this effect was largely driven by considerably higher dropout rates in valbenazine comparisons, which was administered at 80 mg daily in a fixed-dose regimen or adopted flexible titration up to 80 mg daily.[2] In addition, the safety analyses were limited due to relatively small number of events across all 5 trials.[2] This meta-analysis only evaluates up to 12 weeks of VMAT2 inhibitor treatment, so long-term efficacy and safety data are needed.[2]

After review, 6 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[47-52]

New Guidelines:

High Quality Guidelines:

Tardive Dyskinesia

The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia

The APA published updated guidance for schizophrenia treatment in 2020.[3] The guidance was supported by an AHRQ systematic review published in 2017.[53] Most of the guideline is centered on pharmacotherapy and psychosocial interventions to manage schizophrenia. Management of adverse effects associated with antipsychotic medications is discussed in depth. APA recommends that patients who have moderate to severe or disabling TD associated with antipsychotic therapy be treated with a VMAT2 inhibitor (strong recommendation; moderate-quality evidence).[3] The guideline authors concluded that the available studies of valbenazine and deutetrabenazine are of good quality with good sample sizes.[3] However, the duration of the trials was relatively short, as little as 4–6 weeks in some studies. The long-term follow-up data are based only on open-label extension phases of these RCTs. Data on tetrabenazine have a higher RoB, smaller samples sizes, and inadequate blinding, yielding a low strength of research evidence.[3]

In general, deutetrabenazine or valbenazine are preferred over tetrabenazine because of the greater evidence-base supporting their use.[3] In addition, tetrabenazine has a shorter half-life and greater rates of associated depression when used in the treatment of patients with Huntington's disease. In initial studies of tetrabenazine in patients with Huntington's disease, significant rates of depression were noted as well as concerns about suicidal ideas and behaviors. However, in studies of deutetrabenazine and valbenazine in patients with TD, there were no apparent increases in depression or suicidal ideation either in the randomized portions of the clinical trials or in longer open-label extension periods.[3] However, depression or suicidal ideation could occur during treatment for TD, and clinicians will want to be alert to this possibility.[3] The harms of treatment with VMAT2 inhibitors include sedation associated with deutetrabenazine and valbenazine; and extrapyramidal effects, akathisia, insomnia, anxiety, nausea, and falls with associated with tetrabenazine.[3]

Department of Veterans Affairs and the Department of Defense: Management Schizophrenia
In 2023 the VA/DoD updated 2021 guidance for management of schizophrenia.[4] The clinical practice guideline was developed after a systematic review of recent evidence.[4] The guideline was revised to include a recommendation that suggests a trial of a VMAT 2 inhibitor for the treatment of tardive dyskinesia for individuals with schizophrenia and tardive dyskinesia (weak recommendation).[4] The Work Group's confidence in the quality of the evidence was low.[4] The body of evidence had some limitations, including a small sample size, risk of bias, and study imprecision and indirectness.[4] The benefits of improving AIMS scores in individuals with schizophrenia or schizoaffective disorder and TD outweighed the potential harms, which were minimal.[4] Patient values and preferences were similar because most patients who have distressing TD would likely want treatment with an agent that is generally well tolerated.[4]

Huntington's Disease
European Huntington's Disease Network Guidelines for the Treatment of Huntington's Disease
In 2019, the EHDN commissioned an international task force to provide global evidence-based recommendations for treatment of HD.[5] Drug treatment should be considered if chorea causes the patient distress or discomfort.[5] Monotherapy to treat chorea is preferred because combination therapy (tetrabenazine with a neuroleptic) increases the risk of adverse effects and may complicate the management of non-motor symptoms.[5] Two recommendations are included in the guidance for management of HC.

