

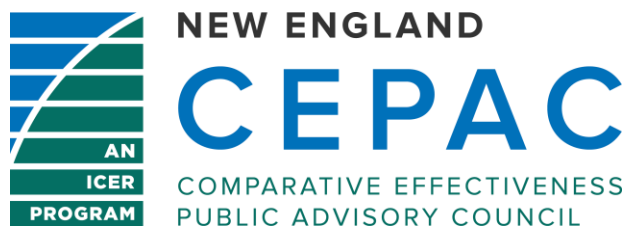


Vesicular Monoamine Transporter 2 Inhibitors for Tardive Dyskinesia: Effectiveness and Value

Final Evidence Report

December 22, 2017

Prepared for



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The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs.

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In the development of this report, ICER’s researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit:

https://icer-review.org/wp-content/uploads/2017/05/NECEPAC_TD_Stakeholder_List_05082017.pdf

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List of Acronyms Used in this Report

AAN	American Academy of Neurology
AHRQ	Agency for Healthcare Research and Quality
AIMS	Abnormal Involuntary Movement Scale
AE	Adverse event
BID	Twice a day
CGIC	Clinical Global Impression of Change
DBPC	Double blind placebo controlled
DRBAs	Dopamine receptor blocking agents
DTBZ	Deutetrabenazine
ESRS	Extrapyramidal Symptoms Rating Scale
HD	Huntington's disease
FDA	Food and Drug Administration
ITT	Intent-to-treat
LTE	Long term extension
MAOIs	Monoamine oxidase inhibitors
mCDQ	Modified Craniocervical Dystonia Questionnaire
mITT	Modified intent-to-treat population
NNH	Number needed to harm
NNT	Number needed to treat
OLE	Open-label extensions
PBO	Placebo
PGIC	Patient Global Impression of Change
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-Adjusted Life Year
RCT	Randomized Control Trial
TBZ	Tetrabenazine
TD	Tardive dyskinesia
TEAEs	Treatment emergent adverse events
TID	Three times a day
USPSTF	U.S. Preventive Services Task Force
VBZ	Valbenazine
VMAT2	Vesicular monoamine transporter-2

Executive Summary

Background

Tardive dyskinesia (TD) is a repetitive, involuntary movement disorder with a delayed onset caused by prolonged use of medications, most commonly antipsychotic drugs, that block the dopamine receptor.^{1,2,3} Overall, 20-50% of individuals taking antipsychotic drugs develop TD, with newer antipsychotic drugs somewhat less likely to cause TD than older drugs.^{6,7,8} Involuntary movements due to TD can be localized or widespread and can result in physical and psychological impairment.¹¹ Patients may not be aware of these movements, especially when involving the face. Symptoms of TD can vary from mild to severe and can adversely affect all aspects of patients' lives including physical and psychological impairment, social isolation, and work-related disability. TD may also decrease compliance with the drugs given to treat the underlying condition.¹²

Until recently there were no FDA-approved therapies for TD. Historically, many treatments have been tried for TD, but there has been limited evidence to guide patients and clinicians.^{2,13,14} For patients with new TD symptoms or who have alternative therapy for the underlying condition, reducing or discontinuing the offending agent would seem logical, but even for these individuals doing so can paradoxically increase TD symptoms on withdrawal and the underlying condition may worsen. The approval by the FDA of two new vesicular monoamine transporter-2 inhibitors, valbenazine and deutetrabenazine, has led to renewed interest in TD and its treatment.¹⁵

The Topic in Context

TD was first described in the 1950s with the introduction of antipsychotic drugs.³ Recognition that TD was a drug-induced condition caused by long-term use of antipsychotic drugs led to the introduction of newer antipsychotic drugs starting in the 1970s, with the goal of decreasing TD and other abnormal movements attributed to these medications. Antipsychotic drugs are believed to work in the brain as dopamine receptor blocking agents (DRBAs). Though antipsychotic drugs are the most common DRBAs used in medical practice, other DRBAs can also cause TD. The prevalence rates of TD have been estimated to range from 20-50% among those using DRBAs.^{6,17} The incidence of new TD is reported to be around 5% per year with older antipsychotic drugs and 3% per year with newer antipsychotic drugs.^{9,10,18} Higher rates are seen with longer duration of use and in female and older patients.⁷

While antipsychotic drugs were initially developed for use in patients with schizophrenia and schizoaffective disorder, they are also used in serious mood disorders such as bipolar disease and major depression. Off-label use of antipsychotics include treatment of obsessive-compulsive

disorder, personality disorders, post-traumatic stress disorder, insomnia, and agitation in dementia. It is estimated that there are 6 million individuals in the United States with these diagnoses who have received antipsychotic drugs.²¹ Among these persons, there may be 500,000 individuals with TD with most having irreversible symptoms, even if the DRBA is stopped.²² If new treatments are targeted to those with moderate or severe TD, approximately 300,000 patients would be eligible for new treatments.

The diagnosis of TD is based upon presence of abnormal, involuntary movements, a history of taking a DRBA for at least three months, and the absence of another condition that may produce such movements. Diagnosis is therefore clinical in nature only, meaning there are no specific tests that can be done to confirm or “prove” the diagnosis. The severity of TD symptoms and the impact of treatment can be assessed using survey questionnaires, such as the Abnormal Involuntary Movement Scale (AIMS).²³ While the AIMS assesses symptom severity, it is unclear how well it reflects the overall impact of TD on a patient's quality of life.

The abnormal, involuntary movements seen in TD most commonly involve the mouth and face region, but can also involve the limbs and trunk. It is difficult to rate the severity of TD symptoms from the patient’s perspective because even limited symptoms involving just one part of the face can be very noticeable and stigmatizing, and the level of stigma can vary significantly based on the patient’s work, school, and/or living situation. Patients may also not be aware of these involuntary movements, and thus, patient reported symptoms may underestimate their severity.

Until recently there were no FDA-approved treatments used to reduce TD symptoms. A wide range of therapies have been tried to treat TD, but the evidence available to support evidence-based recommendations is poor,^{13,24} and few therapies have been shown to produce more than a slight to moderate benefit.^{2,14} Treatment options have included withdrawing or changing the offending drug, off-label use of prescription medications, over-the-counter vitamins and supplements and non-pharmacologic treatments.^{2,13,24} Avoiding antipsychotics where other treatment options are available is preferred, but this is not possible for many patients with severe psychiatric conditions. Though TD symptoms may improve with decreasing and then stopping the offending agent or switching to a different drug, it does not consistently help, and complete resolution of symptoms is uncommon.^{22,26} Moreover, TD symptoms can worsen upon decreasing or stopping the antipsychotic drug.

Interest in the vesicular monoamine transporter-2 (VMAT2) relates to its effect in storing and releasing dopamine from synaptic vesicles in the brain.³⁰ The VMAT2 inhibitor tetrabenazine was approved in 2008 by the FDA for use in Huntington’s disease, a genetic condition that causes involuntary movements, but includes a black box warning for increasing the risk of depression and suicidal thoughts and behaviors. Tetrabenazine has been used in an off-label manner for individuals

with TD symptoms. Guideline recommendations for treating tardive dyskinesia from the American Academy of Neurology in 2013 found limited evidence that several medications, including tetrabenazine, reduced TD symptoms.¹ Concern about side effects and the need for multiple daily dosing led to the search for new VMAT2 inhibitors. Valbenazine (Ingrezza™, Neurocrine Biosciences, Inc.) became the first FDA-approved drug for TD (April 2017) and deutetrabenazine (Austedo®, Teva) was subsequently approved for TD in August 2017. Approval by the FDA of the first two treatments for TD represents a potentially important advance for patients with this frequently debilitating, irreversible condition.

Table ES1. VMAT2 Inhibitors of Interest for the Evidence Review

VMAT2 Inhibitors	Recommended Dose	Dosage Forms & Strengths	FDA Approval Date(S)	Annual WAC (November 2017)
Valbenazine	Initial dose of 40 mg/day. Increase to 80 mg once daily after 1 week	Capsule: 40mg, 80mg	April 11, 2017 (Tardive dyskinesia)	\$75,789*
Deutetrabenazine	Initial dose of 12 mg/day; titrate at a weekly interval by 6mg/day until symptoms improvement, and tolerability, up to a maximum of 48 mg/day given in two divided doses.	Tablets: 6 mg, 9 mg, and 12 mg	April 3, 2017 (Chorea associated with Huntington's disease) August 30, 2017 (Tardive dyskinesia)	\$90,071† (36mg daily dose)
Tetrabenazine	[Off label use in TD] Recommended dose in Huntington's disease: Initial dose of 12.5 mg once daily, then titrated by weekly intervals of 12.5 mg/day until symptoms improvement or unacceptable toxicity. Administered in BID if daily dose is less than 37.5mg. If up to 37.5mg to 50mg, administer in three divided doses. If >50 mg/day is required, test and genotype to determine if poor or extensive metabolizers of CYP2D6; not to exceed 100 mg/day or 37.5 mg/dose	Tablets: 12.5mg & 25mg	Aug 15, 2008 (Chorea associated with Huntington's disease)	\$19,885‡ – \$76,087§ for 25mg daily dose \$79,541‡ - \$304,345§ for 100mg daily dose

*Based on manufacturer input for 80mg dose; †Using the 12mg dose strength for a daily dose of 36mg for TD; ‡cheapest tetrabenazine generic; §Xenazine® cost

Insights Gained from Discussions with Patients and Patient Groups

Discussions with individual patients and patient advocacy groups identified several important insights. They viewed the first approved therapies for TD as giving patients and their clinicians more options for managing TD symptoms and treating the underlying condition that required use of antipsychotic drugs. Patients and patient groups identified several important knowledge gaps. They expressed concern that the common outcome measures used in clinical studies may not adequately capture the impact of TD on social stigmatization, work, family and caregivers, or the treatment of the patient's underlying condition and other co-morbid medical conditions.

They also noted that published studies primarily report provider reported outcomes, and the lack of patient-reported outcomes may lead to underestimating the value of these new treatments. Compounding this is the recognition that some patients may not be fully aware of their symptoms and not be able to adequately judge treatment response. Patients and advocates also raised concern about how TD influences the way clinicians treat the patient's underlying condition. There was concern that because there is currently no data available on how these new drugs may facilitate improved treatment of the patient's underlying condition, attempts to assess their value may not account for their full impact on overall quality of life.

Despite these limitations, patients and patient groups wanted to ensure that their members had access to newly available treatment options that can dramatically affect the patient, caregiver, and family.

Comparative Clinical Effectiveness

We reviewed the clinical evidence of three VMAT2 inhibitors, valbenazine, deutetrabenazine and tetrabenazine for adult patients with moderate to severe tardive dyskinesia for at least three months and a history of use of dopamine receptor blocking agents. We also considered placebo or other types of active medications used off-label to control TD symptoms as comparators of interest.

To inform our analysis, we abstracted evidence from available clinical studies of these agents, whether in published or unpublished form (e.g., conference abstracts or presentations, FDA review documents). We included 26 references relating to five comparative trials, one open label trial, one single-arm study and six observational studies in our assessment. These citations were comprised of 13 publications and 13 conference abstracts/posters. Additional references were included in our review for the safety assessment.

The primary outcome was the Abnormal Involuntary Movement Scale (AIMS).² The AIMS questionnaire is commonly used to measure the severity of TD symptoms, and the impact of treatment on TD. In the valbenazine and deutetrabenazine trials, it was based on the measurement

of the first seven items on the twelve-point scoring tool (measuring four facial/oral movements; two measurements of movement in extremities; and one measuring movement in the trunk). A higher AIMS score reflects increased severity of TD symptoms, and a change in AIMS between baseline and follow-up was the primary outcome. It is unclear what amount of change in AIMS reflects a minimal clinically important difference, but it has been suggested to be 2-3 point change.³ In addition, an AIMS score reduction greater than or equal to 50% can define treatment response.

Secondary outcomes included the clinical global impression of change (CGIC) and the patients' global impression of change (PGIC). The CGIC is a clinician-rated measure evaluating the severity of a patient's TD symptoms. The PGIC reflecting patients' rating of overall improvement. Both have a 7-point scale that ranges from 1 ("very much improved") to 7 ("very much worse"). In the valbenazine and deutetrabenazine trials, patients in the "1" and "2" categories were classified as PGIC responders.

Finally, harms of treatment were assessed (treatment related adverse effects, serious adverse effects and discontinuation due to adverse effects). In addition, we examined adverse events and potential harms of VMAT2 inhibitors in populations with conditions other than TD.

We did not compare the VMAT2 inhibitors to each other through direct or indirect quantitative assessment due to important differences in study characteristics and duration of treatment. For example, the valbenazine trials were six weeks in duration, versus 12 weeks for deutetrabenazine. In addition, moderate-to-severe TD was defined based on qualitative video review in the valbenazine trials, while a minimum AIMS score threshold of 6 was used in the deutetrabenazine trials.

Study and patient characteristics are presented in Table ES2 below. There is limited information on the general profile of TD patients in typical clinical practice. However, stakeholder input suggested that increasing use of antipsychotics in patients with bipolar or other affective disorders may be modulating the distribution of underlying psychiatric conditions in patients with TD, which were heavily weighted towards schizophrenia in the clinical trials.

