Therapeutic Class Overview
Movement Disorder Agents

INTRODUCTION

- Huntington disease (HD) is a progressive neurodegenerative disorder characterized by motor dysfunction, cognitive decline, and neuropsychiatric disturbances (*Coppen and Roos 2017*).
  - Motor dysfunction in HD may include involuntary movements (eg, chorea, dystonia, and tics) and voluntary movements (eg, bradykinesia, apraxia, and motor impersistence) (*Austedo dossier 2017, Coppen and Roos 2017*).
    - Choreic movements are rapid and unpredictable contractions of the facial muscles, trunk, and extremities which vary in frequency, intensity, and amplitude (*Austedo dossier 2017, Suchowersky 2018a*).
    - Dystonia is characterized by sustained or intermittent muscle contractions which lead to abnormal posture of the trunk and extremities. It is more commonly observed in advanced disease stages (*Coppen and Roos 2017*).
    - Motor function slowly deteriorates as HD progresses, and chorea may eventually be replaced by bradykinesia and parkinsonism in advanced stages of the disease (*Suchowersky 2018a, Suchowersky 2018b*).
- HD affects an estimated 1 in 7300 individuals (approximately 43,000 people) in the United States. It is a rare and fatal autosomal dominant genetic disorder associated with onset in early adulthood and death within 20 years of symptom onset (*Austedo dossier 2017, Austedo Food and Drug Administration [FDA] Summary Review 2017*).
- Tardive dyskinesia (TD) is an iatrogenic condition that results from the long-term use of dopamine receptor blocking agents (DRBAs), predominantly antipsychotics/neuroleptics (first generation antipsychotics [FGAs], also known as typical antipsychotics, as well as second-generation antipsychotics [SGAs], which are also known as atypical antipsychotics) and metoclopramide (*Rana et al 2013*).
  - While the pathophysiology of TD is not well-understood, the most prominent theory suggests chronic exposure to neuroleptics results in dopamine-2 (D2) receptor up-regulation with postsynaptic dopamine receptor supersensitivity (*Waln and Jankovic 2013*).
  - Prospective studies of patients treated with FGAs suggest that the annual incidence of TD is between 3 to 8%. With SGAs, the mean annual incidence is estimated at 2.1 to 4.2%. Although TD prevalence has been less studied with metoclopramide, the published data indicate a prevalence ranging from 1 to 10% (*Waln and Jankovic 2013*).
- TD is characterized by rapid, repetitive, stereotypic movements mostly involving the oral, buccal, and lingual area (*Muller et al 2015*). Movements may include tongue thrusting, lip smacking or pursing, grimacing and chewing movements, piano-playing finger movements, trunk and pelvic thrusting, flexion/extension of the ankles or toes, irregular respirations, and various vocalizations (*Rana et al 2013*).
- According to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV), TD develops during exposure to a DRBA for ≥ 3 months (or 1 month in patients ≥ 60 years of age) or within 4 weeks of withdrawal from an oral medication (or within 8 weeks of withdrawal from a depot medication). The disorder should persist for ≥ 1 month after discontinuation of an offending drug to qualify as TD (*Waln and Jankovic 2013*).
- The first step in the treatment of TD is to discontinue the offending agent via slow taper. Sudden withdrawal of the offending drug should be avoided, as symptoms of TD could worsen. In patients with psychiatric conditions which require continued use of a neuroleptic, switching from an FGA to an SGA should be considered. Quetiapine and clozapine are the preferred SGAs due to their low receptor occupancy and fast dissociation from D2 receptors (*Vijayakumar and Jankovic 2016*).
- Ingrezza (valbenazine), the first vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of TD, was FDA-approved on April 7, 2018. Prior to valbenazine's approval, Xenazine (tetrabenazine) and Austedo (deutetrabenazine) were FDA-approved for the treatment of Huntington's chorea in August 2008 and April 2017, respectively. Subsequently, deutetrabenazine received FDA approval for the treatment of TD in August 2017.
  - Deutetrabenazine is a chemically modified form of tetrabenazine with deuterium substituted for hydrogen at specific positions. Compared to tetrabenazine, deutetrabenazine reaches comparable systemic exposure with smaller doses, longer treatment intervals, and lower peak concentrations (*Austedo dossier 2017*, *Coppen and Roos 2017*).
    - While deutetrabenazine has been designated a new molecular entity and an orphan drug, it was approved through the 505(b)(2) pathway with tetrabenazine as the Reference Listed Drug (RLD) (*Austedo FDA Summary Review 2017*).

