



Movement Disorders Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
deutetrabenazine (Austedo®) ¹	Teva	Treatment of chorea associated with Huntington's disease; Treatment of tardive dyskinesia
tetrabenazine (Xenazine®) ²	generic, Lundbeck	Treatment of chorea associated with Huntington's disease
valbenazine (Ingrezza®) ³	Neurocrine Biosciences	Treatment of tardive dyskinesia

OVERVIEW

There are various types of movement disorders, including parkinsonism, tremor, dystonia, dyskinesia, tics, chorea, and other involuntary movements. This therapeutic class review focuses on medications for the treatment of chorea associated with Huntington's disease and tardive dyskinesia.

Huntington's Disease (HD)

Chorea, an abnormal involuntary twisting or writhing movement, is a characteristic feature of Huntington's disease (HD), a rare and fatal genetic disorder resulting in neurodegeneration of the brain, which affects over 35,000 people in the United States (US).^{4,5} As chorea becomes more severe, it can interfere with patients' function. As the disease progresses, chorea is replaced by dystonia and parkinsonism. Chorea affects approximately 90% of people with HD. It often develops early, gradually worsens, and plateaus in late stages. Chorea symptoms may be aggravated by stress and anxiety.

No therapy currently exists to delay the onset of symptoms or prevent the progression of the disease; however, symptomatic treatment may improve the quality of life and prevent complications. Tetrabenazine (Xenazine), a vesicular monoamine transporter 2 (VMAT2) inhibitor, was the first agent approved (2008) by the Food and Drug Administration (FDA) to treat chorea associated with HD.⁶ A deuterated formulation allowing once-daily dosing, deutetrabenazine (Austedo), was approved to treat chorea associated with HD in 2017. Other therapeutic options that are used but lack FDA approval for this use (off-label) include dopamine-depleting agents (e.g., reserpine) and dopamine-receptor antagonists (neuroleptics). However, long-term use of these drugs may carry a high risk of adverse effects. Neuroleptics could also worsen other features of the disease, such as bradykinesia and rigidity, and may lead to further functional decline.

The 2012 American Academy of Neurology (AAN) guidelines recommend tetrabenazine (up to 100 mg per day), amantadine, or riluzole for chorea associated with HD.⁷ The AAN states that neuroleptics may be reasonable options given the behavioral concerns; reserpine and deutetrabenazine are not addressed in the AAN guidelines. The AAN advises that the decision by physicians and patients whether chorea requires pharmacologic treatment should consider matters such as mood disturbance, cognitive decline, drug adverse effects, and polypharmacy risks. These guidelines were reaffirmed in 2015, but an update is in progress.

Tardive Dyskinesia (TD)

Tardive dyskinesia (TD) consists of involuntary movements of the tongue, lips, face, trunk, and extremities that occur in patients treated with medications with dopamine antagonist properties.⁸ It

may consist of movements classified as bradykinesia and/or hyperkinesia. Dopamine transporter dysfunction and chronic central dopamine blockade have been hypothesized to play a role in the development of TD, although multiple other pathophysiologic mechanisms have been proposed.

TD differs from acute movement disorders, often referred to as extrapyramidal symptoms (EPS), which commonly occur in patients treated with dopamine antagonists.⁹ EPS most commonly occurs early in therapy and during dose increases. These acute movement disorders include akathisia, acute dystonia, parkinsonism, and other hyperkinetic dyskinesias. TD generally occurs after long-term treatment with a dopamine antagonizing medication, but the timeline of TD onset varies extensively. Once a patient develops TD, it may be irreversible.

The epidemiology of TD is not well defined, as prevalence evaluations are often done in differing settings. TD can occur in all ages, but the risk increases with age. The incidence after 3 months of dopamine antagonist treatment was determined to be 5.9% in patients aged 7 to 21 years in one study compared to a finding of 29% in elderly patients in another evaluation. Factors associated with a greater vulnerability to TD include age > 55 years; female gender; white or African race/ethnicity; past or current akathisia, acute dystonic reactions, or clinically significant parkinsonism; and presence of a mood disorder, central nervous system injury, or intellectual disability.¹⁰ The differing subtypes of TD vary markedly in frequency.¹¹ For instance, orofacial dyskinesia is more common while tardive dystonia is relatively rare.

While TD is reported most often with first generation antipsychotics (conventional or typical antipsychotics), it can also be seen with second generation antipsychotics (atypical antipsychotics), but the incidence varies more widely with this class. TD occurs at a rate of approximately 4% to 8% per year in adult patients treated with a first generation antipsychotics, which appears to be about 3 times the rate that has been observed with second generation antipsychotics.¹² TD may also occur with other agents that have dopamine antagonist properties, including metoclopramide, droperidol, select antidepressants, and select antihistamines.¹³ Due to treatment options, patients with schizophrenia, mood disorders, and other neuropsychiatric disorders are particularly vulnerable to TD development due to long-term dopamine antagonist use. If possible, a potential offending agent should be switched to an alternative with a lower TD risk, the dose should be reduced, and the duration of use should be limited to prevent TD onset. However, this is not always possible for patients treated with dopamine antagonists.