Table ES2. Valbenazine and Deutetrabenazine Trials

	Valbenazine Trials*		Deutetrabenazine Trials	
	KINECT 3	KINECT 2	AIM-TD	ARM-TD
Study Type	Phase III RCT	Phase II RCT	Phase III RCT	Phase II/ III RCT
Total # of Patients	234	102	293	117
Baseline AIMS Score	10	8	9.7	9.6
Mean Age (Years)	56.1	56.2	56.4	54.6
Treatment Duration (Weeks)	6	6	12	12
Comorbid Psychiatric Condition (%) [†]				
Schizophrenia/Schizoaffective	66.1	58	60	68.4
Bipolar Disorder/Depression	33.9	38	36	48.7
Gastrointestinal Disorder	--	4	--	--

*Includes valbenazine published trials. There are two unpublished trials of Valbenazine (see full report). †The percentages add up to a value greater than 100% in the ARM-TD trial. This is likely because patients could be categorized as having 1 or more comorbid psychiatric condition.

Clinical Benefits

***Valbenazine:* Published evidence from two trials showed statistically significant improvement in AIMS score for valbenazine compared to placebo. A greater percentage of patients receiving valbenazine achieved a reduction of 50% or more in the AIMS score at six weeks relative to those receiving placebo, resulting in numbers needed to treat of four to seven.**

In the Phase III KINECT 3 study, the 40mg and 80mg doses of valbenazine resulted in a statistically significant greater reduction in AIMS score compared to placebo at six weeks (least squares [LS] mean change: -1.9 & -3.2 vs. -0.1; $p < 0.003$); as noted previously, differences observed matched the 2-3 point difference considered to be minimally clinically-important in recent research presented as a poster in 2017.^{3,4} Similarly, a statistically significant greater proportion of patients who were in the 40mg and 80mg valbenazine groups had an AIMS response (greater or equal to 50% reduction in AIMS score) compared to placebo (23.8% & 40% vs. 8.7%; $p < 0.03$).⁴ This resulted in a number needed to treat (NNT) of seven and four, respectively, compared with the placebo group. The KINECT 2 trial also showed a statistically significant greater reduction in the AIMS score and higher AIMS response in the valbenazine arm compared to placebo at six weeks (see Table ES3).

Table ES3. Valbenazine: AIMS Change and AIMS Response Across Trials at Six Weeks

Trials	Baseline AIMS Score (Mean)	AIMS Reduction from Baseline (LS Mean)	≥50% AIMS Improvement (%)
Kinect 3⁴			
Valbenazine 80mg/D	10.4	-3.2 [†]	40.0 [†]
Valbenazine 40mg/D	9.7	-1.9 [*]	23.8 [*]
Placebo	9.9	-0.1	8.7
Kinect 2⁵			
Valbenazine (Max 75mg/D)	8.0	-2.6 [†]	48.9 [†]
Placebo	7.0	-0.2	18.2
KINECT[‡] (Post-Hoc Analysis)⁶			
Valbenazine (50mg/D + 100mg/50mg)	14.6	-1.2	NR
Placebo	15.3	-0.2	NR

[†]p values≤0.001 vs. placebo; ^{*}p values≤0.05; [‡]unpublished data from FDA Medical Review

Evidence is mixed on improvement in TD symptoms as assessed by the clinical and patient global impression of change (CGIC and PGIC) scores.

The KINECT 3 study showed no significant differences between the valbenazine and placebo group on investigator rated CGIC score and CGIC responders at week 6 in the intent-to-treat population (Table ES4).^{4,6} In contrast, the CGIC score and CGIC responders in the KINECT 2 study showed a greater improvement in the valbenazine group compared with the placebo group in the modified intent-to-treat population .⁵

Unpublished PGIC data on KINECT 3 in the FDA medical review document showed that on average, patients in the valbenazine groups (40mg & 80mg) and placebo group did not differ in their report of TD symptom improvement (Table ES4).⁶ In contrast, patients in the valbenazine treatment group in the KINECT 2 study had a greater proportion of patients in the valbenazine group being classified as PGIC responders compared with the placebo group.⁵

Table ES4. Valbenazine: CGIC & PGIC Response Across Trials at Six Weeks

Trials/ Arms	CGIC Responders (%)	PGIC Responders (%)
Kinect 3⁴		
Valbenazine 40mg/D	31.7	31.7 [‡]
Valbenazine 80mg/D	31.4	24.3 ^{*‡}
Placebo	20.3	42.0 [‡]
Kinect 2⁵		
Valbenazine (Max 75mg/D)	66.7 [*]	57.8 [*]
Placebo	15.9	31.8
Kinect¹⁶		
Valbenazine (50mg/D + 100mg/50mg)	NR	24.5
Placebo	NR	30.0

*p values≤0.0001 vs. placebo; ‡ unpublished data from FDA Medical Review

Deutetrabenazine: *Published evidence from two trials showed statistically significant improvement in AIMS score for deutetrabenazine compared to placebo. A greater percentage of patients receiving deutetrabenazine achieved a reduction of 50% or more in the AIMS score at 12 weeks, resulting in numbers needed to treat of five compared to placebo.*

In the AIM-TD trial, the 24mg and 36mg doses of deutetrabenazine resulted in a statistically significant greater improvement in the AIMS score compared to placebo at week 12 (LS Mean change: -3.2 & -3.3 vs. -1.4, p<0.003).⁷ In addition, significantly more patients in the 24mg and 36mg deutetrabenazine groups had a 50% or more reduction in the AIMS score at 12 weeks compared to the placebo group (35% & 33% vs. 12%; p≤0.05; NNT=5). The ARM-TD trial also showed statistically significant greater improvement in the AIMS score in the deutetrabenazine arm compared to placebo at 12 weeks (see Table ES5).

Table ES5. Deutetrabenazine: AIMS Change and AIMS Response Across Trials at 12 Weeks

Trials	Baseline AIMS Score (Mean)	AIMS Reduction from Baseline (LS Mean)	≥50% AIMS Improvement (%)
AIM-TD⁷			
DTBZ 24mg/D	9.4	-3.2 [†]	35 [†]
DTBZ 36mg/D	10.1	-3.3 [*]	33 [†]
Placebo	9.5	-1.4	12
ARM-TD⁸			
DTBZ	9.6	-3.0 [†]	--
Placebo	9.6	-1.6	--

*p values≤0.001 vs. placebo; †p values≤0.05

Evidence is mixed on the impact of deutetrabenazine on the CGIC measure, with differences observed in one of three active treatment arms of one trial, and no differences observed in the other trial. Results from two trials showed no significant differences between deutetrabenazine and placebo in the likelihood of achieving treatment success in patients based on the PGIC scale.

In the AIM-TD study, a statistically significant increase in treatment success on the CGIC was seen in patients receiving deutetrabenazine, but only in the 24 mg/day group (Table ES6).⁷ Similarly, there was no statistically significant difference between the proportion of patients achieving CGIC treatment success in the deutetrabenazine arm and the placebo arm at week 12 in the ARM-TD trial.⁸

In the AIM-TD and ARM-TD trials, the percentage of patients achieving PGIC treatment success favored the deutetrabenazine arms, but the differences were not statistically significant (Table ES6).^{7,8}

Table ES6. Deutetrabenazine: CGIC & PGIC Response Across Trials at 12 weeks.

Trials	CGIC Responders (%)	PGIC Responders (%)
AIM-TD⁷		
DTBZ 24mg/Day	49*	45
DTBZ 36mg/Day	44	40
Placebo	26	31
ARM-TD⁸		
DTBZ	48.2	42.9
Placebo	40.4	29.8

*p value≤0.05 vs. placebo;

Tetrabenazine: Tetrabenazine may reduce the symptoms of TD. However, the lack of randomized controlled trials, use of non-standard and variable clinical measures, and other study design limitations (e.g., stopping neuroleptic medications during trial) severely limits any inferences that can be drawn from the available evidence, and precludes any possibility of even qualitative comparisons to the other VMAT2 inhibitors.

In the only comparative tetrabenazine study of TD we identified, 24 patients with clear signs of oral TD were given placebo for four weeks followed by 50mg to 100mg doses of tetrabenazine per day over six weeks in a non-randomized cross-over fashion.⁹ After six weeks on tetrabenazine, dyskinesia had disappeared completely in eight patients (33%), and reduced significantly in six patients (25%), resulting in a mean oral dyskinesia frequency of 11 per minute in the tetrabenazine group compared to 30 per minute at the end of the placebo period (p<0.0005).⁹

We identified only one tetrabenazine study that used the AIMS score as an outcome measure.¹⁰ This was a 20-week, open label single-arm study conducted in 20 patients with TD (mean duration

of TD: 40 months). Patients were placed on a tetrabenazine dose of 25mg to 150mg per day (mean dose: 57.9mg/day) and were followed prospectively. At approximately 20 weeks follow up, the mean AIMS score as determined by blinded video raters had improved by 9.7 points from baseline (Mean of 17.9 and 8.2 at baseline and 20 weeks respectively; $p < 0.001$).¹⁰

We identified six other single-arm retrospective studies of tetrabenazine conducted in patients with varying hyperkinetic movement disorders including TD where outcomes were separately reported for the underlying disorder (see Appendix Table F8). Results showed a wide range of improvement in the study populations, ranging from 41% to 93% with moderate to marked improvement^{11,12}

Harms

Valbenazine: The most common side effects of valbenazine were somnolence, fatigue, headache, decreased appetite, akathisia, nausea, vomiting and dry mouth. There was no indication of increased rates of depression and suicidal ideation with valbenazine at 6 weeks.

In the pooled analysis of the KINECT 2 and KINECT 3 trials at 6 weeks, the incidence of serious AEs was 6.6% in the valbenazine arm versus 3.9% in the placebo arm, and the discontinuation rate due to adverse events was 4.5% in the valbenazine arm versus 3.2% in the placebo group. All serious AEs were considered not to be treatment related. There was one death in the valbenazine group, which was considered to be unrelated to treatment. Findings from both KINECT 2 and KINECT 3 studies showed that the occurrence of depression and suicidal ideation in the valbenazine groups was not significantly different from the placebo-treated patients.^{4,5}

The most common AE with valbenazine at six weeks was somnolence, occurring in $\geq 5\%$ of patients and with a higher incidence than in the placebo group.^{4,5} Other common AEs with incidence $\geq 3\%$, and with higher incidence in the valbenazine group compared with placebo group were fatigue, headache, decreased appetite, akathisia (agitation/restlessness), nausea, vomiting and dry mouth. Data from the 48-week long term extension study obtained from a conference abstract showed similar pattern of common AEs.¹³

Deutetrabenazine: Somnolence, headache, diarrhea, fatigue, insomnia, anxiety, and nasopharyngitis were the most common side effects reported for deutetrabenazine. There was no indication of increased rates of depression and suicidal ideation with deutetrabenazine at 12 weeks.

At 12 weeks, the incidence of adverse events was similar between patients in the deutetrabenazine and placebo groups in both AIM-TD and ARM-TD trials. In the pooled analysis of both trials, the incidence of serious AEs was 6.3% in the deutetrabenazine arm versus 6.9% in the placebo arm. Of the 13 cases of serious AE occurring in the deutetrabenazine group, only one (suicidal ideation) was

considered to be possibly related to treatment. There were two deaths in the deutetrabenazine group, and both were not considered to be related to treatment.

At 12 weeks, the most common AE occurring in $\geq 5\%$ of patients and with higher incidence than in the placebo group were somnolence, headache and diarrhea. Other common AEs that occurred in $\geq 3\%$ of patients in the deutetrabenazine groups were fatigue, anxiety, nasopharyngitis and insomnia. The incidence of depression and suicidal ideation was similar between treatment groups, and did not show a dose-response relationship. Results from 54-week long-term extension study showed deutetrabenazine was generally well tolerated, with a 5.9% incidence of discontinuation due to adverse events. There was no evidence of increased depression, anxiety, suicidality, restlessness, somnolence and sedation, or Parkinsonism resulting from long-term exposure.

Tetrabenazine: The most common side effects of tetrabenazine were somnolence, fatigue, insomnia, fall, depression, agitation, parkinsonism, akathisia, and anxiety. Although statistical significance was not reported, tetrabenazine resulted in substantially greater incidence of depression compared to placebo group in the trial of Huntington's disease.

Comparative tetrabenazine safety information was primarily informed by two studies (12 week RCT & 80 week open label study) conducted in patients with Huntington's disease, an indication for which tetrabenazine is approved (see Table F9 in Appendix).^{14,15} The most common AEs occurring in $\geq 5\%$ of patients and with greater incidence in the tetrabenazine group compared with the placebo group were somnolence, fatigue, insomnia, fall, depression, agitation, and anxiety.¹⁴ Many of the common AEs, including somnolence and depression, and less common ones, including akathisia and Parkinsonism, were dose limiting, and were managed by dose reductions during the trial. The most common adverse events reported in $\geq 5\%$ of patients with TD from single-arm observational studies include somnolence, fatigue, parkinsonism, depression, insomnia, nervousness/anxiety, akathisia, and nausea/vomiting.