- Tetrabenazine is a first-line treatment for HC unless the patient suffers from poorly managed depression or suicidal ideation (Grade A recommendation: high-quality evidence).[5]
- Second generation neuroleptics (e.g., olanzapine, risperidone, pimozide, and aripiprazole) are first-line treatments for chorea when patients have associated personality and/or behavioral or psychotic disorders (Grade C recommendation: low-quality evidence).[5]

After review, 4 guidelines were excluded due to poor quality.[54-57]

New Formulations or Indications:

- The manufacturer of valbenazine (INGREZZA) added a 60 mg capsule to the available dosing formulations of valbenazine in April 2021.[12] This was added to the other 2 strengths: 40 mg and 80 mg. Depending on response and tolerability, a dose of 40 mg or 60 mg once daily may be considered in some patients.[12] In patients with moderate or severe hepatic impairment or known CYP2D6 poor metabolizers, the maximum recommended dose is 40 mg per day.[12]
- A new extended-release formulation of deutetrabenazine (AUSTEDO XR) received FDA approval February 2023.[16] This formulation is taken once daily with or without food, unlike the immediate-release formulation, which must be taken twice daily with food.[16] The extended-release tablets are available

in 3 strengths: 6 mg, 12 mg, and 24 mg.[16] The approval for the extended-release formulation was based on clinical trials with the immediate-release tablets of deutetrabenazine.[16]

- In August 2023, the FDA approved an expanded indication for valbenazine (INGREZZA) to include chorea associated with HD.[12] A total of 125 adults with genetically confirmed HD were enrolled in a double-blind, placebo-controlled, phase 3 RCT (KINECT-HD) to evaluate the safety and efficacy of valbenazine in managing HC.[17] The primary endpoint was a least-squares mean (LSM) change in UHDRS-TMC score from baseline to week 12.[17] Least-squares mean changes in the UHDRS TMC score over 12 weeks were –4.6 for valbenazine and –1.4 for placebo (LSM mean difference = –3.2, 95% CI –4.4 to –2.0; p<0·0001).[17] The most commonly reported treatment-emergent adverse event was somnolence (ten [16%] with valbenazine, two [3%] with placebo).[17] No clinically important changes in vital signs, electrocardiograms, or laboratory tests were found.[17] No suicidal behaviour or worsening of suicidal ideation was reported in participants treated with valbenazine.[17]

New FDA Safety Alerts:

Table 3. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Valbenazine	INGREZZA	7/2019	Warnings and Precautions	Parkinsonism: Cases of Parkinson-like symptoms, some of which were severe, have been reported in the post marketing period. Reduce the dose or discontinue INGREZZA treatment in patients who develop clinically significant Parkinson-like signs or symptoms.[12]

Randomized Controlled Trials:

A total of 24 citations were manually reviewed from the initial literature search. After further review, 22 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 2 trials are summarized in the table below. The Full abstracts are included in **Appendix 2**.

Table 4. Description of Randomized Clinical Trials

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Jankovic J., et al.[9] ARTISTS 1 Phase 2/3 DB, MC, PC, PG, RCT	1. Deutetrabenazine immediate release 3 mg PO BID titrated over 7 weeks up to 48 mg per day per weight-based dosing protocol and assessment of CYP2D6 impairment (n=59). Maintenance phase lasted 5 weeks. vs. 2. Placebo PO BID (n=60).	- Ages 6 to 16 yo - TS - Weight ≥20 kg - YGTSS-TTS score ≥ 20 points	Change in the YGTSS-TTS score from baseline to week 12	LSM change in YGTSS-TTS score at 12 weeks 1. -9.1 2. -8.4 Difference: -0.7 95% CI -4.1 to 2.8 P=0.69	-Medical history was comparable between the deutetrabenazine and placebo groups, except for the proportion of patients with psychiatric disorders (81% vs 67%), including ADHD (63% vs 52%). -Method of titrating matching placebo doses to maintain blinding not described. - Trial duration may have been too short to identify changes in tic severity associated with TS, as