Valbenazine (Ingrezza) was the first FDA-approved medication for the treatment of TD and deutetrabenazine (Austedo) received this indication shortly after. Early TD symptoms were previously treated by reducing the dose or discontinuing the medication causing the symptoms as described above. In 2013, the AAN published guidelines on the treatment of tardive syndromes.¹⁴ Potential interventions assessed included discontinuing dopamine receptor antagonists, switching from first generation to second generation antipsychotics, pharmacological medications, chemodeneration with botulinum toxin (BoNT), and surgical therapy, such as pallidal deep brain stimulation (DBS). Data were insufficient to support or refute TD treatment by discontinuation of a dopamine receptor antagonist, switching from first generation to second generation antipsychotics, BoNT, or DBS therapies. Data were also insufficient on the use of pharmacological interventions except for the use of clonazepam and ginkgo biloba as short-term options, which were noted as probably effective in treating TD (Level B recommendation). These

guidelines were last reaffirmed in 2019. Deutetrabenazine and valbenazine have not been addressed in clinical practice guidelines from the AAN.

In 2020, the American Psychiatric Association (APA) updated their guidelines for the treatment of schizophrenia.¹⁵ They recommend routine assessment for TD in patients using antipsychotics. They recommend that patients who have moderate to severe or disabling TD related to antipsychotic therapy be treated with a reversible inhibitor of the vesicular monoamine transporter 2 (VMAT2), specifically deutetrabenazine, tetrabenazine, or valbenazine (1B). Patients with mild TD can also be considered for treatment with a VMAT2 inhibitor following an assessment of several factors, such as patient preference, impairment, and psychosocial functioning impact. They state that deutetrabenazine or valbenazine is preferred over tetrabenazine due to the data supporting their use (e.g., efficacy, safety, pharmacokinetic considerations). Other factors should also be considered when selecting which agent is most appropriate for a specific patient (e.g., hepatic impairment, renal impairment, metabolizer status, drug interactions).

PHARMACOLOGY^{16,17,18}

All 3 agents within this class are VMAT2 inhibitors. Via reversible inhibition at this transporter, these agents decrease uptake of monoamines (e.g., dopamine, norepinephrine, serotonin, histamine) into synaptic vesicles, thus depleting monoamines stores from nerve terminals.

The exact mechanism of deutetrabenazine (Austedo) and tetrabenazine (Xenazine) in the role of chorea treatment is unknown, but is thought to be related to the monoamine depletion. The exact mechanism by which deutetrabenazine and valbenazine (Ingrezza) exert their effects in the treatment of TD is unknown.

PHARMACOKINETICS^{19,20,21}

Drug	Food Effect	Tmax (hr)	Metabolism	Half-Life (hr)	Excretion (%)
deutetrabenazine (Austedo)	No effect on overall exposure; peak concentration increased by 50%	3–4 (metabolites)	Extensively metabolized to multiple metabolites, primarily α -HTBZ and β -HTBZ (both active)	9–10 (metabolites)	Primarily renal
tetrabenazine (Xenazine)	No effect on peak concentration or overall exposure	1–2 (metabolites)	Extensively metabolized to ≥ 19 metabolites, some active, including dihydrotetrabenazine (HTBZ)	5–12 (metabolites)	Urine: 75 Feces: 7–16
valbenazine (Ingrezza)	High-fat meal decreases peak concentration and overall exposure of parent drug; no effect on key metabolite	0.5–1	Extensively metabolized to primary metabolite, [+]- α -HTBZ, and other minor metabolites	15–22 (parent and primary metabolite)	Urine: 60 Feces: 30

Tmax = time to maximum serum concentration

CONTRAINDICATIONS/WARNINGS^{22,23,24}

Both deutetrabenazine (Austedo) and tetrabenazine (Xenazine) are contraindicated in patients who are actively suicidal or in patients with Huntington’s disease who have untreated or inadequately treated

depression. Both are also contraindicated in patients taking monoamine oxidase inhibitors (MAOIs), or taking reserpine. Neither agent should be used in combination with an MAOI or within a minimum of 14 days of discontinuing therapy with an MAOI. Likewise, at least 20 days should elapse after discontinuation of reserpine prior to starting therapy with tetrabenazine or deutetrabenazine. Both agents are also contraindicated in patients with hepatic impairment. Deutetrabenazine and tetrabenazine should not be used concomitantly or with valbenazine (Ingrezza).

Valbenazine is contraindicated in patients with hypersensitivity to it or any of product's components. Hypersensitivity reactions have included rash, urticaria, and reactions consistent with angioedema (e.g., swelling of the lips, face, and/or mouth).

Both deutetrabenazine and tetrabenazine carry a boxed warning for depression and suicidality as they may increase the risk of depression and suicidal thoughts and behavior in patients with HD. Prescribers should balance these risks with the clinical need to control chorea, and patients should be monitored for the emergence of worsening depression, behavior changes, and suicidality. These products should be used cautiously in patients with a history of depression or prior suicidal ideation or attempts and patients, including families and caregivers, should be informed of these risks.