- Differences between valbenazine and deutetrabenazine include once-daily dosing (vs twice-daily dosing) and the absence of a boxed warning for depression and suicidality in patients with HD. Of note, valbenazine has not been studied in patients with HD.

- Medispan class: Psychotherapeutic and Neurological Agents – Misc.; Movement Disorder

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Austedo (deutetrabenazine)	-
Ingrezza (valbenazine)	-
Xenazine (tetrabenazine)	✔

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. FDA Approved Indications

Indication	Austedo (deutetrabenazine)	Ingrezza (valbenazine)	Xenazine (tetrabenazine)
Chorea associated with HD	✔		✔
Treatment of adults with TD	✔	✔	

(*Prescribing information: Austedo 2017, Ingrezza 2018, Xenazine 2017)*

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Huntington Disease (HD)

- The approval of deutetrabenazine was supported by the First-Time Use of Austedo in HD (First-HD) study conducted by the Huntington Study Group (HSG). The Phase 3, double-blind (DB), multicenter (MC), randomized controlled trial (RCT) compared deutetrabenazine with placebo for 12 weeks, followed by a 1-week washout in 90 adults with HD (*HSG 2016*).
  - The study included patients with a Unified Huntington's Disease Rating Scale (UHDRS) total maximal chorea (TMC) score ≥ 8 at baseline and a UHDRS total functional capacity score ≥ 5 at screening (TMC score ranges from 0 to 28, with higher scores indicating more severe chorea) (*Coppen and Roos 2017, Geschwind and Paras 2016*).
  - The primary endpoint was the change from baseline in UHDRS-TMC score.
    - The placebo-adjusted mean change from baseline in TMC with deutetrabenazine was -2.5 points (95% confidence interval [CI], -3.7 to -1.3; $p < 0.001$).
    - In the deutetrabenazine group, the mean TMC scores improved by -4.4 points from 12.1 (95% CI, 11.2 to 12.9) to 7.7 (95% CI, 6.5 to 8.9) over 12 weeks. In the placebo group, mean TMC scores improved by -1.9 points from 13.2 (95% CI, 12.2 to 14.3) to 11.3 (95% CI, 10.0 to 12.5).
  - Four secondary endpoints were assessed hierarchically in the following order: Patient Global Impression of Change (PGIC), Clinical Global Impression of Change (CGIC), 36-Item Short Form (SF-36) physical functioning subscale score, and Berg Balance Test (BBT). For the PGIC and CGIC, treatment success was defined as an answer of "much" or "very much" improved overall HD symptoms at week 12.
    - The proportion of patients who reported treatment success on the PGIC was 31.1% greater with deutetrabenazine than placebo ($p = 0.002$).
    - The proportion of clinicians who reported treatment success on the CGIC was 28.9% greater with deutetrabenazine than placebo ($p = 0.002$).
    - The placebo-adjusted improvement in the SF-36 physical functioning subscale was 4.34 points with deutetrabenazine ($p = 0.03$).
    - BBT improvement observed with deutetrabenazine did not achieve statistical significance over placebo ($p = 0.14$).
  - In the First-HD study, the incidence of overall, psychiatric, and nervous system adverse events (AEs) was similar between the deutetrabenazine and placebo groups.