Notably, the incidence of depression in tetrabenazine treated patients was substantially greater than in the placebo group (15% vs. 0%).¹⁴ Data from the long term extension study showed that the incidence of depression had risen to 23% at 80-week follow-up.¹⁵ Additionally, there was one case of suicide occurring in a patient with undetected depression during the RCT phase, and one case of a suicide attempt during the long term extension study.^{14,15} Based upon the findings from these studies, tetrabenazine was given a black box warning for the risks of depression and suicidality.¹⁶

Controversies and Uncertainties

A number of key controversies and areas of uncertainty were identified based upon our clinical evidence review and in developing our cost-effectiveness model with important input from relevant stakeholders. We did not identify any randomized controlled trials of tetrabenazine for patients

with TD. Therefore, our assessment of the use of tetrabenazine in TD was limited and qualitative in nature. We identified four placebo-controlled randomized controlled trials assessing valbenazine and deutetrabenazine, but there were no studies directly comparing these two agents. As a result, we could only compare the benefits and harms of VMAT2 inhibitors to placebo. We considered performing a network meta-analysis, but the absence of such head-to-head evidence, the limited number of available studies, as well as differences in study populations and duration of treatment precluded such comparisons.

Another major limitation of the identified evidence base is the lack of outcome measures that directly reflect the burden of TD in affected individuals. The primary outcome in the clinical trials, the AIMS scale, was provider assessed. Its measurement was based on blinded, external, expert review of office video recordings that does not reflect how therapy directed at TD symptoms is assessed in routine clinical settings. Moreover, studies demonstrated that assessments done by local investigators who were not blinded to the order of the videos resulted in different outcomes than those from external, blinded reviews.¹⁷

It is also unclear that the score from the seven items used to calculate the AIMS score provides an accurate assessment of the overall severity of symptoms. For example, patients with severe facial symptoms that are quite impairing may have the same AIMS score as someone with minimal symptoms in four different body locations, but may feel a much greater burden from facial symptoms because of their place of employment or education. In addition, none of the trials reported data on three items assessing global severity that are included in the original AIMS scale (items 8 -10). Finally, while the statistical significance of changes in AIMS scores were assessed in these trials, there is yet no established threshold for what constitutes a clinically-important difference for change in AIMS score.

Given the impact of TD on quality of life, patient reported measures were included as secondary outcomes in both the valbenazine and deutetrabenazine trials. However, patient reported outcomes comparing valbenazine or deutetrabenazine to placebo generally did not demonstrate a statistically significant beneficial impact of active treatment, even though TD symptoms were rated as significantly improved by blinded central raters using the AIMS scale. It is not clear why provider-based and patient-reported measures of success differed. Some patients may not have appreciated the amount of benefit that was observed on video reviews. As a result of these limitations in assessing the impact of therapy in patients with TD, the observed outcomes may not fully capture the potential benefit of the VMAT2 inhibitors.

The side effect profile of the VMAT2 inhibitors is another area of uncertainty. Although, the risk of depression and suicidality was similar between treatment groups in the trials of deutetrabenazine in patients with Huntington's disease (HD), a boxed warning for depression and suicidality was

added to its label for the treatment of HD (in all likelihood because of its chemical similarity to tetrabenazine). The current blinded, placebo controlled clinical trials of valbenazine and deutetrabenazine in patients with TD are limited to only a few weeks’ duration. These trials are not sufficiently long enough to conclude that their side effect profiles are similar to placebo or superior to that of tetrabenazine. However, both valbenazine and deutetrabenazine appear to be well tolerated in the TD clinical trials. Nevertheless, given the similar mechanism of action and multiple overlapping metabolites with tetrabenazine, the long-term safety of these drugs compared to placebo or other treatments remains to be determined.

Some stakeholders have suggested that the new VMAT2 inhibitors could have a significant impact on controlling the underlying psychiatric conditions, particularly for conditions in which antipsychotic drugs are preferred. This is based on the assumption that better TD management will increase adherence to antipsychotics and reduce the need to modify antipsychotic doses and agents as a treatment strategy. While this is a plausible concept, it has not been evaluated in clinical studies to date, and so real-world data will be needed to assess these effects.

Finally, while the development of the new VMAT2 inhibitors is a step forward in the management of TD, there are still unanswered questions regarding the use of this class of drugs in clinical practice. Future studies should evaluate the patient or clinical factors (e.g. age, TD symptoms, baseline AIMS score, TD duration, ongoing use of DRBAs) that predict the likelihood of response to VMAT2 inhibitors. In addition, pragmatic clinical trials that include patients with other comorbid conditions or severe mental disorders encountered in routine clinical practice will be helpful. Furthermore, future studies should evaluate not only the short-term effect of these drugs but also the factors that will predict the durability of these effects and long term functional improvement.

Summary and Comment

We assigned ICER evidence ratings independently for each of the VMAT2 inhibitors, valbenazine, deutetrabenazine and tetrabenazine.

Table ES7. ICER Evidence Ratings

VMAT2 Inhibitors	ICER Evidence Rating
Valbenazine	P/I
Deutetrabenazine	P/I
Tetrabenazine	I

Valbenazine

For adults with tardive dyskinesia for at least three months and history of use of dopamine receptor blocking agents, we have moderate certainty that valbenazine provides a comparable, small, or

substantial net health benefit. However, because of the lack of clear benefit on Clinical Global Impression of Change (CGIC) scores and the patient reported outcome (PGIC scores), as well as the absence of long-term safety data compared to usual care, we cannot definitively rule out the possibility of a small net harm. Therefore, we consider the evidence on valbenazine to be “promising but inconclusive” (P/I).

- Treatment with valbenazine resulted in a greater reduction in AIMS scores and more patients with a substantial improvement in AIMS scores compared to placebo.
- Despite improvements in AIMS scores, treatment with valbenazine did not consistently result in improvement on CGIC scores. Additionally, currently available data on patient reported outcome (PGIC scores) do not demonstrate a benefit for valbenazine over placebo.
- Although valbenazine was generally well tolerated in the six-week trials, this is a new therapy that requires ongoing use, and important adverse effects could become apparent over time in larger patient populations.

Deutetrabenazine

For adults with tardive dyskinesia for at least three months and history of use of dopamine receptor blocking agents, we have moderate certainty that deutetrabenazine provides a comparable, small, or substantial net health benefit. However, because of the lack of clear benefit on the clinician assessed CGIC scores and the patient reported PGIC scores, as well as the absence of long-term safety data compared to usual care, we cannot definitively rule out the possibility of a small net harm. Therefore, we consider the evidence on deutetrabenazine to be “promising but inconclusive” (P/I).

- Treatment with deutetrabenazine resulted in a greater reduction in AIMS scores, and more patients with a substantial improvement in AIMS scale compared to placebo.
- Despite improvements on AIMS score, treatment with deutetrabenazine did not result in improvement on CGIC scores. Additionally, currently available data on patient reported outcome (PGIC scores) do not demonstrate a benefit for deutetrabenazine over placebo.
- Although deutetrabenazine was generally well tolerated in the 12-week trials, this is a new therapy that requires ongoing use, and important adverse effects could become apparent over time.

Tetrabenazine

Although tetrabenazine appears to have some potential benefit, we cannot be certain whether tetrabenazine is comparable, or possibly even inferior to placebo or other therapies due to the lack of direct comparative evidence in patients with tardive dyskinesia and the potential unfavorable

safety profile. We therefore consider the evidence for tetrabenazine in adults with TD for at least three months and history of use of DRBAs to be “insufficient” (I).

Comparative Value

Overview

We conducted a lifetime cost-effectiveness analysis using a simulation model of the two FDA-approved VMAT2 inhibitors, valbenazine and deutetrabenazine, for treating the symptoms of moderate-to-severe TD compared to placebo. We modeled the effects and costs of the highest doses reported in clinical trials (valbenazine 80mg and deutetrabenazine 36mg per day) because those doses were generally associated with the highest effects.^{18,19} The modeled population was adult patients with underlying schizophrenia/schizoaffective, bipolar, and major depressive disorders. Based on estimates from the literature, the proportion of patients with schizophrenia/schizoaffective disorders was set at 70.2%, the proportion with bipolar and other affective disorders was set at 29.8%, and the average expected age was 39 years.^{20,21} We incorporated clinical parameters based on applicable clinical trial data. Utilities, mortality rates, and treatment costs were obtained from drug manufacturers and published literature identified through the systematic review. Health care costs associated with TD, beyond the primary drug treatment costs, were unavailable in the literature and were estimated based on expert opinion.

The primary outcomes of the model included discounted total payer costs, life years, quality-adjusted life years (QALYs) gained, and incremental cost-effectiveness ratios, using a health-care system perspective over a lifetime horizon. Uncertainty was addressed through sensitivity analyses of key model inputs. Scenario analyses, including a scenario analysis using a modified societal perspective to allow for productivity costs as well as the potential for savings related to the indirect effect of TD control on the underlying conditions, were also conducted.

Methods

We developed a *de novo* semi-Markov model, consisting of four health states in the base-case model for the treatment arms: improved TD (where patients remained on treatment for TD), moderate to severe TD (where patients had discontinued TD therapy, either after an initial one-month trial or at a later time due to adverse events or lack of efficacy), discontinued therapy with improved TD (where patients had improved TD symptoms despite discontinuing therapy), and death. The placebo arm did not include the discontinued therapy health state. Costs and quality-adjusted life years were discounted at an annual rate of 3%, beginning with the second model cycle.

There were several key assumptions made in the development of the base case model.

- Patients receiving metoclopramide for gastrointestinal conditions and developing tardive dyskinesia were not modeled in this analysis.
- Before entering the model, all patients received one month of treatment and incurred one month of treatment costs as an initial cost.
- Patient response to the first month of treatment was reflected in their initial health states.
- Patients not responding to treatment with valbenazine or deutetrabenazine discontinued their treatment.
- Response to treatment remained constant for all responders. Patients did not improve or decline beyond their initial response to therapy while remaining in the “improved TD” state.
- Long-term discontinuation rates were modeled from open-labeled studies with less than one year of observation.^{18,22} Following the first cycle, discontinuation rates were modeled as being 50% of that observed in the first cycle.
- Patients who responded to treatment were assumed to have no additional primary care and neurologist visit costs related to TD. Patients not responding to treatment were assumed to have two additional primary care and two additional neurologist visits per year.
- TD treatments do not have a direct effect on mortality.
- Treatment of TD has no effect on the outcomes or costs of treating the underlying conditions.

A detailed description of key model assumptions can be found in Table 5.1 of the full report.

Model Inputs

Patients entered the model as having improved or not, following the first month of therapy. The effectiveness of valbenazine and deutetrabenazine was based on the proportion of patients that experienced a $\geq 50\%$ improvement in the AIMS score at the maximal tolerated dose in the clinical trials (80mg for valbenazine and 36mg for deutetrabenazine).^{18,19} Treatment effectiveness estimates for valbenazine 80mg and deutetrabenazine 36mg were 40% and 33.1% respectively, with their respective placebo responses at 8.7% and 12%. Because serious adverse events were uncommon in clinical trials and occurred at a rate similar to that observed in the placebo arm, the model did not directly incorporate the impact of adverse events in either arm. However, discontinuation rates were included in the model. Discontinuation rates used in the model were calculated based on discontinuation rates in clinical trials. For both drugs, we assumed a 50% decrease in discontinuation rate after the first year (valbenazine – 17.6%; deutetrabenazine – 13%) for all subsequent years (valbenazine – 8.8%; deutetrabenazine – 6.5%). Gains in utility from improvement in TD symptoms were modeled using estimates available in the literature (Appendix Table H4). The mean utility for the modeled population with improved TD was 0.82, which reflects utility scores associated with the underlying conditions.^{23,24} To this utility, we applied a utility

decrement of 0.095 to those patients with moderate to severe TD.²⁵ We modeled mortality using estimates from the general population adjusted to reflect rates in those with the underlying affective disorders,²⁶⁻²⁸ but assuming that TD and TD-related therapies did not impact mortality. TD-related drug and non-drug costs are listed in Table ES8. As both TD drugs were only recently approved, we do not have an estimate of their net price and hence applied a 27% industry-wide average branded-drug discount to the WAC to arrive at the net price for these drugs.²⁹

Table ES8. Cost Inputs

Drug Name, Administration Route	Strength	Annual WAC	Annual Net Price
Valbenazine, Oral Tablet	80mg daily	\$75,789 ^{29,30}	\$55,326
Deutetrabenazine, Oral Tablet	36mg daily	\$90,071 ^{29,30}	\$65,751
Management of TD Costs			
General Practitioner Visit (CPT Code 99213, Non-Institutional Charge)		\$73.93	
Specialist (Neurologist) Visit (CPT Code 99213, Non-Institutional Charge)		\$108.74	

Base-Case Results

Valbenazine and deutetrabenazine both resulted in increased costs and increased QALYs compared to placebo over a lifetime time horizon (Table ES9). The total discounted lifetime costs for valbenazine and the placebo comparator were approximately \$185,200 and \$6,900, respectively. The total discounted quality-adjusted life years (QALYs) for valbenazine and placebo were 15.35 and 15.12, respectively. Deutetrabenazine and its placebo comparator had lifetime discounted costs of approximately \$220,000 and \$6,600 and lifetime discounted QALYs of 15.37 and 15.18, respectively. The incremental cost-effectiveness ratios over a lifetime horizon were approximately \$752,000 per QALY for valbenazine and approximately \$1.101 million per QALY for deutetrabenazine (Table ES10).