Huntington's disease is a progressive disorder and VMAT2 inhibitors may worsen mood, cognition, rigidity, and functional capacity. Prescribers should periodically re-evaluate the need for deutetrabenazine and tetrabenazine by assessing clinical benefit and adverse effects. A dose decrease or temporary discontinuation may assist the provider in determining if a patient's symptoms are related to disease progression or a treatment-related adverse effect. In some patients, chorea may improve over time, decreasing the need for a VMAT2 inhibitor.

Prior to initiation with tetrabenazine, genotype should be tested to determine if the patient is a CYP2D6 poor, extensive, or intermediate metabolizer. A dose adjustment is required in poor metabolizers.

Neuroleptic malignant syndrome (NMS) has been associated with drugs that reduce dopaminergic transmission. While NMS has not been reported with deutetrabenazine, it has been reported in patients treated with tetrabenazine. Symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia. Management of NMS should include immediate discontinuation of the suspected offending agent(s) and symptomatic treatment and medical monitoring. NMS recurrence has been reported; patients should be monitored for recurrence if further therapy is needed following NMS recovery.

Patients treated with deutetrabenazine or tetrabenazine may be at increased risk for experiencing akathisia, agitation, and restlessness. Parkinsonism may also occur in patients treated with deutetrabenazine, tetrabenazine, or valbenazine; however, since rigidity is also seen with Huntington's disease, it may be difficult to distinguish between drug-induced effects of deutetrabenazine or tetrabenazine and the underlying disease. Signs and symptoms in reported cases have included bradykinesia, gait changes (which may lead to falls), and an emerging or worsening tremor. Most cases of parkinsonism with deutetrabenazine and valbenazine have occurred within the first 2 weeks after starting or increasing the dose. In reported cases, symptoms resolved following treatment discontinuation. If parkinsonism symptoms occur, a dose reduction is recommended for both deutetrabenazine and valbenazine and a dose reduction should be considered in patients using

tetrabenazine. Discontinuation is another recommended option for those taking valbenazine and is recommended as a consideration for those taking deutetrabenazine or tetrabenazine.

Deutetrabenazine and tetrabenazine may cause sedation and somnolence. Valbenazine also carries a warning for somnolence. Patients using these agents should not perform activities requiring mental alertness to maintain safety (e.g., operating heavy machinery, driving a car) until they know how the drug will affect them. Sedation is the most common dose-limiting adverse effect of tetrabenazine.

Deutetrabenazine, tetrabenazine, and valbenazine may lead to a clinically relevant QT prolongation in some patients, particularly those who are CYP2D6 poor metabolizers or are also taking a strong CYP2D6 inhibitor. Dose reductions may be required. Strong CYP3A4 inhibitors may also increase the risk in patients taking valbenazine. Avoid use of tetrabenazine in these patient populations, and all 3 agents in this class should be avoided in patients with a history of cardiac arrhythmias or long QT syndrome. Use of tetrabenazine should also be avoided with other medications known to prolong the QT interval, including select antipsychotics, select antibiotics, and Class IA or III antiarrhythmic medications. **When administered in the recommended dosage range, the clinical impact of deutetrabenazine on QT prolongation is not clinically significant.** Dose adjustments are required in patients taking valbenazine and a concomitant strong CYP3A4 inhibitor and may be required with concomitant use of strong CYP2D6 inhibitors in those who are poor CYP2D6 metabolizers. The QT interval should be assessed prior to any valbenazine dose increases in patients at an increased risk of a prolonged QT interval.

Serum prolactin levels were not evaluated in the deutetrabenazine studies; however, 4- to 5-fold increases have been reported with tetrabenazine. If hyperprolactinemia is suspected, appropriate laboratory testing should be performed in patients treated with either agent. Discontinuation should be considered in the presence of hyperprolactinemia.

Deutetrabenazine, tetrabenazine, and their metabolites may accumulate in melanin-containing tissues, including the eyes. While ophthalmologic exams were not included in clinical studies, ophthalmologic toxicities cannot be ruled out; clinical relevance of melanin accumulation is unknown. Prescribers should be aware of the potential for effects on the eyes with long-term therapy.

Tetrabenazine also carries a warning for hypotension and orthostatic hypotension; tetrabenazine-induced postural hypotension has occurred in clinical trials.

Dysphagia is a component of HD; however, drugs associated with reduced dopaminergic transmission may also cause esophageal dysmotility and dysphagia, which could lead to aspiration pneumonia. Thus, tetrabenazine also carries a warning for dysphagia and dysphagia has been reported in clinical trials of tetrabenazine.

DRUG INTERACTIONS^{25,26,27}

Agents within this class should not be used concomitantly.