  - While generally mild to moderate, AEs resulted in dose reductions for 3 patients (6.7%) in each group. Serious AEs resulted in drug suspension for 1 patient (2.2%) in each group.
  - Somnolence and diarrhea were reported more frequently with deutetrabenazine than with placebo.
- The Phase 3, open-label (OL), MC, long-term Alternatives for Reducing Chorea in HD (ARC-HD) study evaluated the safety and efficacy of deutetrabenazine in 112 patients in 2 cohorts (*Austedo dossier 2017, Frank et al 2017*).
  - The rollover cohort included 75 patients from the First-HD study who underwent washout of deutetrabenazine or placebo. The switch cohort included 37 patients previously on tetrabenazine who were switched overnight to deutetrabenazine at approximately half their previous tetrabenazine dose.
  - Patients in the switch cohort demonstrated improved TMC from baseline with deutetrabenazine 8 weeks following conversion (-2.0 points, $p < 0.001$). Improvements in TMC from baseline were also observed in the rollover cohort at week 2 (-1.9; $p < 0.0001$; n = 58) and maintained through week 28 (-4.4; $p = 0.0055$; n = 14). Common AEs included somnolence, falls, depression, and insomnia.
- A DB, RCT was conducted in 84 ambulatory patients with HD who received tetrabenazine at a maximum dose of 100 mg daily (n = 54) or placebo (n = 30) for 12 weeks. Tetrabenazine treatment resulted in a statistically significant reduction in chorea severity, measured as a change in the chorea score of the UHDRS, compared with placebo (5 unit reduction [tetrabenazine group] vs 1.5 unit reduction [placebo]; adjusted mean effect size -3.5; 95% CI, -5.2 to -1.9; $p < 0.0001$). This change represented a clinically meaningful 24% reduction in chorea from baseline severity. There were 5 study withdrawals and 5 serious AEs in 4 patients (suicide, complicated fall, restlessness/suicidal ideation, and breast cancer) in the tetrabenazine group, compared to 1 withdrawal and no serious AEs in the placebo group (*HSG 2006*).

Tardive Dyskinesia (TD)

- The safety and efficacy of deutetrabenazine was established in the ARM-TD and AIM-TD trials, which were 12-week DB, placebo-controlled (PC), MC, RCTs. Both studies evaluated the change from baseline in items 1 to 7 of the Abnormal Involuntary Movement Scale (AIMS) score as the primary efficacy endpoint. The AIMS total score ranges from 0 to 28, and a decreased score indicates improvement (*Anderson et al 2017, Fernandez et al 2017*).
  - The Phase 2/3 ARM-TD study randomized 117 adults with moderate to severe TD to receive deutetrabenazine titrated to an optimal dose or placebo. The mean dose of deutetrabenazine at the end of titration was 38.8 mg/day. Significant reductions in AIMS scores were observed in patients who received deutetrabenazine compared to placebo (*Fernandez et al 2017*).
    - The least squares mean AIMS score improved by -3.0 points in the deutetrabenazine group vs -1.6 points in the placebo group (treatment difference -1.4; 95% CI, -2.6 to -0.2; $p = 0.019$).
    - Secondary endpoints included proportion of patients who experienced treatment success at week 12 on the CGIC and PGIC. Although CGIC and PGIC results were numerically higher for the deutetrabenazine group, the difference was not statistically significant.
    - The rates of AEs were similar between the deutetrabenazine and placebo groups, including depression and suicidal ideation.
  - The Phase 3 AIM-TD study randomized 298 adults with TD to receive 1 of 3 fixed doses of deutetrabenazine (12, 24, or 36 mg/day) or placebo. Significant reductions in AIMS scores were observed in patients who received 24 or 36 mg of deutetrabenazine per day (*Anderson et al 2017*).
    - The least squares mean AIMS score improved by -3.3, -3.2, -2.1, and -1.4 points in the deutetrabenazine 36 mg/day, 24 mg/day, 12 mg/day, and placebo groups, respectively. The treatment difference was -1.9 points (95% CI, -3.09 to -0.79; $p = 0.001$) with deutetrabenazine 36 mg/day, -1.8 points (95% CI, -3.00 to -0.63; $p = 0.003$) with deutetrabenazine 24 mg/day, and -0.7 points (95% CI, -1.84 to 0.42; $p = 0.217$) with deutetrabenazine 12 mg/day.
    - The overall rate of AEs was similar between groups (51%, 44%, 49%, and 47% for deutetrabenazine 36 mg/day, 24 mg/day, 12 mg/day, and placebo, respectively).
    - Rates of depression, depressed mood, and suicidal ideation were low in all treatment arms; no dose-response relationship was detected.
- The FDA approval of valbenazine was based on the results from the KINECT 3 trial, a 6-week, phase 3, DB, PC, MC, RCT with 224 patients with moderate to severe TD. Patients received valbenazine 40 mg once daily, valbenazine 80 mg once daily, or placebo (*Hauser et al 2017, FDA Ingrezza Medical Review*).
  - In this trial, 85.5% received concomitant antipsychotics (16.7% on FGAs and 76.7% on SGAs). The mean baseline AIMS dyskinesia score was 10.0 (range 0 to 20) between the treatment groups.