Table ES9. Base-Case Discounted Costs and Outcomes

Treatment	Total Costs	Total QALYs
Valbenazine	\$185,167	15.35
Placebo (Valbenazine Comparison)	\$6,876	15.12
Deutetrabenazine	\$220,423	15.37
Placebo (Deutetrabenazine Comparison)	\$6,627	15.18

Table ES10. Pairwise Results for VMAT2 Inhibitors Compared to Placebo

Regimen	Incremental Costs	Incremental QALYs	Incremental Cost-Effectiveness Ratio vs. Placebo
Valbenazine	\$178,291	0.24	\$752,080
Deutetrabenazine	\$213,795	0.19	\$1,100,773

Costs per TD symptom-reduced year were approximately \$71,000 and \$105,000 for valbenazine and deutetrabenazine versus placebo respectively (Table ES11). It is difficult to judge the importance of these results, however, as there are no clear benchmarks of cost per TD symptom-reduced year for comparison.

Table ES11. Cost per TD Symptom-Reduced Year

Treatment	Cost per TD Symptom-Reduced Year
Valbenazine vs. Placebo	\$71,448
Deutetrabenazine vs. Placebo	\$104,573

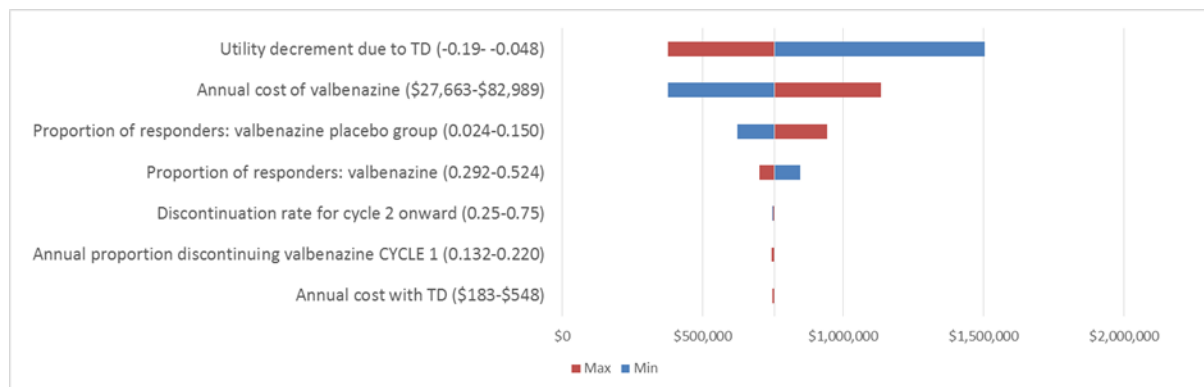
Sensitivity Analyses over Different Time Horizons

The estimated incremental cost-effectiveness ratios were higher over shorter time horizons and all surpassed commonly utilized thresholds of \$50,000 - \$150,000 per QALY in the base case analysis. The full results for these sensitivity analyses are reported in Appendix H5.

One- and Two-Way Sensitivity Analyses

We conducted one-way sensitivity analyses for each intervention to assess model uncertainty. Results of the one-way sensitivity analyses for valbenazine are shown in Figure ES1 and Table ES12. Altering the proportion of responders in either treatment or placebo group, discontinuation rates, drug costs, cost of TD, and disutility across reasonable bounds resulted in incremental cost effectiveness ratios that were consistently above the \$150,000 per QALY gained threshold. Results for deutetrabenazine are similar and available in Figures 5.3 and 5.7 of the full report. Two-way sensitivity analyses, in which we varied both the utility decrement and the proportion of responders, did not result in incremental cost-effectiveness ratios below the willingness to pay threshold of \$150,000 per QALY for either therapy compared with placebo (see Figure 5.4 and Figure 5.5 in the full report).

Figure ES1. Tornado Diagram for Valbenazine One-Way Sensitivity Analyses



Base-Case Incremental Cost-Effectiveness Ratio: \$752,080 per QALY gained

Table ES12. One-Way Sensitivity Analyses: Valbenazine

Parameters	Base Case Value	Sensitivity Analysis Value		Incremental Cost per QALY	
		Min	Max	at input min	at input max
Proportion of Responders: Placebo	0.087	0.024	0.150	\$624,754	\$942,574
Proportion of Responders: Valbenazine (80mg)	0.400	0.292	0.524	\$846,715	\$701,109
Annual Discontinuation*	0.176	0.132	0.220	\$750,100	\$745,151
Discontinuation rate for cycle 2 to end of time horizon	50% of first cycle	25% of first cycle	75% of first cycle	\$748,933	\$755,000
Annual Cost of Valbenazine	\$55,326	\$27,663	\$82,989	\$374,116	\$1,130,039
Annual Cost of TD Care	\$365	\$183	\$548	\$754,000	\$750,158
Utility Decrement due to TD	-0.095	-0.19	-0.048	\$376,040	\$1,504,160

Probabilistic Sensitivity Analysis Results

A Monte Carlo probabilistic sensitivity analysis based on probabilistic inputs for the base case model was conducted using 10,000 simulations. Distributions were assigned based on available data. The results are summarized in Appendix H5. None of the incremental cost effectiveness ratios for either drug in any of the simulations were below the \$150,000 per QALY threshold.

Threshold Analysis

In single-input threshold analyses, prices for each drug to achieve commonly-cited cost-effectiveness thresholds ranging from \$50,000 to \$150,000 per QALY gained are presented in Table ES13.

Table ES13. Threshold Analysis Results for Valbenazine and Deutetrabenazine

	Annual WAC	Annual Price to Achieve \$50,000 Per QALY	Annual Price to Achieve \$100,000 Per QALY	Annual Price to Achieve \$150,000 Per QALY
Valbenazine 80mg capsules (dose = 80 mg per day)	\$75,789	\$3,941	\$7,600	\$11,260
Deutetrabenazine 9 mg tablets (dose = 36 mg per day)	\$90,071	\$3,205	\$6,181	\$9,158

Scenario Analyses

An analysis from a modified societal perspective was undertaken, varying the annual lost productivity due to TD, resulted in only small improvements in the cost-effectiveness ratios for the two agents (see model structure and inputs in Appendix Figure H3 and Table H6). Two additional scenario analyses attempted to account for potential but unproven benefits of TD treatment in improved maintenance and medication adherence for patients' underlying conditions of schizophrenia/schizoaffective disorders and bipolar disorders. The incremental cost effectiveness ratios for these scenario analyses were predictably lower compared with the base case analysis (Table 5.9), but remained well above commonly-cited thresholds.

Model Validation

Model validation followed standard practices in the field. Three modelers tested the mathematical functions in the model as well as therapy-specific inputs and corresponding outputs. We also compared the ICER model to previously published models. One previously published model which assessed the cost-effectiveness of second-generation antipsychotics in reducing the risk of TD in adults with schizophrenia was compared to the ICER model, but only from a structural perspective.³¹ Additional detail regarding model comparisons can be found in the full report.

Potential Budget Impact

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using one of the two VMAT2 inhibitors rather than existing care for the treated population, calculated as differential health care costs minus any offsets in these costs from averted health care events.

We derived the number of eligible patients (adult patients with moderate to severe TD who were on antipsychotic drug therapy to treat underlying affective disorders) using estimated TD prevalence, which in 2016 was 573,000 patients in the US, of which 359,000 had moderate to

severe TD. Epidemiological data projecting TD prevalence up to 2025 was used to estimate the prevalence of moderate to severe TD between 2017 and 2021, to arrive at a five-year average prevalence of 360,000 patients. Assuming uptake of the new therapies over five years results in an estimated 72,000 patients per year.

Costs for the VMAT2 inhibitors were calculated using the WAC, discounted WAC, and three threshold prices (Tables ES14 and ES15). When treating the eligible cohort with valbenazine, the highest average potential budgetary impact (adjusted for differing periods of drug utilization and associated cost-offsets over the five-year period) was seen when using the WAC (\$75,789) and discounted WAC (\$55,326), at an additional per patient cost of approximately \$30,100 and \$22,000, respectively. Approximately 15% and 21% of the eligible patient cohort could be treated in a given year before the budget crossed the ICER annual budget impact threshold of \$915 million, using the WAC and discounted WAC of valbenazine.

Table ES14. Per-Patient Budget Impact Calculations for Valbenazine Over a Five-year Time Horizon

	Average Annual Per Patient Budget Impact				
	WAC	Discounted WAC	\$150,000/QA LY	\$100,000/QA LY	\$50,000/QALY
Valbenazine	\$30,495	\$22,325	\$4,313	\$3,281	\$1,816
Usual Care	\$345				
Difference	\$30,150	\$21,980	\$4,001	\$2,936	\$1,471

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

When treating the eligible cohort with deutetrabenazine, the highest average potential budgetary impact (adjusted for differing periods of drug utilization and associated cost-offsets over the five-year period) was seen when using the WAC (\$90,071) and discounted WAC (\$65,752) at an additional per patient cost of approximately \$31,000 and \$22,600, respectively. Approximately 14% and 20% of the eligible patient cohort could be treated in a given year before the budget crossed the ICER annual budget impact threshold of \$915 million, using the WAC and discounted WAC of deutetrabenazine.

Table ES15. Per-Patient Budget Impact Calculations for Deutetrabenazine Over a Five-year Time Horizon

	Average Annual Per Patient Budget Impact				
	WAC	Discounted WAC	\$150,000/QALY	\$100,000/QALY	\$50,000/QALY
Deutetrabenazine	\$31,307	\$22,924	\$3,428	\$2,398	\$1,368
Usual Care	\$333				
Difference	\$30,974	\$22,591	\$3,095	\$2,065	\$1,035

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

Value-Based Benchmark Prices

Our value-based benchmark annual prices for valbenazine and deutetrabenazine are presented in Table ES16. As noted in the initial ICER methods document (<http://icer-review.org/wpcontent/uploads/2016/02/Value-Assessment-Framework-slides-for-July-29-webinar-FINALcorrected-8-22-1.pdf>), the value-based benchmark price for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between \$100,000 and \$150,000 per QALY gained. For both drugs, the discounts required to meet both threshold prices are greater than the currently assumed discount from WAC.

Table ES16. Value-Based Benchmark Prices for Valbenazine and Deutetrabenazine for the Treatment of Moderate to Severe Tardive Dyskinesia

	Annual WAC	Annual Price to Achieve \$100,000 Per QALY	Annual Price to Achieve \$150,000 Per QALY	Discount from WAC To Reach Thresholds
Valbenazine 80mg capsules (dose = 80 mg per day)	\$75,789	\$7,600	\$11,260	85%-90%
Deutetrabenazine 9 mg tablets (dose = 36 mg per day)	\$90,071	\$6,181	\$9,158	90%-93%

Summary and Comment

We estimated the cost-effectiveness of the two recently-approved VMAT2 inhibitors compared to placebo in patients with TD. Our base-case cost-effectiveness analyses show that both VMAT2 inhibitors far exceed commonly cited cost-effectiveness thresholds, when compared with placebo. Varying key model parameters within reasonable ranges in one-way sensitivity analyses did not result in either of the VMAT2 inhibitors showing cost-effectiveness ratios below the \$150,000 per QALY threshold relative to placebo. In addition, probabilistic sensitivity analyses showed very low likelihood of both drugs approaching commonly cited cost-effectiveness thresholds.

Our model has several limitations. Key limitations include:

- effectiveness data that were based on limited intermediate measures from clinical trials,
- current TD severity measures that do not accurately reflect disease burden on overall quality of life,

- a lack of data on discontinuation of TD medication due to adverse events beyond the first year,
- lack of robust data on non-drug costs of TD,
- inability to include sub-populations that may differ from the average TD patient, due to a lack of sub-population data.

Our budget impact analyses indicated that using either valbenazine or deutetrabenazine at net prices in place of no TD-focused treatment would result in being able to treat only 21% and 20% of the entire eligible cohort per year before crossing the ICER annual budget impact threshold of \$915 million.

In summary, our analyses suggest that the clinical benefits associated with the VMAT2 inhibitors will lead to increased quality-adjusted life expectancy over no specific treatment for TD symptoms (i.e., placebo). At current prices, however, the estimate lifetime cost-effectiveness of these agents far exceeds commonly-cited cost-effectiveness thresholds.

Additional Considerations

Tables ES17 and ES18 seek to provide information on other benefits and contextual considerations offered by VMAT2 inhibitors to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness.