					drug was titrated upward over 7 weeks with a 5-week maintenance period at the final dose.
Coffey, B., et al[8] ARTISTS 2 Phase 3, DB, MC, PC, PG, RCT	1. Low dose: Deutetrabenazine immediate release 36 mg/day titrated over 4 weeks to the target dose followed by a 4-week maintenance phase (n=54). vs. 2. High dose: Deutetrabenazine 48 mg/day titrated over 4 weeks to the target dose followed by a 4-week maintenance phase (n=52). vs. 3. Matching placebo titrated according to protocol (n=52).	-Ages 6 to 16 yo -TS - Weight >20 kg -YGTSS-TTS score ≥ 20 points	Primary: Change in the YGTSS-TTS score from baseline to week 8 for high-dose deutetrabenazine compared with placebo Secondary: Change in the YGTSS-TTS score from baseline to week 8 for low-dose deutetrabenazine compared with placebo	Primary: LSM change in YGTSS-TTS score at 8 weeks for high-dose deutetrabenazine 1. -7.8 3. -7.0 Difference: -0.8 95% CI -3.9 to 2.3 P=0.60 Secondary: LSM change in YGTSS-TTS score at 8 weeks for low-dose deutetrabenazine 2. -5.9 3. -7.0 Difference: 1.1 95% CI -1.9 to 4.2 P=0.47	-Prior TS treatment was more common in the deutetrabenazine high-dose group (83%) and low-dose group (83%) than the placebo group (63%). -Trial duration may have been too short to identify changes in tic severity associated with TS. -Majority of participants were non-Hispanic, White children, which limits generalizability to more diverse populations.
Abbreviations: BID = twice daily; CI = Confidence Interval; DB = double blind; LSM = least squares mean; MC = multi-center; PC = placebo controlled; PG = parallel group; PO = orally; RCT = randomized controlled trial; TEAEs = treatment emergent adverse events; TD = tardive dyskinesia; TS = Tourette syndrome; YGTSS-TTS = Yale Global Tic Severity Scale-Total Tic Score; yo = years old					

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
deutetrabenazine	AUSTEDO 12MG START TITR(WK1-4)	ORAL	TAB DS PK	N
deutetrabenazine	AUSTEDO TD TITRATN PK (WK 1-2)	ORAL	TAB DS PK	N
deutetrabenazine	AUSTEDO XR	ORAL	TAB ER 24H	N
deutetrabenazine	AUSTEDO	ORAL	TABLET	N
tetrabenazine	TETRABENAZINE	ORAL	TABLET	N
tetrabenazine	XENAZINE	ORAL	TABLET	N
valbenazine tosylate	INGREZZA INITIATION PACK	ORAL	CAP DS PK	N
valbenazine tosylate	INGREZZA	ORAL	CAPSULE	N

Appendix 2: Abstracts of Comparative Clinical Trials

Safety and Efficacy of Flexible-Dose Deutetrabenazine in Children and Adolescents With Tourette Syndrome: A Randomized Clinical Trial[9]