- The primary endpoint, which was a modified version of the AIMS score, included 7 items rating involuntary movements in the orofacial region, extremities, and trunk on a scale from 0 (no dyskinesia) to 4 (severe dyskinesia).
  - At week 6, the AIMS dyskinesia score was reduced by 3.2 in the valbenazine 80 mg group compared to 0.1 in the placebo group ($p < 0.001$). In the valbenazine 40 mg group, the AIMS dyskinesia score decreased by 1.9 compared to 0.1 in the placebo group ($p = 0.002$).
- The percentage of patients who achieved an AIMS response (defined in the trial as a reduction of ≥ 50% from baseline score) was 40.0% in the 80 mg group ($p < 0.001$) and 23.8% in the 40 mg group ($p = 0.02$), compared to 8.7% in the placebo group.
- The key secondary endpoint of mean Clinical Global Impression of Change - Tardive Dyskinesia (CGI-TD) score, which investigators used to rate the overall change in TD at week 6, did not reach statistical significance for either valbenazine dosage group when compared to placebo ($p = 0.056$ and $p = 0.074$ for valbenazine 80 mg and 40 mg, respectively).
- The mean PGIC score, which characterized the patient's perception of improvement in their TD symptoms, was slightly worse in both valbenazine treatment groups compared to placebo at week 6; however, the differences did not reach nominal statistical significance.
- The most common AEs observed with valbenazine (both dosage groups combined) vs placebo were somnolence (5.3% vs 3.9%), akathisia (3.3% vs 1.3%), and dry mouth (3.3% vs 1.3%). Suicidal ideation was the most common AE in the placebo group (5.3% vs 2.6% in both valbenazine groups combined).

- A meta-analysis was conducted using two 12-week DB, PC, RCTs with deutetrabenazine (12 to 48 mg/day) (n = 413) and four 4 to 6 week DB, RCTs with valbenazine (12.5 to 100 mg/day) (n = 488). With respect to AIMS scores, both deutetrabenazine (standardized mean difference [SMD] -0.40; 95% CI, -0.19 to -0.62; $p < 0.001$; weighted mean difference [WMD] -1.44; 95% CI, -0.67 to -2.19; $p < 0.001$) and valbenazine (SMD -0.58; 95% CI, -0.26 to -0.91; $p < 0.001$; WMD -2.07; 95% CI, -1.08 to -3.05; $p < 0.001$) demonstrated statistically significant improvement over placebo. Results were confirmed regarding responder rates (≥ 50% AIMS total score reduction for deutetrabenazine: risk ratio [RR] 2.13; 95% CI, 1.10 to 4.12; $p = 0.024$; number-needed-to-treat [NNT], 7; 95% CI, 3 to 333; $p = 0.046$; valbenazine: RR 3.05; 95% CI = 1.81 to 5.11; $p < 0.001$; NNT, 4; 95% CI, 3 to 6; $p < 0.001$). Inconsistent improvements were noted in PGIC ($p = 0.15$) and CGIC scores for deutetrabenazine ($p = 0.088$), and for CGIC scores for valbenazine ($p = 0.67$). In a 54-week, OL extension study of deutetrabenazine and a dose-blinded valbenazine study (48 weeks), responder rates increased over time. No increase in cumulative or specific AEs vs placebo was observed (*Solmi et al 2018*).

CLINICAL GUIDELINES

Huntington Disease (HD)

- **American Academy of Neurology (AAN):** Pharmacologic treatment of chorea in HD (*Armstrong and Miyasaki 2012*)
  - Whether chorea requires treatment should be an individualized decision for providers and their patients with HD.
    - While some studies reported that improving chorea decreases disability or increases quality of life, other studies failed to show an association between chorea and functional decline in HD.
    - The impact of chorea on quality of life should be weighed against other issues, including mood disturbance, cognitive decline, AEs, and polypharmacy risks.
  - For HD chorea which requires pharmacological management, tetrabenazine (up to 100 mg/day), amantadine (300 to 400 mg/day), or riluzole (200 mg/day) are recommended.
    - Tetrabenazine likely provides very important antichoreic benefits, and riluzole 200 mg/day likely provides moderate benefits. The degree of benefit is unknown for amantadine.
    - Patients on tetrabenazine should be monitored for parkinsonism and depression/suicidality while patients on riluzole should be monitored for elevated liver enzymes.
  - Nabilone may be used for modest decreases in HD chorea, but there is insufficient evidence to recommend long-term use, particularly given concerns for abuse potential.
  - While neuroleptic agents (eg, clozapine) may be reasonable options with a historical suggestion of antichoreic benefit, formal recommendations are not provided due to a lack of studies with sufficient sample sizes and validated outcome measures.
  - The guideline has not been updated since the FDA approval of deutetrabenazine.