Other Benefits

Table ES17. Potential Other Benefits

Other Benefits	Description
This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.	Data from available studies may not capture the full range and magnitude of benefit from the use VMAT2 inhibitors. For example, because of the challenges of capturing the social impact of TD on individual patients, patients and patient groups expressed concerns that the outcome measures used in clinical literature may underestimate the magnitude of the impact of these drugs. The VMAT2 inhibitors may also have positive impacts on adherence to management of underlying psychiatric and other medical conditions, but as of yet no data are available on these potential benefits.
This intervention offers reduced complexity that will significantly improve patient outcomes.	N/A
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	N/A
This intervention will significantly reduce caregiver or broader family burden.	For individuals with severe, disabling tardive dyskinesia, the use of VMAT2 inhibitors may decrease caregiver/family burden, but as of yet no data are available.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.	Valbenazine and deutetrabenazine are the first FDA approved treatments for patients with tardive dyskinesia due to use of DRBAs. Approval of these drugs for tardive dyskinesia represents a potentially important advancement for individuals with this frequently irreversible condition.
This intervention will have a significant impact on improving return to work and/or overall productivity.	Tardive dyskinesia can have a significant impact on ability to work. Studies of VMAT2 inhibitors have not evaluated return to work or productivity outcomes. However, patients and advocacy organizations described how for some patients with tardive dyskinesia, treating symptoms with VMAT2 inhibitors may make it easier to find a job and/or maintain a job.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	Among VMAT2 inhibitors, tetrabenazine requires 2-3 times per day dosing, deutetrabenazine requires twice a day dosing, and valbenazine requires once daily dosing. Adherence with treatment may be somewhat improved by using medications that require less frequent dosing, although the degree of potential improvement is unclear.

Contextual Considerations

Table ES18. Potential Contextual Considerations

Contextual Consideration	Description
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	Studies of valbenazine and deutetrabenazine had eligibility criteria that will not be available when used as part of routine clinical practice. Thus, it remains to be determined which patients with tardive dyskinesia will be treated with these new VMAT2 inhibitors.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	For patients with serious psychiatric conditions in whom DRBAs are the most effective treatments available, patient concerns about side effects, including tardive dyskinesia, may influence their decision to take DRBAs or comply with therapy if prescribed. More effective treatment for individuals with tardive dyskinesia in whom DRBAs are the therapy of choice may improve compliance with DRBA therapy and the control of the underlying psychiatric condition.
This intervention is the first to offer any improvement for patients with this condition.	Though many questions remain about the benefits and harms of VMAT2 inhibitors for tardive dyskinesia, there is considerable interest among patients and their healthcare professionals in having an FDA approved treatment for this condition.
Compared to usual care, there is significant uncertainty about the long-term risk of serious side effects of this intervention.	For many patients, tardive dyskinesia is a chronic condition and treatment, if effective, will require long-term use. As newly approved drugs, the long-term risks of valbenazine and deutetrabenazine will only become apparent with ongoing use in comparative studies involving a large number of treated individuals.
Compared to usual care, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	The only comparative data for VMAT2 inhibitors is to placebo, and the duration of the randomized portion of clinical trials was only 6-12 weeks. Thus, it is unclear how the long-term benefits of valbenazine and deutetrabenazine may compare to each other and to other therapies that have been used off-label for tardive dyskinesia. In addition, the magnitude and durability of ongoing use of VMAT2 inhibitors compared to usual care is uncertain and will require prospective study.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	N/A

Potential Cost-Saving Measures in Tardive Dyskinesia

We sought to identify areas of waste and low-value care in psychiatry that could be reduced to make way in health care budgets for new innovations. We reached out to clinicians, patients and patient groups, manufacturers, and other payers for input on potential targets for waste reduction. The following areas were highlighted by stakeholders:

- *Stakeholders from Mental Health America (MHA)* suggested that early intervention programs can be cost-saving over the long term for standard mental health services by delivering better initial intervention for patients with first-time psychosis. The suggestion is strengthened by a small study conducted in Australia which found cost savings in a small group of patients who were treated for up to two years with an early psychosis intervention, and yielded better health outcomes and lower health care costs eight years later.³²
- *Stakeholders from the Depression and Bipolar Support Alliance (DBSA)* highlighted the results from a 2015 DBSA survey on agitation and emergency care, which showed that about 60% of patients presenting with agitation in the ED returned within a year (34% within 60 days). They suggested that patients should be routinely provided with information about mental health services in the community or be referred to psychiatrists upon discharge from the ED to decrease return visits and their associated costs to the health care system.

Additionally, we reviewed the American Board of Internal Medicine's Choosing Wisely® campaign, which encourages specialty societies to identify areas of low-value care that could be reduced or eliminated. Below are recommendations we identified that could potentially be cost-saving.

- *Choosing Wisely* suggests ensuring an appropriate initial evaluation and ongoing monitoring for patients before prescribing antipsychotic medications for any indication due to metabolic, neuromuscular, and cardiovascular side effects.³³ These side effects may potentially result in additional costs.
- *Choosing Wisely* also recommends against prescribing antipsychotics as first choice to treat behavioral and psychological symptoms of dementia, and as a first-line intervention for insomnia in adults, because the evidence demonstrates that the risks (e.g. cerebrovascular effects, parkinsonism, extrapyramidal signs, TD, confusion, increased body weight) outweigh the potential benefits in these populations.^{33,34}

Summary of the Votes and Considerations for Policy

At the December 5 meeting, the New England CEPAC Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of VMAT2 Inhibitors for treating symptoms of Tardive Dyskinesia. Following the evidence presentation and public comments (public comments from the meeting can be accessed [here](#), starting at minute 1:42:23), the CEPAC Panel voted on key questions concerning the comparative clinical effectiveness, and other benefits and contextual considerations related to VMAT2 inhibitors. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making.

Given the high incremental cost effectiveness ratios – that far exceeded commonly agreed upon thresholds for cost effectiveness—the panel did not vote on any questions related to the long-term value for money. The voting results are presented below. Specific considerations mentioned by CEPAC Panel members during the voting process are included in the full report.

Patient Population for all questions: Adults ages 18 and older with symptoms of tardive dyskinesia for at least three months and history of use of dopamine receptor blocking agents (DRBAs).

1. Is the evidence adequate to demonstrate a positive net health benefit from treating patients with TD with valbenazine?

Yes: 11 votes

No: 4 votes

2. Is the evidence adequate to demonstrate a positive net health benefit from treating patients with TD with deutetrabenazine?

Yes: 10 votes

No: 5 votes

3. Is the evidence adequate to demonstrate a positive net health benefit from treating patients with TD with tetrabenazine?

Yes: 2 votes

No: 13 votes

4. Is the evidence adequate to distinguish between the net health benefit of valbenazine and deutetrabenazine in the treatment of TD?

Yes: 1 vote

No: 14 votes

5. Does treating patients with one of the new FDA approved drugs offer one or more of the following “other benefits”? (select all that apply)

# of Votes	Other Benefits
8	This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.
3	This intervention offers reduced complexity that will significantly improve patient outcomes.
2	This intervention will reduce important health disparities across racial, ethnic, gender, socioeconomic, or regional categories.
3	This intervention will significantly reduce caregiver or broader family burden.
12	This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.
5	This intervention will have a significant impact on improving return to work and/or overall productivity.

6. Are any of the following contextual considerations important in assessing the new FDA approved drugs’ long-term value for money in patients with tardive dyskinesia? (select all that apply)

# of Votes	Contextual Considerations
9	This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
8	This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
3	This intervention is the first to offer any improvement for patients with this condition.
14	Compared to usual care, there is significant uncertainty about the long-term risk of serious side effects of this intervention.
12	Compared to usual care, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.

Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the New England CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on VMAT2 inhibitors in treating patients with tardive dyskinesia to policy and practice. The policy roundtable members included two patient representatives; two clinical experts, representing the fields of neurology and psychiatry; two payers, both public and private; and a representative from each of the drug manufacturers with the newly approved therapies of focus in this review. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken

as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below, and conflict of interest disclosures for all meeting participants can be found in [Appendix J].

Table ES19. Policy Roundtable Members

Name	Title and Affiliation
Victor Abler, DO	Senior Global Medical Director for Neurodegenerative Diseases, Teva Pharmaceuticals
Teri Brister, PhD	Director Knowledge Integration Information, National Alliance on Mental Illness
Oliver Freudenreich, MD.	Co-Director, Mass General Hospital Schizophrenia Clinical Research Program
Patrick Hendry	Vice President of Peer Advocacy Support and Services, Mental Health America
Barbara Henry, RPh	Lead Clinical Pharmacy Specialist, Harvard Pilgrim
Paul Jeffrey, PharmD	Director of Pharmacy, MassHealth
Daniel Tarsy, MD	Professor of Neurology; Parkinson's Disease and Movement Disorders Center, Beth Israel, Harvard Medical School
Chuck Yonan, PharmD	Senior Director HEOR, Medical Affairs, Neurocrine Bioscience

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations are organized by audience and summarized below. Full descriptions of each recommendation are provided in the full report.

Manufacturers

- 1. In order to provide reasonable value and thereby facilitate improved access and affordability for patients, prices for the VMAT2 inhibitors should be reduced to better align with their demonstrated short-term clinical benefits.*
- 2. Manufacturers should support studies of patients with TD to generate evidence on the relative long-term benefits and harms of individual VMAT2 inhibitors and other treatment options.*
- 3. Manufacturers and researchers should support studies to directly compare VMAT2 inhibitors by standardizing research protocols and outcome assessments to permit real-world, long-term outcome assessment.*

Payers

- 4. Given that the new VMAT2 inhibitors are priced far beyond their relative benefits for patients, payers should use available evidence, along with patient and clinical expert input, to develop prior authorization criteria, periods of authorized treatment, and methods for feedback to clinicians regarding the potential for alternative management of TD (e.g., switching from an offending DRBA to another agent).*

5. *Payers can leverage competitive market forces by negotiating for the best possible price in exchange for exclusive formulary placement of only one VMAT2 inhibitor. Other drugs in the class should remain available through an individual appeal process.*

Patient Advocacy Organizations and Researchers

6. *Patients and their representatives should work with researchers to develop outcome measures that better document the impact of TD on functional domains related to work, family, and social interactions.*

Specialty Societies

7. *Professional societies should accept the responsibility to update their clinical practice guidelines rapidly following the advent of paradigm-changing treatment options like the VMAT2 inhibitors.*
8. *Given that VMAT2 inhibitors may be prescribed by a larger group of specialist and primary care clinicians, professional societies should develop educational materials to educate clinicians about TD management and to encourage close coordination among all clinicians caring for these patients.*

Regulators

9. *Regulators should require post-approval, long-term comparative outcomes studies for treatments initially evaluated and approved in very short-term randomized trials, but for which long-term therapy would be expected.*

Affordability & Access Alert

ICER is issuing an Affordability and Access Alert as part of its final report on VMAT2 inhibitors for treating TD. During the public meeting of the New England CEPAC, we asked clinical experts and patient advocates on our policy roundtable what the appropriate target should be for the percentage of eligible patients who should receive treatment with either of the new drugs for TD. Their view was that insurance coverage should facilitate a trial of treatment with the new therapies for all patients with moderate-to-severe TD. We used this target for optimal clinical application of the new drugs, and assumed treatment initiation would be spread over 5 years. Our estimates of the potential net budget impact of VMAT2 inhibitors indicated that at an estimated national average discount price of 27% off the WAC price for each drug, only 21% and 20% of all eligible patients could be treated with valbenazine and deutetrabenazine, respectively, before costs would exceed ICER's potential budget impact threshold of \$915 million per year. At the prices that would

meet ICER's value-based price benchmark, all eligible patients could be treated without exceeding the potential budget impact threshold.

Given that optimal clinical uptake at current estimated discount prices would lead to 5-year costs far in excess of this threshold, ICER's Affordability and Access Alert is intended to provide a signal to manufacturers, insurers, patient groups, and other stakeholders when the amount of added health care costs associated with these new treatments may be difficult for the health care system to absorb over the short term without displacing other needed services or contributing to rapid growth in health care insurance costs that threaten sustainable access to high-value care for all patients. ICER encourages all stakeholders to consider whether action should be taken to achieve additional price discounts, prioritize treatment access, find ways to reduce waste to provide additional resources, or take other policy steps to manage these budget implications.

1. Background

1.1 Introduction

Background

Tardive dyskinesia (TD) is a repetitive, involuntary movement disorder with a delayed onset caused by prolonged use of medications that block the dopamine receptor.³⁵ The most common medications causing TD are antipsychotic drugs used to treat individuals with schizophrenia and schizoaffective disorder, mood disorders such as bipolar disease and major depression, and dementia, personality disorders, post-traumatic stress disorder, and insomnia.^{36,37} Less commonly-used medications associated with TD include metoclopramide for gastrointestinal disorders and certain antidepressants with dopamine receptor blocking properties such as amoxapine.^{38,39}

Overall, 20-50% of individuals taking antipsychotic drugs develop TD, with increased prevalence associated with longer duration of use, older age, female gender, and the specific antipsychotic drug used.^{40,41} Newer antipsychotic drugs, referred to as second-generation or atypical agents, are somewhat less likely to cause TD than older, first-generation antipsychotic drugs.⁴² The incidence of developing TD is reported to be around 5% per year with first-generation and 3% per year with second-generation antipsychotics.^{43,44} However, the increased use of newer antipsychotic drugs mean that they represent most new cases of TD.