Concomitant use of strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine, bupropion) has been shown to increase the systemic exposure to the major active metabolites of deutetrabenazine (Austedo), tetrabenazine (Xenazine), and valbenazine (Ingrezza). Dosage of deutetrabenazine, tetrabenazine, **and valbenazine** should be adjusted when used concomitantly with strong CYP2D6

inhibitors. Similarly, a dose reduction of valbenazine is recommended in patients who are known CYP2D6 poor metabolizers.

Concomitant use of valbenazine with a strong CYP3A4 inhibitor (e.g., itraconazole, ketoconazole, clarithromycin) requires a valbenazine dose reduction due to the risk of increased exposure-related adverse reactions. Similarly, concomitant use of valbenazine with a strong CYP3A4 inducer (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) is not recommended due to reduced exposure and efficacy.

As reserpine binds irreversibly to VMAT2, concomitant use is contraindicated with 2 of the 3 VMAT2 inhibitors in this class: deutetrabenazine and tetrabenazine. Prescribers should wait for chorea to re-emerge prior to administering deutetrabenazine or tetrabenazine to avoid overdose and depletion of serotonin and norepinephrine in the central nervous system. At least 20 days should elapse after reserpine discontinuation prior to initiation of deutetrabenazine or tetrabenazine therapy.

Use of deutetrabenazine or tetrabenazine is contraindicated in patients using MAOIs. Neither agent should be used within 14 days of MAOI discontinuation. Concomitant use of MAOIs with valbenazine may increase the concentration of monoamines in the synapse, potentially leading to adverse effects (e.g., serotonin syndrome) or attenuate treatment; concomitant use should be avoided.

Concomitant use of alcohol or other sedating drugs (e.g., central nervous system [CNS] depressants) may have additive effects and can worsen sedation and somnolence with deutetrabenazine and tetrabenazine. Likewise, the risk for parkinsonism, NMS, and akathisia may be increased when 1 of these agents is used concomitantly with other dopamine antagonists.

Use of other agents, including select antipsychotics, select antibiotics, and Class IA or III antiarrhythmic medications, that may prolong the QT interval should be avoided with tetrabenazine as described in the warnings above.

Concomitant use of valbenazine with digoxin may increase digoxin levels due to inhibition of intestinal P-glycoprotein (P-gp). A dosage adjustment of digoxin may be needed.

ADVERSE EFFECTS^{28,29,30}

Drug	Akathisia	Anxiety	Depression	Fall	Fatigue	Insomnia	Nausea	Parkinsonism	Sedation/ Somnolence	Upper Respiratory Tract Infection
deutetrabenazine (Austedo) for chorea, n=45 (placebo, n=45)	4 (2)	4 (2)	4 (0)	nr	9 (4)	7 (4)	nr	nr	11 (4)	nr
deutetrabenazine (Austedo) for TD, n=279 (placebo, n=131)	2 (1)	nr	2 (1)	nr	nr	4 (1)	nr	nr	nr	nr
tetrabenazine (Xenazine), n=54 (placebo, n=30)	19 (0)	15 (3)	19 (0)	15 (13)	22 (13)	22 (0)	13 (7)	9 (0)	31 (3)	11 (7)
valbenazine (Ingrezza) n=262 (placebo, n=183)	2.7 (0.5)	reported	nr	4.1* (2.2)	10.9 [†] (4.2)	reported	2.3 (2.1)	nr	10.9 [†] (4.2)	reported

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for placebo group are reported in parentheses. nr = not reported.

* Includes falls, gait disturbance, dizziness, and balance disorders

† Reported as somnolence, fatigue, and sedation

Other adverse effects with an incidence \geq 4% reported in clinical trials with deutetrabenazine and more frequently than with placebo include (deutetrabenazine incidence versus placebo, respectively) diarrhea (9% versus 0%), dry mouth (9% versus 7%), urinary tract infection (7% versus 2%), anxiety (4% versus 2%), constipation (4% versus 2%), nasopharyngitis (4% versus 2%), and confusion (4% versus 2%). The most common adverse effect leading to dose reduction in clinical trials with deutetrabenazine for Huntington's chorea was dizziness (4%) and agitation led to discontinuation in 2% of patients treated with deutetrabenazine. A reduction of dose was needed in 4% of deutetrabenazine-treated patients with TD compared to 2% of placebo-treated patients. Suicidality was reported in 2% of patients treated with deutetrabenazine for Huntington's chorea compared to no patients treated with placebo.

Other adverse effects with an incidence \geq 4% reported in clinical trials with tetrabenazine include (tetrabenazine incidence versus placebo, respectively) irritability (9% versus 3%), decreased appetite (4% versus 0%), obsessive reaction (4% versus 0%), balance difficulty (9% versus 0%), dizziness (4% versus 0%), dysarthria (4% versus 0%), dysphagia (4% versus 3%), unsteady gait (4% versus 0%), headache (4% versus 3%), vomiting (6% versus 3%), laceration (6% versus 0%), ecchymosis (6% versus 0%), shortness of breath (4% versus 0%), bronchitis (4% versus 0%), and dysuria (4% versus 0%). In addition, any extrapyramidal event (bradykinesia, parkinsonism, extrapyramidal disorder, hypertonia) was reported in 33% of patients receiving tetrabenazine compared to 0 patients receiving placebo. Postmarketing adverse effects reported with tetrabenazine include tremor, confusion, worsening aggression, pneumonia, hyperhidrosis, and skin rash.