Tardive dyskinesia (TD)

- As a follow-up to the 2013 AAN evidence-based treatment guidelines for tardive syndromes (TS) (*Bhidayasiri et al 2013*), Bhidayasiri published a treatment algorithm based on a systematic review of the literature for TS in 2018. Published studies were evaluated for effectiveness of pharmacologic and surgical treatments for TS from 2012 to 2017, using the same rating system ranging from A (highest level of evidence for effectiveness) to U (insufficient evidence) (*Bhidayasiri et al 2018*).
  - While the 2013 guidelines did not make any Level A recommendations, the 2018 update recommends the new generation VMAT2 inhibitors, valbenazine and deutetrabenazine, as Level A treatment options. Tetrabenazine may be used only if new VMAT2 inhibitors are unavailable.
  - If TS remains troublesome, treatment with a Level B (recommendation should be done based on benefit/risk profile) recommendation, such as gingko biloba extract or clonazepam, should be utilized.
  - If TS continues to be troublesome, short-term amantadine, tetrabenazine, deep brain stimulation, or globus pallidus interna may be tried (Level C; recommendation may or might be done; lowest recommendation level considered useful within the scope of practice).
  - There continues to be insufficient evidence to support or refute TS treatment by withdrawing causative agents or switching from typical to atypical DRBAs (Level U).

SAFETY SUMMARY

- **Contraindications**
  - Deutetrabenazine and tetrabenazine are contraindicated in the following populations:
    - Patients with HD who are actively suicidal, or have untreated or inadequately treated depression
    - Patients with hepatic impairment
    - Patients concurrently on monoamine oxidase inhibitors (MAOIs) or who have discontinued MAOI therapy within 14 days
    - Patients concurrently on another VMAT2 inhibitor
  - Valbenazine has no contraindications.
- **Warnings/precautions**
  - **Boxed warning** for deutetrabenazine and tetrabenazine**:** Depression and suicidality in patients with HD
    - Patients with HD have a greater risk of depression and suicidality. Treatment with deutetrabenazine may further increase this risk in patients with HD. Patients on deutetrabenazine should be closely monitored for worsening depression, suicidal thoughts, or unusual changes in behavior.
  - Additional key warnings and precautions for deutetrabenazine and tetrabenazine include:
    - Clinical worsening (eg, decline in mood, cognition, rigidity, and functional capacity) and AEs (eg, sedation, depression, parkinsonism, akathisia, restlessness, cognitive decline) in patients with HD
    - Neuroleptic malignant syndrome (NMS) in patients with HD and TD
      - NMS is a potentially fatal syndrome associated with hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability. While NMS has not been observed with deutetrabenazine, it has been observed with its RLD, tetrabenazine. Deutetrabenazine should be discontinued immediately if NMS occurs.
    - Akathisia, agitation, and restlessness in patients with HD and TD
      - In the First-HD study, akathisia, agitation, or restlessness was reported by 4% of patients treated with deutetrabenazine and 2% of patients on placebo. In patients with TD, 2% of patients treated with deutetrabenazine and 1% of patients on placebo experienced these events.
    - Parkinsonism in patients with HD
      - Patients with HD often develop rigidity as part of their underlying disease progression. Drug-induced parkinsonism may cause more functional impairment than untreated chorea. Patients who develop parkinsonism during treatment with deutetrabenazine should reduce their dosage.
    - Sedation and somnolence (also a warning for valbenazine)
      - Sedation is a common dose-limiting AE with deutetrabenazine. In the First-HD study, 11% of patients treated with deutetrabenazine reported somnolence compared with 4% of patients on placebo.
    - QTc prolongation (also a warning for valbenazine)
- **Adverse effects**

- The most common AEs (incidence > 8% and greater than placebo) with deutetrabenazine in the First-HD study included somnolence, diarrhea, dry mouth, and fatigue. In the TD studies, the most common AEs (incidence > 3% and greater than placebo) with deutetrabenazine included nasopharyngitis and insomnia.
- The most common AEs (incidence > 10% and at least 5% greater than placebo) with tetrabenazine included sedation/somnolence, fatigue, insomnia, depression, akathisia, anxiety, and nausea.
- The most common AEs (incidence ≥ 2%) with valbenazine included somnolence, anticholinergic AEs (dry mouth, constipation, blurred vision, urinary retention), balance disorders/falls, headache, akathisia, vomiting, nausea, and arthralgia.