The movements associated with TD can be localized or widespread and can result in physical and psychological impairment.⁴⁵ TD commonly involves the mouth and face region with lip smacking or pursing, chewing, facial grimacing, and tongue movements. TD can also affect the head and neck with abnormal asymmetrical postures, and the limbs and trunk with foot tapping, finger movements, and shoulder shrugging. Patients may not be aware of these movements, especially when involving the face. For most, symptoms are mild to moderate. When severe, TD can lead to difficulty swallowing, trouble walking, and impaired speech. Thus, TD can be extremely debilitating and result in social isolation, problems in the workplace, and decreased compliance with the drugs given to treat the underlying condition.⁴⁶

Many treatments have been tried for TD, but there has been limited evidence generated to date that can guide patients and clinicians.^{26,36,47} Although reducing or discontinuing the offending agent would seem logical, this is often not possible because TD symptoms can paradoxically increase on withdrawal and the underlying condition may worsen. Until recently there were no FDA-approved therapies for TD. However, the approval by the FDA of novel vesicular monoamine transporter-2 (VMAT2) inhibitors, valbenazine and deutetrabenazine, has led to new interest in TD and its treatment.⁴⁸

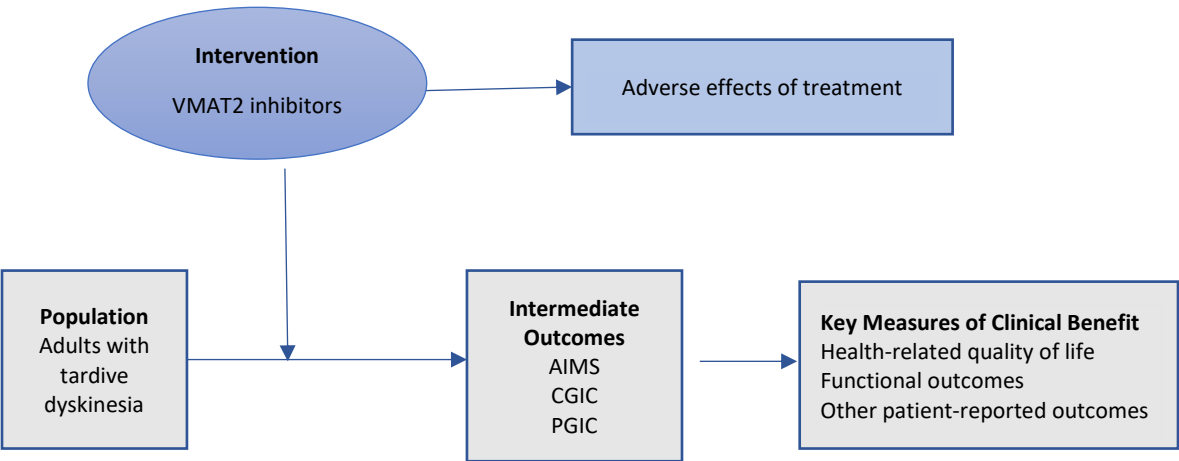
Scope of the Assessment

This review evaluated the comparative clinical effectiveness of the VMAT2 inhibitors valbenazine, deutetrabenazine, and tetrabenazine for the treatment of adults with TD. Evidence was collected from available randomized controlled trials, non-randomized clinical trials, comparative observational studies, as well as high-quality systematic reviews. We limited our review to those studies that captured the outcomes of interest; however, when assessing adverse events and harms, we also looked for randomized trials of the VMAT2 inhibitors for conditions other than TD. We did not restrict studies according to study duration or study setting; however, we limited our review to those that measured the outcomes of interest and included at least 10 patients. We supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see <http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/>). We sought out head-to-head studies of these interventions in order to consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes.

Analytic Framework

The analytic framework for this assessment is depicted in Figure 1.1.

Figure 1.1. Analytic Framework: Management of Tardive Dyskinesia



VMAT2: vesicular monoamine transporter 2; AIMS= Abnormal Involuntary Movement Scale; CGIC= Clinical Global Impression of Change; PGIC= Patient Global Impression of Change

Populations

The primary population of focus for the review was adults ages 18 and older with symptoms of TD for at least three months and history of use of dopamine receptor blocking agents (DRBAs).⁴⁹ In addition to children and adolescents, we also excluded studies of adults with movement disorders related to other conditions (e.g., Huntington's disease) or whose disorder was not thought to be medication-induced. However, populations with conditions other than TD that use the interventions of interest were also assessed when examining adverse events and other potential harms.

We also sought evidence on key subpopulations of interest, including: (a) patients with incident or new onset TD; (b) patients with localized versus generalized TD symptoms; (c) patients with schizophrenia/schizoaffective disorders versus other underlying conditions that may be associated with TD. Other subgroups of interest included age, gender, and severity of symptoms as assessed by both clinicians and patients (i.e., mild, moderate, or severe).

Interventions

We considered all VMAT2 inhibitors including those with FDA indications for TD as well as one drug that is used off-label for TD. Interventions of interest are listed below.

- Valbenazine (Ingrezza™, Neurocrine Biosciences, Inc)
- Deutetrabenazine (Austedo®, Teva)
- Tetrabenazine (Xenazine®, Lundbeck and generics [off-label use])

Comparators

We examined studies comparing VMAT2 inhibitors to placebo or other types of active medications that are used off-label to control TD symptoms. Wherever possible, we evaluated head-to-head trials of the interventions. If suitable data was available, the review sought to include head-to-head comparisons through methods such as network meta-analysis.

Outcomes

This review examined key clinical outcomes associated with TD. However, when assessing adverse events and harms, we also looked for randomized trials of the interventions of interest for conditions other than TD. We engaged with patient groups and clinical experts to ascertain which outcomes are of greatest importance to patients, and sought patient-reported outcomes or other evidence sources to enrich the available data. Discussion with patients, patient groups, and clinicians indicated that clinical trials often lack robust information on patient-reported outcomes and burdens associated with TD.

Outcomes of interest included:

- Symptom improvement (Abnormal Involuntary Movement Scale [AIMS], Clinical Global Impression of Change [CGIC])
- Patient reported outcome (Patient Global Impression of Change [PGIC])
- Health-related quality of life
- Treatment-related adverse events (e.g., somnolence, suicide, worsening of underlying mental health illness)
- Discontinuation due to adverse events
- Costs and cost-effectiveness

We also sought evidence on additional patient-reported outcomes as available. Importantly, long-term use of antipsychotic drugs is also associated with the development of other extrapyramidal symptoms and movement disorders, but the focus of this assessment was on TD symptoms only.

Evidence tables were developed for each selected study and results were summarized in a qualitative fashion. If available data permitted, we sought to perform meta-analysis to quantitatively summarize outcomes for the therapies of interest, and network meta-analysis to combine direct and indirect evidence of effectiveness.

Timing

Evidence on intervention effectiveness was derived from studies of any duration if they meet the study design criteria set forth above and measure the outcomes of interest.

Settings

All relevant settings were considered, including outpatient/clinic, office, and home settings.

2. The Topic in Context

TD was first described in the 1950s with the introduction of first-generation antipsychotic drugs (e.g., chlorpromazine).³⁷ Recognition that TD was a drug-induced condition caused by long-term use of antipsychotic drugs led to the introduction of clozapine and other newer antipsychotic drugs (also called atypical or second-generation antipsychotic drugs) starting in the 1970s, with the goal of decreasing TD and other abnormal movements attributed to these medications. Antipsychotic drugs are believed to work in the brain as dopamine receptor blocking agents (DRBAs), and the newer antipsychotic drugs have properties that were intended to decrease the likelihood of TD and other abnormal movements while maintaining the drugs' beneficial effects. Though antipsychotic drugs are the most common DRBAs used in medical practice, other DRBAs such as metoclopramide, which is used to treat certain gastrointestinal problems that cause nausea and vomiting, can also cause TD.

2.1 How Common is Tardive Dyskinesia?

TD is common in patients treated with DRBAs for long periods of time. The prevalence rates of TD have been estimated to range from 20-50%, and is thought to be higher for first-generation (30%) than for second-generation (13-20%) agents.^{40,50} The incidence of new TD is reported to be around 5% per year with first-generation antipsychotic drugs and 3% per year with second-generation antipsychotic drugs.^{43,44,51} Higher rates are seen with longer duration of use and in female and older patients.⁴¹ Though newer antipsychotic drugs may have a somewhat lower risk of TD, rates are not as low as initially hoped, and the use of these agents have increased with an expanding range of off-label indications.^{52,53}

While antipsychotic drugs were initially developed for use in patients with schizophrenia and schizoaffective disorder, they are also used in serious mood disorders such as bipolar disease and major depression. Off-label use of antipsychotics include treatment of obsessive-compulsive disorder, personality disorders, post-traumatic stress disorder, insomnia, and agitation in dementia. Symptoms of TD can vary from mild to severe and can adversely affect all aspects of patient's lives including physical and psychological impairment, social isolation, and work-related disability. It is estimated that there are 6 million individuals in the United States with these diagnoses who have received antipsychotic drugs.⁵⁴ Among these persons, there may be 500,000 individuals with TD if the prevalence is 25%, for example. For most, TD symptoms are irreversible, even if the DRBA is stopped.⁵⁵ Younger individuals and those on DRBAs for shorter periods of time may have decreased TD symptoms with cessation, but complete resolution is uncommon. If new treatments are targeted to those with moderate or severe TD and 60% have such symptoms, then one may estimate that 300,000 patients would be eligible for new treatments.

2.2 How is Tardive Dyskinesia Diagnosed?

The diagnosis of TD is based upon presence of abnormal, involuntary movements, a history of taking a DRBA for at least three months, and the absence of another condition that may produce such movements. Diagnosis is therefore clinical in nature only, meaning there are no specific tests that can be done to confirm or “prove” the diagnosis. The severity of TD symptoms and the impact of treatment can be assessed using survey questionnaires. The most common is the Abnormal Involuntary Movement Scale (AIMS) that has been used in clinical and research settings.² The AIMS score is based on the measurement of seven items (four involving facial/oral movements, two involving the extremities, and one the trunk), with severity rated from 0 (none) to 4 (severe). The total score ranges from 0-28 with higher AIMS scores reflecting increased severity of TD symptoms. (see Appendix Table F1). While the AIMS assesses symptom severity, it is unclear how well it reflects the overall impact of TD on a patient's quality of life.

The abnormal, involuntary movements seen in TD are slow, rhythmical, and stereotyped, and can be generalized or limited to specific parts of the body. Most common is involvement of the mouth and face region with abnormal movements of the lips, jaw, tongue, and face. TD can also involve the limbs, such as repetitive foot tapping and finger movements, and trunk, including rocking and rotatory movements of the neck, shoulders, and hips. It is difficult to rate the severity of TD symptoms from the patient's perspective because even limited symptoms involving just one part of the face can be very noticeable and stigmatizing, and the level of stigma can vary significantly based on the patient's work, school, and/or living situation. Moreover, depending on the underlying disease, patients may not be aware of these involuntary movements, and thus, patient reported symptoms may underestimate their severity. A further challenge in assessing outcomes of treatments for TD is that there are different ways to rate severity of symptoms, including provider's global rating or using a minimum score on the AIMS, calculated either by the treating clinician or by blinded experts reviewing recorded patient videos.

2.3 Treatment Options for Tardive Dyskinesia

Despite over 50 years of experience with antipsychotic drugs and awareness of TD, until recently there were no FDA-approved treatments used to reduce TD symptoms. Many studies have evaluated a wide range of therapies to treat TD, but the overall quality of the studies and the evidence available to support evidence-based recommendations is poor.^{1,26} The American Psychiatric Association released a practice guideline for the treatment of patients with schizophrenia in 2004, but it does not specifically address management of antipsychotic drug-related TD.⁵⁶ The American Academy of Neurology (see Section 3 for details) published an

evidence-based guideline for treatment of TD, and a systematic review of interventions for treating or preventing antipsychotic drug-induced TD was produced for the U.K. National Institute for Health Research.^{1,26} These reports generally highlight an insufficient level of data to make evidence-based recommendations.

Treatment options have included 1) withdrawing the offending antipsychotic drug, 2) changing to a different antipsychotic drug, 3) off-label use of prescription medications, 4) over-the-counter vitamins and supplements, and 5) non-pharmacologic treatments such as electroconvulsive therapy and deep brain stimulation.^{1,26,36} Avoiding long-term use of antipsychotics for conditions where evidence of benefit is lacking or other treatment options are available is preferred. However, for many patients with severe psychiatric conditions, antipsychotic drugs may be the best available option. Neither decreasing and then stopping the offending agent nor switching to a different antipsychotic drug has consistently been shown to be an effective treatment option. Moreover, it is often not possible to stop the antipsychotic drug immediately, because TD symptoms can worsen upon withdrawal. Though TD symptoms may improve with these changes, complete resolution of symptoms is uncommon, especially for patients who have taken antipsychotic drugs for long periods of time.⁵⁵⁻⁵⁷ Long-lasting or permanent symptoms can be seen even in patients who successfully are taken off the antipsychotic drug.^{58,59} Therefore, other treatments have been sought to decrease symptoms of patients with TD.

Though a wide range of pharmacologic treatments for TD have been studied, few therapies have been shown to produce more than a slight to moderate benefit.^{36,47} Other drugs used have included second-generation antipsychotic drugs, cholinergic agents, anticholinergic agents, antioxidants, benzodiazepines, dopamine agonists, dopamine depleting agents, GABA agonists, calcium channel blockers, buspirone, botulinum toxin and many others.^{1,26}

2.4 Vesicular Monoamine Transporter 2 (VMAT2) Inhibitors

The precise mechanism that results in TD from prolonged exposure to DRBAs is not well-understood. One hypothesis involves the secondary upregulation and hypersensitivity of the dopamine receptor.^{38,60} Vesicular monoamine transporter-2 (VMAT2) is responsible for storing and releasing dopamine from synaptic vesicles in the brain.⁶¹ The VMAT2 inhibitor tetrabenazine was approved in 2008 by the FDA for use in Huntington's disease. Tetrabenazine has also been used in an off-label manner for individuals with moderate to severe TD symptoms. VMAT2 inhibitors may offset the movement related side effects of antipsychotic drugs and other DRBAs by modulating the pre-synaptic packaging and release of dopamine into the nerve cell synapse. This depletion of dopamine storage in pre-synaptic vesicles results in less dopamine release.