Objective: To examine whether deutetrabenazine is effective and safe for the treatment of Tourette syndrome in children and adolescents.
Design, setting, and participants: This phase 2/3, randomized, double-masked, placebo-controlled, parallel-group, dose-titration study included children and adolescents (aged 6-16 years) with Tourette syndrome with active tics causing distress or impairment (i.e., Yale Global Tic Severity Scale-Total Tic Score [YGTSS-TTS] ≥20). The trial was conducted over 12 weeks, with 1 week of follow-up from February 2018 to November 2019 at 36 centers in the United States, Canada, Denmark, Russia, Serbia, and Spain. Data analysis was conducted from January 31 to April 22, 2020.
Intervention: Patients were randomized (1:1) to receive deutetrabenazine or placebo, titrated during 7 weeks to an optimal level, followed by a 5-week maintenance period. The maximum total daily deutetrabenazine dose was 48 mg/d.
Main outcomes and measures: The primary efficacy end point was change from baseline to week 12 in YGTSS-TTS. Key secondary end points included changes in Tourette Syndrome-Clinical Global Impression, Tourette Syndrome-Patient Global Impression of Impact, and Child and Adolescent Gilles de la Tourette Syndrome-Quality of Life Activities of Daily Living subscale score. Safety was assessed based on treatment-emergent adverse events, vital signs, questionnaires, and laboratory parameters.
Results: A total of 119 participants were randomized to deutetrabenazine (59 participants; mean [SD] age, 11.5 [2.5] years; 53 [90%] boys; 49 [83%] White; 3 [5%] Black) and placebo (60 participants; mean [SD] age, 11.5 [2.6] years; 51 [85%] boys; 53 [88%] White; 3 [5%] Black). At week 12, the difference in YGTSS-TTS score was not significant between deutetrabenazine and placebo (least squares mean difference, -0.7; 95% CI, -4.1 to 2.8; P = .69; Cohen d, -0.07). There were no nominally significant differences between groups for key secondary end points. Treatment-emergent adverse events were reported for 38 patients (66%) and 33 patients (56%) receiving deutetrabenazine and placebo, respectively, and were generally mild or moderate.
Conclusions and relevance: In this study of deutetrabenazine in children and adolescents with Tourette syndrome, the primary efficacy end point was not met. No new safety signals were identified. These results may be informative for future studies of treatments for tics in Tourette syndrome.
Trial registration: ClinicalTrials.gov Identifier: NCT03452943.

Efficacy and Safety of Fixed-Dose Deutetrabenazine in Children and Adolescents for Tics Associated With Tourette Syndrome: A Randomized Clinical Trial.[8]

Importance: Tourette syndrome is a neurodevelopmental disorder characterized by childhood onset of motor and phonic tics, often accompanied by behavioral and psychiatric comorbidities. Deutetrabenazine is a vesicular monoamine transporter 2 inhibitor approved in the US for the treatment of chorea associated with Huntington disease and tardive dyskinesia.
Objective: To report results of the ARTISTS 2 (Alternatives for Reducing Tics in Tourette Syndrome 2) study examining deutetrabenazine for treatment of Tourette syndrome.
Design, setting, and participants: This phase 3, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study was conducted over 8 weeks with a 1-week follow-up (June 21, 2018, to December 9, 2019). Children and adolescents aged 6 to 16 years with a diagnosis of Tourette syndrome and active tics causing distress or impairment were enrolled in the study. Children were recruited from 52 sites in 10 countries. Data were analyzed from February 4 to April 22, 2020.
Interventions: Participants were randomized (1:1:1) to low-dose deutetrabenazine (up to 36 mg/d), high-dose deutetrabenazine (up to 48 mg/d), or a matching placebo, which were titrated over 4 weeks to the target dose followed by a 4-week maintenance period.

Main outcomes and measures: The primary efficacy end point was change from baseline to week 8 in the Yale Global Tic Severity Scale-Total Tic Score (YGTSS-TTS) for high-dose deutetrabenazine. Key secondary end points included changes in YGTSS-TTS for low-dose deutetrabenazine, Tourette Syndrome Clinical Global Impression score, Tourette Syndrome Patient Global Impression of Impact score, and Child and Adolescent Gilles de la Tourette Syndrome-Quality of Life Activities of Daily Living subscale score. Safety assessments included incidence of treatment-emergent adverse events, laboratory parameters, vital signs, and questionnaires.
Results: The study included 158 children and adolescents (mean [SD] age, 11.7 [2.6] years). A total of 119 participants (75%) were boys; 7 (4%), Asian; 1 (1%), Black; 32 (20%), Hispanic; 4 (3%), Native American; 135 (85%), White; 2 (1%), multiracial; 9 (6%), other race; and 1 (0.6%), of unknown ethnic origin. Fifty-two participants were randomized to the high-dose deutetrabenazine group, 54 to the low-dose deutetrabenazine group, and 52 to the placebo group. Baseline characteristics for participants were similar between groups. Of the total 158 participants, 64 (41%) were aged 6 to 11 years, and 94 (59%) were aged 12 to 16 years at baseline. Mean time since Tourette syndrome diagnosis was 3.3 (2.8) years, and mean baseline YGTSS-TTS was 33.8 (6.6) points. At week 8, the difference in YGTSS-TTS was not significant between the high-dose deutetrabenazine and placebo groups (least-squares mean difference, -0.8 points; 95% CI, -3.9 to 2.3 points; P = .60; Cohen d, -0.11). There were no nominally significant differences between groups for key secondary end points. Treatment-emergent adverse events were reported for 34 participants (65%) treated with high-dose deutetrabenazine, 24 (44%) treated with low-dose deutetrabenazine, and 25 (49%) treated with placebo and were generally mild or moderate.
Conclusions and relevance: In this fixed-dose randomized clinical trial of deutetrabenazine in children and adolescents with Tourette syndrome, the primary efficacy end point was not met. No new safety signals were identified.
Trial registration: ClinicalTrials.gov Identifier: NCT03571256.