- **Drug Interactions**
  - Deutetrabenazine and tetrabenazine
    - These agents are contraindicated in patients taking MAOIs, reserpine, or other VMAT2 inhibitors.
    - Strong cytochrome P450 (CYP) 2D6 inhibitors increase the systemic exposure to the metabolites of these agents.
    - Concurrent use with neuroleptic drugs (ie, dopamine antagonists, antipsychotics) may increase risk for parkinsonism, NMS, and akathisia.
    - Concomitant use with other drugs that are known to cause QT prolongation should be avoided.
  - Valbenazine
    - Concomitant use of an MAOI is not recommended.
    - Concomitant use with strong CYP3A4 inducers is also not recommended, as this could lead to reduced levels of valbenazine.
    - Valbenazine dose may need to be decreased when given concomitantly with strong CYP3A4 and CYP2D6 inhibitors.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Austedo (deutetrabenazine)	Tablets	Oral	Twice daily	Initial daily dose: 6 mg (HD) or 12 mg (TD); maximum daily dose = 48 mg; dose should be titrated at weekly intervals; administer with food
Ingrezza (valbenazine)	Capsules	Oral	Daily	A lower dose should be administered in patients with moderate to severe hepatic failure
Xenazine (tetrabenazine)	Tablets	Oral	1 to 3 times daily (depending on dose)	Dose should be titrated slowly at weekly intervals and individualized; titration should be stopped or slowed down if patient experiences AEs; patients who require > 50 mg/day should first be tested to determine if they are poor or extensive metabolizers

See the current prescribing information for full details

CONCLUSION

- Deutetrabenazine represents an additional oral therapeutic option for patients with TD or chorea associated with HD.
  - For HD chorea, deutetrabenazine is comparable in safety and efficacy to its RLD, tetrabenazine. The use of both products in HD is limited by dose-related AEs (eg, somnolence, parkinsonism) and a boxed warning for depression and suicidality in a population that is already at a significantly increased risk.

- The first step in the treatment of TD is to discontinue the offending agent by slow taper. The patient can switch to quetiapine and clozapine (SGA of choice) if needed.
- The First-HD study, which compared deutetrabenazine with placebo for 12 weeks demonstrated a statistically significant improvement in the TMC score in the deutetrabenazine group compared to placebo. Secondary endpoints such as PGIC and CGIC also showed improvement.
- The KINECT 3 trial demonstrated a significant reduction in AIMS dyskinesia score of -3.2 in the valbenazine 80 mg/day group and -1.9 in the valbenazine 40 mg/day group, however, there were no significant improvements in the CGI-TD score or patient-perceived improvement in function or quality of life.
  - The extension trial continued to demonstrate reductions in AIMS dyskinesia score from baseline to week 48 in both dosage groups.
- The ARM-TD and AIM-TD trials demonstrated significant reductions in AIMS score in patients who received deutetrabenazine compared to placebo.
- For TD, valbenazine is an alternative with the same mechanism of action and a once-daily dosing schedule compared to twice-daily deutetrabenazine.
- The AAN 2012 guideline for the treatment of chorea associated with HD recommends treatment with tetrabenazine, amantadine, or riluzole (Level B; recommendation should be done based on benefit/risk profile). Nabilone may also be used for modest decreases in HD chorea (Level C; recommendation may or might be done; lowest recommendation level considered useful within the scope of practice), but information is insufficient to recommend long-term use, particularly given abuse potential concerns (Level U; insufficient evidence). Data are insufficient to make recommendations regarding the use of neuroleptics or donepezil for HD chorea treatment (Level U).
- A treatment algorithm for TS was published in 2018, as a follow-up to the 2013 AAN evidence-based treatment guideline for TS. The most important change in recommendations was related to the addition of the new generation VMAT2 inhibitors, valbenazine and deutetrabenazine, as Level A (highest level of evidence for effectiveness) treatment options. Tetrabenazine is recommended as an alternative if new VMAT2 inhibitors are unavailable. Gingko biloba and clonazepam continued to be recommended in the Level B category as well as amantadine and tetrabenazine in the Level C category.

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