Several small controlled and observational studies of tetrabenazine have shown varying improvement in symptoms, but the need for thrice-daily dosing and side effects, including sedation and worsening of depression and anxiety, have limited its usefulness. In addition, it carries a “black box” warning for depression as well as suicidal thoughts and behavior.

The approval of tetrabenazine for chorea associated with Huntington’s disease led to renewed interest in how this mechanism and class of drugs might be used to treat a variety of hyperkinetic movement disorders. Deutetrabenazine (Austedo®, Teva) contains deuterium, a naturally occurring form of hydrogen, which slows metabolism and clearance. Approved for the treatment of chorea associated with Huntington’s disease in April of 2017, it is dosed twice daily and carries the same boxed warnings as tetrabenazine. Deutetrabenazine was approved for use in patients with TD on August 30, 2017.

Similar to tetrabenazine and deutetrabenazine, valbenazine (Ingrezza™, Neurocrine Biosciences, Inc.) is a VMAT2 inhibitor, but it has different binding affinities and is dosed once a day. In April 2017, it became the first FDA-approved drug for TD. It does not carry a black box warning or specific contraindications.

Approval by the FDA of the first two treatments for TD represents a potentially important advance for individuals with this frequently irreversible condition. It is noteworthy that the recent systematic review of treatments for TD that was performed before publication of the studies that formed the basis for FDA approval concluded “we still do not know how to treat people with/at risk of TD effectively,” and “people with TD feel disappointed and angry at the length of time it has taken for researchers to address the issue of how to treat TD.”²⁶

Table 2.1. VMAT2 Inhibitors of Interest for the Evidence Review

VMAT2 Inhibitors	Recommended Dose	Dosage Forms & Strengths	FDA Approval Date(S)	Annual WAC (September 2017)
Valbenazine	Initial dose of 40 mg/day. Increase to 80 mg once daily after 1 week	Capsule: 40mg, 80mg	April 11, 2017 (Tardive dyskinesia)	\$75,789
Deutetrabenazine	Initial dose of 12 mg/day; titrate at a weekly interval by 6mg/day until symptoms improvement, and tolerability, up to a maximum of 48 mg/day given in two divided doses.	Tablets: 6 mg, 9 mg, and 12 mg	April 3, 2017 (Chorea associated with Huntington's disease) August 30, 2017 (Tardive dyskinesia)	\$90,071* (36mg daily dose)
Tetrabenazine	[Off label use in TD] Recommended dose in Huntington's disease: Initial dose of 12.5 mg once daily, then titrated by weekly intervals of 12.5 mg/day until symptoms improvement or unacceptable toxicity. Administered in BID if daily dose is less than 37.5mg. If up to 37.5mg to 50mg, administer in three divided doses. If >50 mg/day is required, test and genotype to determine if poor or extensive metabolizers of CYP2D6; not to exceed 100 mg/day or 37.5 mg/dose	Tablets: 12.5mg & 25mg	Aug 15, 2008 (Chorea associated with Huntington's disease)	\$19,885 [†] – \$76,087 [‡] for 25mg daily dose \$79,541 [†] - \$304,345 [‡] for 100mg daily dose

*Using the 12mg dose strength for a daily dose of 36mg for TD; [†]cheapest tetrabenazine generic; [‡]Xenazine cost

2.5 Insights Gained from Discussions with Patients and Patient Groups

In developing and executing this report, we received valuable input from individual patients and patient advocacy groups throughout the scoping and evidence development process. Below we summarize the key insights derived from this input.

A recurring theme has been that the common outcome measures used in clinical literature may not adequately capture the impact of TD on social stigmatization, work, family and caregivers, or the treatment of the patient's underlying condition and other co-morbid medical conditions. The involuntary movements caused by TD can cause enormous social stigmatization. For patients already facing the social isolation and symptoms associated with an underlying condition such as schizophrenia or a mood disorder, the added impact of TD can dramatically worsen feelings of isolation, low self-worth, and depression. This can lead to difficulty finding and maintaining a job, and may contribute to lifestyle changes such as inactivity, poor diet, and weight gain that can result in development or exacerbation of chronic medical conditions.

Patients and patient groups identified the lack of valid measures of patient reported symptoms and quality of life with TD as a major limitation of the evidence. Published studies primarily report provider reported outcomes (most commonly the AIMS score). The lack of validated patient-reported outcomes may lead to inaccurate assessment of treatment benefit and potentially underestimate their value. This is made more complex by difficulty in assessing the severity of TD symptoms and by the recognition that some patients may not be fully aware of these symptoms – both leading to uncertainty about how to measure severity and assess the impact of potential treatments. Lastly, there is little evidence that supports translating severity and level of impairment into more formal quality of life measures.

Patients and advocates also raised concern about how TD influences the way clinicians treat the patient's underlying condition. Though physicians may recommend changing to a different antipsychotic drug or stopping such therapy altogether, this often isn't an effective strategy from the perspective of patients. For some, there are no good alternatives to antipsychotic drugs, and changing from one to another may not improve the TD and can adversely affect the control of the underlying condition. Furthermore, stopping all antipsychotic drugs may not lead to decreased TD symptoms, especially for those who have been on these agents for long periods of time. Given the evidentiary and clinical challenges presented by historical attempts to treat TD, patients and patient groups hope that the availability of new, effective treatments for TD may give patients and their clinicians more options for managing both the underlying condition and TD symptoms. There was concern that, because there is currently no data available on how VMAT2 inhibitors will change treatment of the patient's underlying condition, attempts to assess the value may not account for the full impact of these medications on overall quality of life.

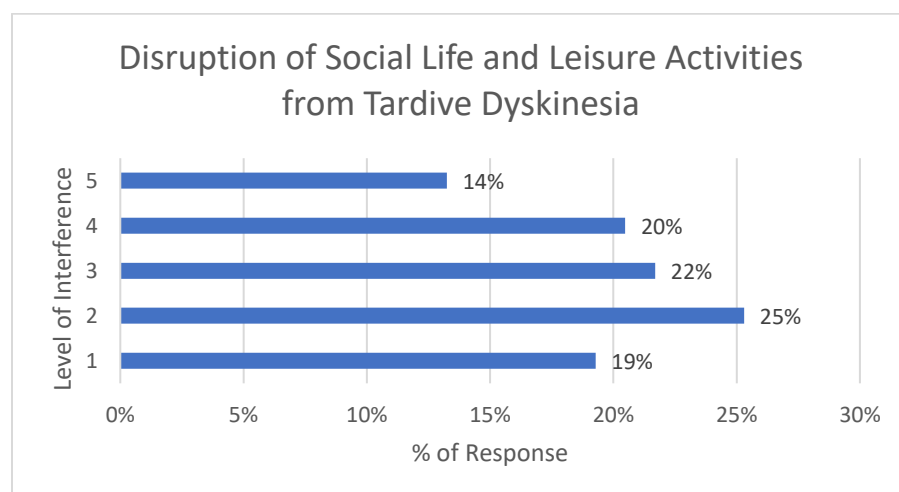
With the advent of the first approved therapies for TD, patient groups wanted to ensure that their members had access to newly available treatment options. Despite limitations previously mentioned, they view these new therapies as giving patients and their clinician more options for treating the underlying condition that required use of DRBAs, and for managing TD symptoms that can dramatically affect the patient, caregiver, and family.

Depression and Bipolar Support Alliance Survey

The Depression and Bipolar Support Alliance (DBSA), a leading patient advocacy group, deployed an online survey to members in August 2017 to gather information about the experience of individuals with TD. A total of 85 individuals responded. Respondents were predominantly diagnosed with bipolar disorder (84%), although patients were also diagnosed with depression (34%), schizophrenia/schizoaffective disorder (15%), insomnia (14%), and stomach problems (3.5%). The duration of TD was generally longstanding: 52% of the sample had symptoms for at least one year, and 25% had symptoms for longer than 6 years. However, 20 patients (24%) reported they no longer had symptoms. Survey respondents reported the many ways doctors attempted to moderate their TD symptoms, including switching the medication that caused the TD to a different one (47%), reducing the dose or stopping the medication that caused the TD (35%), and adding a new prescription or over-the-counter medication to improve the symptoms (40%).

Respondents were asked to describe how much their TD symptoms impacted various aspects of their lives: nearly 60% reported moderate to severe levels of interference (Figure 2.1).

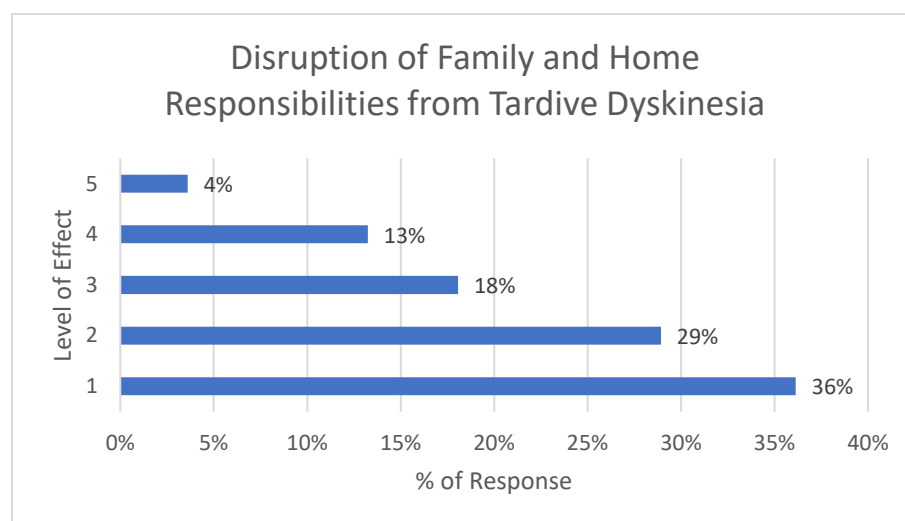
Figure 2.1. How Much Do Health Problems Related to Tardive Dyskinesia Disrupt Your Social Life or Leisure Activities?



1=No, 2=Low, 3=Moderate, 4=High, 5=Severe

Survey respondents were also asked to rate how much the symptoms of TD disrupt daily responsibilities. In contrast to results for social/leisure impacts, over half of respondents indicated that their symptoms had no effect to minimal effect on daily responsibilities (Figure 2.2).

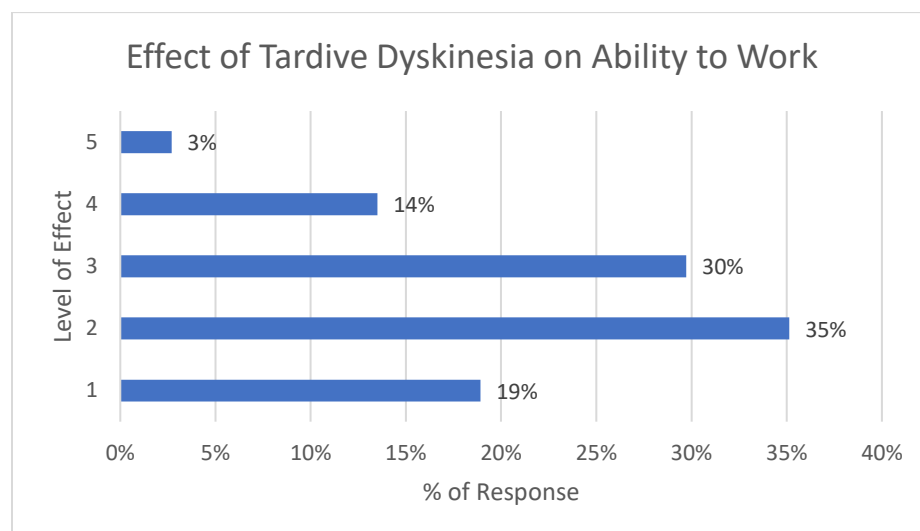
Figure 2.2. How Much Do Symptoms Related to Tardive Dyskinesia Disrupt Your Family Life/Home Responsibilities?



1=No effect on daily activities, 2=Minimal effect, 3=Moderate effect, 4=Major effect, 5=Completely prevented me from doing daily activities

A total of 37 individuals reported that they were currently employed or had been employed while experiencing TD. Overall, 47% of employed respondents reported a moderate, serious, or completely negative impact on their ability to work (Figure 2.3).

Figure 2.3. How Much Do Health Problems Related to Tardive Dyskinesia Affect Your Ability to Work?