Other adverse reactions reported with valbenazine with an incidence $\geq 2\%$ and more frequently than with placebo include (valbenazine incidence versus placebo, respectively) anticholinergic effects (5.4% versus 4.9%), headache (3.4% versus 2.7%), vomiting (2.6% versus 0.6%), nausea (2.3% versus 2.1%), and arthralgia (2.3% versus 0.5%). Other adverse reactions reported in at least 1% of patients taking valbenazine and more frequently than placebo include increased blood glucose, increased weight, drooling, dyskinesia, extrapyramidal symptoms (non-akathisia), increased prolactin, increased alkaline phosphatase, and increased bilirubin. Notably, the latter 2 laboratory abnormalities suggest a potential risk for cholestasis. Hypersensitivity reactions have also been reported.

Postmarketing cases of parkinsonism have been reported with both deutetrabenazine and valbenazine.

SPECIAL POPULATIONS^{31,32,33}

Pediatrics

Safety and effectiveness of any agent in this class have not been established in pediatric patients.

Geriatrics

There are insufficient data to determine whether patients over 65 years of age respond to deutetrabenazine (Austedo) differently from younger subjects. Likewise, the pharmacokinetics of tetrabenazine (Xenazine) have not been formally evaluated in geriatric patients.

In 3 of the randomized, placebo-controlled clinical trials of valbenazine (Ingrezza), 16% of the population included patients that were ≥ 65 years old. Results were similar in patients older than 65 years when compared to younger adults. No dose adjustment is recommended due to age.

Pregnancy

There are no data on the developmental risk associated with the use of deutetrabenazine in pregnant women; however, in animal studies, tetrabenazine use during pregnancy was associated with an increased risk of stillbirths and postnatal offspring mortality. Previously, tetrabenazine was assigned Pregnancy Category C, but its labeling has been updated in compliance with the Pregnancy and Lactation Labeling Rule (PLLR); there are no adequate and well-controlled studies in pregnant women.

Data are too limited on the use of valbenazine in pregnant women to inform of the drug-related risk. Pregnant women should be advised of the potential harm to a fetus.

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of deutetrabenazine, tetrabenazine, and their primary metabolites has not been formally studied. Based on the available data with tetrabenazine, there is a large increase in exposure to its active metabolites in patients with hepatic impairment; however, the full clinical impact of this exposure is unknown. Deutetrabenazine and tetrabenazine are contraindicated in patients with hepatic impairment.

A dose reduction of valbenazine is recommended in patients with moderate or severe hepatic impairment (Child Pugh score of 7 to 15) due to higher exposure in this population compared to patients with normal hepatic function.

Renal Impairment

No clinical studies have been conducted to assess the effect of renal impairment on the pharmacokinetics of deutetrabenazine. There are no dosing recommendations for patients with renal impairment treated with tetrabenazine.

A dosage adjustment of valbenazine is not needed in patients with mild, moderate, or severe renal impairment.

Poor CYP2D6 Metabolizers

Although not fully studied, it is expected that patients who are poor CYP2D6 metabolizers may have an increased exposure to the active metabolites of deutetrabenazine and tetrabenazine; therefore, the dosage of deutetrabenazine and tetrabenazine should be decreased in this population. Likewise, increased exposure is anticipated in CYP2D6 poor metabolizers using valbenazine; a dose reduction of valbenazine is recommended for patients who are known CYP2D6 poor metabolizers.