Appendix 3: Tardive Dyskinesia and Huntington's Disease Assessments

Table 1. Outcome Assessment Measurements for Tardive Dyskinesia and Chorea Symptoms[18]

Outcome	Description	Minimal Clinically Significant Change	Clinical Relevance
Tardive Dyskinesia			
Abnormal Involuntary Movement Scale **(AIMS)**	Validated 12-item scale with a total score ranging from 0-28 in the first 7 items. Higher scores indicate increased severity of TD symptoms. Amplitude and quality of movement are evaluated using a numeric severity scale ranging from zero (no abnormalities) to four (severe movements).	Not defined	Interpretation of scores has not been well-established and may lack sensitivity due to limited range and non-specificity for movement frequency.
Huntington's disease			
Unified Huntington's disease Rating Scale Total Motor Score **(UHDRS-TMS)**	Scoring ranges from 0-106 points with higher scores indicating greater disability.	Not defined	Limited evidence suggests a 1-point increase, in patients in the early stages of HD, correlates with an approximately 10% loss of the likelihood of being able to work, manage finances, drive and supervise children.
Unified Huntington's disease Rating Scale– total chorea movement subscore **(UHDRS-TCS)**	Subscore is based on frequency and severity of chorea in 7 areas of the body on a scale of 0-28, with a higher number indicating worse disease.	Not defined	Most studies show a difference of 2-4 points which represents a 7-14% change.
Tardive Dyskinesia and Huntington's Disease			
Patients' Global Impression of Change (**PGIC)** score	PGIC measures patient's perspective on overall improvement in movement dysfunction. This is a 1–7-point Likert scale with a score of 1 representing "very much improved" and a score of 7 suggesting "very much worse".	Not defined	Patient's perception of symptom improvement is critical in justifying use of therapy.
Clinical Global Impression of Change **(CGIC)**	CGIC is a clinician perspective of the severity of the patient's symptoms using a 1–7-point Likert scale with a score of 1 representing "very much improved" and a score of 7 suggesting "very much worse".	Not defined	Limitations of this assessment tool is reliance on provider recall to determine symptom improvement.
Clinical Global Impression – Tardive Dyskinesia **(CGI-TD)**	CGI-TD is a modified version of the CGIC utilizing the same Likert scale with a focus on tardive dyskinesia symptoms.	Not defined	Limitations of this assessment tool is reliance on provider recall to determine symptom improvement.
Abbreviations: HD = Huntington's disease; TD = tardive dyskinesia			

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) 1996 to June Week 2 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to June 19, 2023

1	Tardive Dyskinesia/ or Dyskinesia, Drug-Induced/	4157
2	Chorea/ or Huntington Disease/	12178
3	exp Tourette Syndrome/	3241
4	exp Tetrabenazine/	624
5	valbenazine.mp.	104
6	Vesicular Monoamine Transport Proteins/ or deutetrabenazine.mp.	1241
7	1 or 2 or 3	19427
8	4 or 5 or 6	1567
9	7 and 8	250
10	limit 9 to (english language and humans and yr="2018 -Current")	122
11	limit 10 to (clinical trial, all or clinical trial, phase iii or clinical trial or comparative study or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	24

Appendix 5: Prior Authorization Criteria

Vesicular Monoamine Transporter 2 (VMAT2) Inhibitors

Goal(s):
- Promote safe use of VMAT2 inhibitors in adult patients.
- Promote use that is consistent with medical evidence.