DOSAGES^{34,35,36}

Drug	Dosage	Available Strengths																		
deutetrabenazine (Austedo)	<p>Huntington's chorea: 6 mg once daily (in those not being switched from tetrabenazine), titrated at weekly intervals by 6 mg per day to a tolerated dose that reduces chorea (maximum dose, 48 mg/day)</p> <p>When switching from tetrabenazine, initiate deutetrabenazine 1 day after the last dose of tetrabenazine and use the following dosage conversion table</p> <table border="1" data-bbox="418 447 1133 877"> <thead> <tr> <th>Current tetrabenazine daily dosage</th> <th>Initial deutetrabenazine dose</th> </tr> </thead> <tbody> <tr> <td>12.5 mg</td> <td>6 mg once daily</td> </tr> <tr> <td>25 mg</td> <td>6 mg twice daily</td> </tr> <tr> <td>37.5 mg</td> <td>9 mg twice daily</td> </tr> <tr> <td>50 mg</td> <td>12 mg twice daily</td> </tr> <tr> <td>62.5 mg</td> <td>15 mg twice daily</td> </tr> <tr> <td>75 mg</td> <td>18 mg twice daily</td> </tr> <tr> <td>87.5 mg</td> <td>21 mg twice daily</td> </tr> <tr> <td>100 mg</td> <td>24 mg twice daily</td> </tr> </tbody> </table> <p>Tardive dyskinesia: 6 mg twice daily, titrated at weekly intervals by 6 mg per day to a tolerated dose that reduces dyskinesia (maximum dose, 48 mg/day)</p> <p>Administer total daily dosages of ≥ 12 mg in 2 divided doses; take with food; swallow whole</p> <p>Dosage of deutetrabenazine should be adjusted to no more than 18 mg as a maximum single dose and a maximum total daily dose of 36 mg in patients taking concomitant strong CYP2D6 inhibitors or CYP2D6 poor metabolizers</p> <p>Deutetrabenazine may be discontinued without tapering; if treatment is interrupted for > 1 week, treatment should be re-titrated when resumed; interruptions of < 1 week do not require retitration</p>	Current tetrabenazine daily dosage	Initial deutetrabenazine dose	12.5 mg	6 mg once daily	25 mg	6 mg twice daily	37.5 mg	9 mg twice daily	50 mg	12 mg twice daily	62.5 mg	15 mg twice daily	75 mg	18 mg twice daily	87.5 mg	21 mg twice daily	100 mg	24 mg twice daily	Tablets: 6 mg, 9 mg, 12 mg
Current tetrabenazine daily dosage	Initial deutetrabenazine dose																			
12.5 mg	6 mg once daily																			
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Dosages (continued)

Drug	Dosage	Available Strengths
tetrabenazine (Xenazine)	<p>Huntington's chorea: dosing should be individualized and titrated slowly over several weeks</p> <p>Dosing ≤ 50 mg/day: 12.5 mg once daily in the morning; after 1 week, increase to 25 mg/day, given as 12.5 mg twice daily; titrate up at weekly intervals by 12.5 mg/day to identify a tolerate dose that reduces chorea; doses of 37.5 to 50 mg should be divided into 3 doses; the maximum single dose is 25 mg</p> <p>Dosing > 50 mg/day: patients requiring dosing above 50 mg/day should be first evaluated for CYP2D6 metabolizer status; those qualifying for doses above 50 mg/day (intermediate to extensive CYP2D6 metabolizers) should be titrated slowly by 12.5 mg/day at weekly intervals; doses exceeding 50 mg/day should be given in 3 divided doses; the maximum daily dose is 100 mg and the maximum single dose is 37.5 mg</p> <p>Dosage of tetrabenazine should be adjusted to no more than 25 mg as a maximum single dose and a maximum total daily dose of 50 mg in patients taking concomitant strong CYP2D6 inhibitors or CYP2D6 poor metabolizers</p> <p>Tetrabenazine may be discontinued without tapering; re-emergence of chorea may occur within 12 to 18 hours following the last tetrabenazine dose; if treatment is interrupted for > 5 days, treatment should be re-titrated when resumed; interruptions of < 5 days does not require retitration</p>	Tablets: 12.5 mg (non-scored), 25 mg (scored)
valbenazine (Ingrezza)	<p>Tardive dyskinesia: 40 mg once daily with or without food; dose can be increased to 80 mg once daily after 1 week of treatment</p> <p>Moderate to severe hepatic impairment (Child-Pugh, 7 to 15), CYP2D6 poor metabolizer, or co-administered with a strong CYP2D6 inhibitor or strong CYP3A4 inhibitor: 40 mg once daily</p>	Capsules: 40 mg, 80 mg, 4-week Initiation Pack containing 7 x 40 mg capsules and 21 x 80 mg capsules

CLINICAL TRIALS

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials for FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Huntington's Chorea

deutetrabenazine (Austedo) versus placebo

FIRST-HD: The efficacy of deutetrabenazine was evaluated in a randomized, double-blind, placebo-controlled, multicenter trial.³⁷ The primary endpoint was the Total Chorea Score (TCS), 1 of the items on the Unified Huntington's Disease Rating Scale (UHDRS; chorea is rated from 0 to 4 for 7 different parts of the body with lower scores representing less chorea; range, 0 to 28). This trial enrolled 90 adults diagnosed with Huntington's disease and a baseline chorea score of 8 or higher. Subjects were ambulatory at enrollment and were randomized to receive deutetrabenazine (n=45) or placebo (n=45) in a double-blind fashion at over 30 treatment sites. The duration of treatment was 12 weeks, including an 8-week dose titration period and a 4-week maintenance period, followed by a 1-week washout. Deutetrabenazine or placebo was started at 6 mg per day and titrated upward, at weekly intervals, in 6 mg increments until satisfactory treatment of chorea was achieved, intolerable side effects occurred, or until a maximal dose of 48 mg per day was reached. The mean dose after titration was 40 mg per day. A total of 87 patients (mean age, 53.7 years; 40 women [44.4%]) completed the study. TCS for patients receiving deutetrabenazine improved by approximately 4.4 units from baseline to the maintenance period (average of week 9 and week 12), compared to approximately 1.9 units in the placebo group. The treatment effect of -2.5 units was statistically significant (95% confidence interval [CI], -3.7 to -1.3; $p < 0.0001$). Treatment success, as measured by the Patient Global Impression of Change (PGIC) and the Clinical Global Impression of Change (CGIC), occurred in 51% and 42% of those treated with deutetrabenazine, respectively, compared with 20% and 13% with placebo, respectively ($p = 0.02$ for both measures versus placebo). A statistically significant difference was also found in the mean 36-Item Short Form physical functioning subscale score (SF-36) ($p = 0.03$) but not in the Berg Balance Test ($p = 0.14$).

tetrabenazine (Xenazine) versus placebo

TETRA-HD: A multicenter, randomized, double-blind, placebo-controlled trial assessed the effectiveness and safety of tetrabenazine in ambulatory patients with chorea secondary to HD (n=84).^{38,39} The diagnosis of HD was based on family history, neurological exam, and genetic testing. Patients were randomized to tetrabenazine or placebo and treatment duration was 12 weeks, which included a 7-week dose titration period and a 5-week maintenance period followed by a 1-week washout. Tetrabenazine was initiated at 12.5 mg/day and was titrated by 12.5 mg/day in weekly increments to satisfactory control of chorea, intolerable adverse effects, or a maximum dose of 100 mg/day. The primary endpoint was the TCS, which declined by an estimated 5 units during the maintenance period (average of week 9 and week 12 scores versus baseline) compared to an estimated 1.5 units in the placebo group (difference, 3.5 units; 95% CI, -5.2 to -1.9; $p = 0.0001$). At the week 13 follow-up (following 1-week washout), the TCS of patients previously treated with tetrabenazine returned to baseline. An evaluation of physician-rated Clinical Global Impression (CGI) showed a statistical difference favoring tetrabenazine (treatment difference, 0.7; $p = 0.007$). Generally, there were no differences in measured functional capacity and cognition; however, a single functional measure (Part 4 of the UHDRS), a 25-item scale assessing the capacity for patients to perform certain activities of daily living, demonstrated a decrement for patients treated with tetrabenazine compared to placebo (statistically significant). An extension study of 80 weeks in 45 subjects tolerating tetrabenazine and electing to continue in this trial demonstrated maintained chorea improvement from baseline.⁴⁰

Tardive Dyskinesia

deutetrabenazine (Austedo) versus placebo

AIM-TD: A 12-week multicenter, randomized, double-blind, placebo-controlled trial assessed the efficacy and safety of deutetrabenazine for the treatment of TD (n=222).⁴¹ Ambulatory adults with TD caused by dopamine receptor antagonists use for at least 3 months (or ≥ 1 month in those ≥ 60 years) were randomized 1:1:1:1 to 12 mg deutetrabenazine, 24 mg deutetrabenazine, 36 mg deutetrabenazine, or placebo. The 12-week treatment period consisted of a 4-week dose escalation period and an 8-week maintenance period, which was then followed by a 1-week washout. At baseline, the population was 21 to 81 years old (mean, 57 years), 48% male, and 79% Caucasian. The primary endpoint was improvement in TD, as measured by a change from baseline in TD symptoms using the first 7 measures on the Abnormal Involuntary Movement Scale (AIMS; range, 0 to 28 with higher scores indicated greater severity). At 12 weeks, the least squares mean change from baseline in AIMS was -3.3 (standard error [SE], 0.42), -3.2 (SE, 0.45), and -2.1 (0.42) with deutetrabenazine 36 mg/day, 24 mg/day, and 12 mg/day compared to -1.4 (SE, 0.41) with placebo (12 mg difference, -0.7 [95% CI, -1.84 to 0.42]; 24 mg difference, -1.8 [95% CI, -3 to -0.63]; 36 mg difference, -1.9 [95% CI, -3.09 to -0.79]). Only the 36 mg/day dosing demonstrated superiority over placebo when adjusting for multiplicity.

ARM-TD: A 12-week multicenter, randomized, double-blind, placebo-controlled trial assessed the efficacy and safety of deutetrabenazine for the treatment of TD (n=113).⁴² Ambulatory adults with TD caused by dopamine receptor antagonist use for at least 3 months (or ≥ 1 month in those ≥ 60 years) were randomized to flexible-dose deutetrabenazine or placebo. Deutetrabenazine doses were started at 12 mg per day with increases allowed in 6 mg increments (maximum 48 mg/day) at 1-week intervals until satisfactory control of dyskinesia was achieved or until intolerable side effects occurred. The 12-week treatment period consisted of a 6-week dose titration period and a 6-week maintenance period, which was then followed by a 1-week washout. At baseline, the population was 25 to 75 years old (mean, 55 years), 48% male, and 70% Caucasian. The mean dose of deutetrabenazine after treatment was 38.3 mg/day. The primary endpoint was improvement in TD, as measured by a change from baseline in TD symptoms using the first 7 measures on the AIMS tool. At 12 weeks, the least squares mean change from baseline in AIMS was -3 (SE, 0.45) with deutetrabenazine and -1.6 (SE, 0.46) with placebo (difference, -1.4; 95% CI, -2.6 to -0.2; p=0.019).