Length of Authorization:
- Initial: Up to 2 months
- Renewal: Up to 12 months

Requires PA:
- All VMAT2 inhibitors

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code. Go to #2	
2. Is the request for continuation of vesicular monoamine transporter 2 (VMAT2) inhibitor therapy previously approved by FFS criteria (patient has completed 3-month trial)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the request for a patient 18 years or older with a diagnosis of chorea as a result of Huntington's disease?	**Yes:** Go to #4	**No:** Go to #6

Approval Criteria		
4. Does the patient have a baseline total maximal chorea score of 8 or higher as assessed by the Unified Huntington's disease Rating Scale–Total Chorea Movement subscore **(**UHDRS-TCS**)**?	**Yes:** Go to #5 Document baseline score: _____	**No:** Pass to RPh. Deny; medical appropriateness
5. Has it been determined that the patient does not have uncontrolled depression or at risk of violent or suicidal behavior?	**Yes:** Approve for 3 months.	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the request for deutetrabenazine or valbenazine in a patient 18 years or older with a diagnosis of moderate to severe tardive dyskinesia?	**Yes:** Approve for 3 months. Document baseline modified AIMS* score: _____	**No:** Go to #7
7. Is the request for tetrabenazine in a patient with tics associated with Tourette syndrome?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Has the patient tried and failed an adequate trial of at least **2** of the following guideline directed medications[1]: a. Clonidine or guanfacine OR b. Topiramate OR c. One of the following antipsychotics: pimozide, aripiprazole or risperidone? OR Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity to the guideline directed medications?	**Yes:** Approve for 3 months Document baseline Yale Global Tic Severity Score (YGTSS) Total Tic Severity (range 0 to 50)_____	**No:** Pass to RPh. Deny; medical appropriateness

* The dyskinesia score for the modified Abnormal Involuntary Movement Scale (AIMS) for numbers 1-7

1. Pringsheim T, Okun MS, Müller-Vahl K, et al. Practice guideline recommendations summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders. *Neurology.* 2019;92(19):896-906.

Renewal Criteria		
1. Is the request for a renewal of valbenazine or deutetrabenazine in a patient with tardive dyskinesia?	**Yes:** Go to #2	**No:** Go to #3
2. Has the patient been taking the requested VMAT2 inhibitor for >3 months and has there been documented evidence of clinical improvement by a reduction in AIMS dyskinesia score from baseline?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for valbenazine, tetrabenazine or deutetrabenazine in a patient with chorea as a result of Huntington's disease?	**Yes:** Go to #4	**No**: Go to #6
4. Has the patient been taking the requested VMAT2 inhibitor for >2 months and has there been documented evidence of improvement in total maximal chorea score as assessed by the Unified Huntington's disease Rating Scale–Total Chorea Movement subscore **(**UHDRS-TCS**),** of at least 2 points from baseline?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has it been determined that the mental status of the patient is stable and there is no indication of uncontrolled depression or risk of violent or suicidal behavior?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the request for tetrabenazine in a patient with tics associated with Tourette syndrome?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Has the patient been taking tetrabenazine for >2 months and has there been documented evidence of reduced tic severity from baseline as assessed by the Yale Global Tic Severity Score (YGTSS) Total Tic Score (range 0-50) ?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 10/23 (DM); 1/2018(KS)
Implementation: 11/1/23; 3/1/18