valbenazine (Ingrezza) versus placebo

KINECT 3: A 6-week, phase 3, randomized, double-blind, placebo-controlled, parallel, fixed-dose study was performed for efficacy, safety, and tolerability of valbenazine for the treatment of TD (n=234). Patients with moderate to severe TD with stable schizophrenia, schizoaffective disorder, or a mood disorder were randomized 1:1:1 to receive valbenazine 40 mg, valbenazine 80 mg, or placebo once daily for 6 weeks.^{43,44} The primary endpoint was improvement in TD, as measured by a change from baseline in TD symptoms using the first 7 measures on the AIMS tool as assessed by central video raters in the intent-to-treat population (n=225). Mean baseline AIMS scores were 9.9, 9.7, and 10.4 in the placebo, valbenazine 40 mg, and valbenazine 80 mg groups, respectively. After 6 weeks of treatment, the change in AIMS score in the 80 mg treatment group was -3.2 and was -1.9 in the valbenazine 40 mg group compared to -0.1 with placebo (p \leq 0.001 for both active treatments versus placebo). Also at week 6, 23.8% of participants in the 40 mg/day group (p=0.02 versus placebo) and 40% of those in the 80 mg/day

group ($p < 0.001$ versus placebo) had an AIMS response, defined as a reduction $\geq 50\%$ from baseline in dyskinesia score, compared with 8.7% of those in the placebo group. No differences in Clinical Global Impression for TD (CGI-TD) score were found between valbenazine and placebo in the ITT population. No drug interactions with psychotropics medication were reported. Adverse effects were similar among groups. A long-term, open-label study aimed primarily to assess safety found valbenazine continued to be well-tolerated, and patients demonstrated persistent improvements in TD.⁴⁵

SUMMARY

All 3 agents within this class are vesicular monoamine transporter 2 (VMAT2) inhibitors used to treat select movement disorders in adults. Both deutetrabenazine (Austedo) and tetrabenazine (Xenazine) are approved for the treatment of chorea associated with Huntington's disease (HD). Due to its deuterated formulation, deutetrabenazine is dosed twice daily for doses ≥ 12 mg for HD, compared to tetrabenazine, which is dosed 2 or 3 times a day, depending on total daily dose. The optimal dose of each agent is determined individually for each patient based on reduction of chorea and patient tolerability; however, dose reductions are recommended in patients who are taking strong CYP2D6 inhibitors or are poor CYP2D6 metabolizers.

Both tetrabenazine and deutetrabenazine are contraindicated in patients who are actively suicidal or in patients with untreated or inadequately treated depression, with hepatic impairment, taking monoamine oxidase inhibitors (MAOIs), or taking reserpine. Similarly, both agents carry a boxed warning for depression and suicidality as they may increase the risk of depression and suicidal thoughts and behavior in patients with Huntington's disease. Other warnings are similar between the 2 agents. The types of adverse effects are similar between deutetrabenazine and tetrabenazine, although the incidence of adverse effects appears higher with tetrabenazine.

Deutetrabenazine and tetrabenazine have both demonstrated superiority over placebo but have not been compared head-to-head in controlled trials. The American Academy of Neurology (AAN) recommended tetrabenazine (up to 100 mg per day) and select medications off-label for chorea associated with HD in their 2012 guidelines. Deutetrabenazine has not been addressed in these clinical practice guidelines; however, an update to the guidelines is in progress.

Deutetrabenazine and valbenazine (Ingrezza) are the only FDA-approved medications for the treatment of tardive dyskinesia (TD). Early TD symptoms have been previously treated by reducing the dose or discontinuing the medication causing the symptoms. In 2013, the AAN published guidelines on the treatment of tardive syndromes, but deutetrabenazine and valbenazine have not been addressed by the AAN. In 2020, the American Psychiatric Association updated their guidelines for the treatment of schizophrenia. They recommend that patients who have moderate to severe or disabling TD related to antipsychotic therapy be treated with a reversible VMAT2 inhibitor (1B), stating deutetrabenazine or valbenazine are preferred over tetrabenazine due to the data supporting their use.

While valbenazine carries fewer warnings than the other 2 agents within this class, like deutetrabenazine and tetrabenazine, it has warnings for somnolence and QT prolongation. Adverse effects are similar to the other VMAT2 inhibitors in this class but, like deutetrabenazine, the incidence of the adverse effects appears lower with valbenazine compared to tetrabenazine. Valbenazine is dosed once daily and deutetrabenazine is dosed twice daily for TD. A dosage reduction is required in select patients using

these medications (e.g., hepatic impairment, hepatic metabolism status). Both agents have demonstrated superiority over placebo in key clinical trials, but they have not been compared to each other or to other treatment strategies for TD (e.g., short-term clonazepam, causative medication adjustment).

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