1=No effect, 2=Minimal effect, 3=Moderate effect, 4=Serious effect, 5=Completely prevented me from working

2.6 Definitions of Outcome Measures Used in Clinical Trials

Abnormal Involuntary Movement Scale (AIMS)²

The AIMS questionnaire is commonly used to measure the severity of TD symptoms, and the impact of treatment on TD. It is based on the measurement of 12 items, although only seven items (four involving facial/oral movements, two involving the extremities, and one the trunk) were assessed in the clinical trials (see Appendix Table F1). Items 1-7 are measured on a five-point scale of severity from 0-4, with a total score ranging from 0-28. A higher AIMS score reflects increased severity of TD symptoms. Both valbenazine and deutetrabenazine trials used an AIMS score reduction greater than or equal to 50% to define treatment response. Items 8-12 were not measured in any of the clinical trials in our review (items 8-10 assess the global severity; and items 11-12 assess problems with the teeth or dentures).

Clinical Global Impression of Change (CGIC)

The CGIC is a clinician-rated measure evaluating the severity of a patient's TD symptoms on a 7-point scale at the time of assessment relative to the clinician's past experience. The score ranges from 1 ("very much improved") to 7 ("very much worse"). In the valbenazine and deutetrabenazine trials, patients in the "1" and "2" categories were classified as CGIC responders.

Patients' Global Impression of Change (PGIC)

The PGIC, a 7-point scale reflecting patients' rating of overall improvement, ranges from 1 ("very much improved") to 7 ("very much worse"). In the valbenazine and deutetrabenazine trials, patients in the "1" and "2" categories were classified as PGIC responders.

Modified Craniocervical Dystonia Questionnaire (MCDQ-24)⁶²

The Craniocervical Dystonia Questionnaire (CDQ-24) is a 24-item patient-reported quality of life assessment tool for use in patients with craniocervical dystonia. It measures five domains: stigma, emotional well-being, pain, activities of daily living, and social/family life. In the trials, certain questions in the five domains were modified to make it relevant to patients living with TD. The modified version (mCDQ-24) was used to assess the impact of TD on the patient's quality of life.

3. Summary of Clinical Guidelines and Coverage Policies

To understand current policy and practice, we identified and reviewed major clinical guidelines for treating TD, and surveyed insurance coverage in New England for pharmacotherapies for TD. We identified one clinical guideline by the American Academy of Neurology (AAN), most recently updated in 2013.¹ All therapies evaluated in the AAN guidelines were for off-label use of prescription drugs, procedures, or over-the-counter vitamins or supplements.

American Academy of Neurology (AAN)¹

<https://www.aan.com/Guidelines/Home/GetGuidelineContent/613>

The AAN guidelines found that there was insufficient evidence for many interventions used to treat TD, including withdrawing the DRBA, switching from older (first-generation) to newer (atypical or second-generation) antipsychotic DRBAs, as well as other pharmacologic and health system treatments. The guideline could not recommend for or against withdrawing DRBAs or switching from older to newer antipsychotic DRBAs. Short-term studies suggest that TD symptoms can worsen after withdrawal. Increasing the dosage of or switching to specific older antipsychotic DRBAs may suppress TD symptoms for short periods, but worsen long-term TD, and it may increase the risk of developing akinetic-rigid syndrome. Antipsychotic DRBAs may also cause symptoms of TD and mask rather than treat TD symptoms.

The guideline found limited evidence that tetrabenazine reduces TD symptoms, although there is no long-term evidence, and highlighted a risk of Parkinsonism over the long term. The guidelines suggested that amantadine, clonazepam (in data linked to patients with schizophrenia), and ginkgo biloba may also be effective in reducing TD symptoms; the use of galantamine, eicosapentaenoic acid, and diltiazem was discouraged. Table B1 in the Appendix lists the interventions evaluated in the AAN guidelines.

National Institute for Health Research²⁶

<https://www.journalslibrary.nihr.ac.uk/hta/hta21430#/abstract>

A more recent systematic review sponsored by the U.K. National Institute for Health Research reported similar results. This review found insufficient evidence due to small and low-quality studies, leading to the conclusion that it is not possible to assess the impact of withdrawing DRBAs, changing to new antipsychotic DRBAs or of any specific treatment to reduce the symptoms of TD.²⁶

Coverage Policies

We analyzed insurance coverage for AAN-recommended off-label treatment options as well as the recently approved agents evaluated in this review in six New England state Medicaid programs, and 13 silver-tiered insurance plans on individual marketplaces across New England.

All but two commercial plans surveyed covered tetrabenazine. In most circumstances, the generic tetrabenazine was preferred and listed on tiers one or two. Roughly one-third of the plans surveyed required prior authorization for tetrabenazine, and nearly a half of those surveyed required the prescription to be filled at a specialty pharmacy. According to interviews with several payers during our scoping phase, the absolute annual numbers of off-label prescriptions for use of tetrabenazine in TD were very small.

Only three plans covered deutetrabenazine and valbenazine, and each of the three plans listed these therapies on higher level tiers requiring prior authorization. Since both deutetrabenazine and valbenazine were recently approved for their initial indications in April 2017 or later, these lower rates of coverage are unsurprising.

All commercial plans covered both amantadine and clonazepam on their lowest tiers without prior authorization. Ginkgo biloba can be purchased over-the-counter.

In the six New England Medicaid programs, tetrabenazine, valbenazine, and deutetrabenazine were not preferred and all required prior authorization. Amantadine was covered on the preferred drug list in all plans. In Massachusetts and Rhode Island, clonazepam required prior authorization, although it was preferred in the other four states.

Table 3.1. Coverage of Therapies in Major New England Carriers Indicated and Off-Label for Tardive Dyskinesia (See Appendices Table C1 for Full List)

Commercial Plans			
	Covered	Highest Tier(s)	Requires Prior Authorization
Tetrabenazine	85%	27%	31%
Valbenazine	23%	100%	100%
Deutetrabenazine	23%	100%	100%
Amantadine	100%	0%	0%
Clonazepam	100%	0%	0%
New England Medicaid Programs			
	On Preferred Drug List	Requires Prior Authorization	
Tetrabenazine	0%	100%	
Valbenazine	0%	100%	
Deutetrabenazine	0%	100%	
Amantadine	100%	0%	
Clonazepam	67%	33%	

4. Comparative Clinical Effectiveness

4.1 Overview

To inform our analysis of the comparative effectiveness of the VMAT2 inhibitors valbenazine, deutetrabenazine, and tetrabenazine for the treatment of TD, we abstracted evidence from available clinical studies of these agents, whether in published or unpublished form (e.g. conference abstracts or presentations, FDA review documents).

We focused on evidence of the comparative clinical effectiveness of VMAT2 inhibitors in comparison with placebo or other off-label treatments in our target population of adults age 18 years and older with symptoms of TD for at least three months, and history of use of DRBAs. In addition, we examined adverse events and potential harms of VMAT2 inhibitors in populations with conditions other than TD. Importantly, due to key differences in study characteristics, outcomes assessed, and duration of therapy, we did not compare the VMAT2 inhibitors to each other through direct or indirect quantitative assessment.

Our review focused on key clinical benefits common to TD trials including clinician assessed and patient reported outcomes, as well as reported harms.

- Clinical benefits
 - Clinician assessed outcomes including symptom improvement (e.g., Abnormal Involuntary Movement Scale [AIMS], Clinical Global Impression of Change [CGIC])
 - Patient reported outcomes (e.g., Patient Global Impression of Change [PGIC])
 - Health-related quality of life (e.g., modified Craniocervical Dystonia Questionnaire [mCDQ]-24)
- Harms
 - Treatment-related adverse events (e.g. somnolence, headache, worsening of underlying conditions, depression, suicidal ideation)
 - Treatment tolerability (e.g., discontinuation due to adverse events)
 - Death

Where data were available, results for key outcomes were stratified by underlying diagnosis or underlying use of specific DRBAs.

4.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on VMAT2 inhibitors for TD followed established research methods.^{63,64} We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.⁶⁵ The PRISMA guidelines include a checklist of 27 items, further detail of which is available in Appendix Table A1.

We searched MEDLINE, PsycINFO, Cochrane Central Register of Controlled Trials, and EMBASE for relevant studies. We limited each search to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. To supplement the above searches and ensure optimal and complete literature retrieval, we performed a manual check of the references of recent peer-reviewed publications and public reports. Further details of the search algorithms, methods for study selection, and data extraction are available in Appendices A and G.

Study Selection

We included evidence from all relevant published clinical studies irrespective of whether they used a comparative study design. We did not restrict our search by study duration or study setting; however, studies that did not meet a minimum sample size of ten patients were excluded. In recognition of the evolving evidence base for TD, we supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature that met ICER standards for review (for more information, see <http://icer-review.org/methodology/icers-methods/icer-value-assessmentframework/grey-literature-policy/>).

For our review of adverse events, we accepted additional VMAT2 inhibitor RCTs in other movement disorders such as Huntington's disease. Abstracts that reported duplicative data available in published articles were excluded.

Data Synthesis and Statistical Analyses

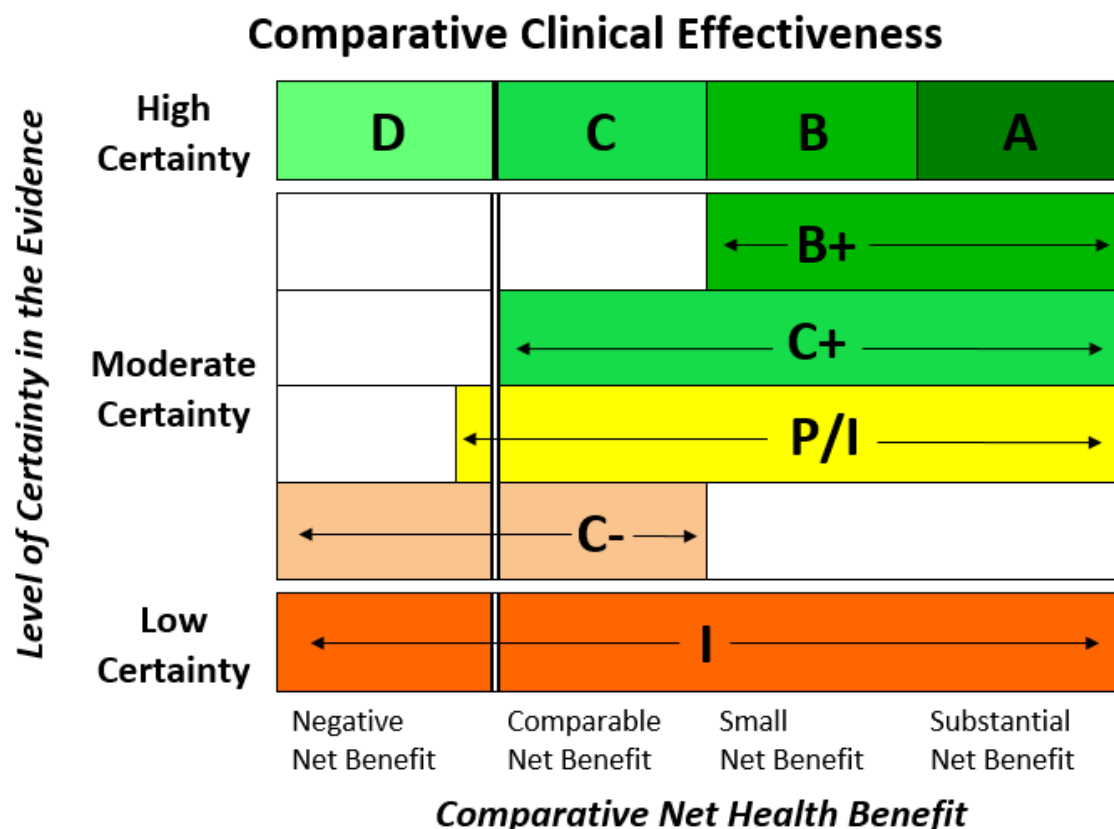
Data on relevant outcomes were summarized in evidence tables (see Appendix G) and are synthesized qualitatively in the text of the report. Due to differences in study characteristics, outcomes assessed, and duration of therapy, we did not compare the VMAT2 inhibitors to each other through quantitative indirect assessment, and therefore focused attention on the comparisons made within the clinical trials of each VMAT2 inhibitor.

Assessment of Level of Certainty in Evidence

We used the [ICER Evidence Rating Matrix](#) (see Figure 4.1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

- The **magnitude** of the difference between a therapeutic agent and its comparator in “net health benefit” – the balance between clinical benefits and risks and/or adverse effects AND
- The level of **certainty** in the best point estimate of net health benefit.⁶⁶

Figure 4.1. ICER Evidence Rating Matrix



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit

B = "Incremental" - High certainty of a small net health benefit

C = "Comparable" - High certainty of a comparable net health benefit

D = "Negative" - High certainty of an inferior net health benefit

B+ = "Incremental or Better" - Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit

C+ = "Comparable or Better" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit

P/I = "Promising but Inconclusive" - Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit

C- = "Comparable or Inferior" - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior

I = "Insufficient" - Any situation in which the level of certainty in the evidence is low

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias using the clinicaltrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. Any such studies may have provided qualitative evidence for use in ascertaining whether there was a biased representation of study results in the published literature. For this review, we identified two completed studies of valbenazine that have not yet been published (NCT01688037 [KINECT trial] & NCT01393600). However, the results of both studies were available in other publicly available sources (FDA medical review document & clinicaltrials.gov) and are discussed as part of the body of evidence.

4.3 Results

Study Selection

Our literature search identified 417 potentially relevant references (see Appendix Figure A1), of which 26 references relating to five comparative trials, one open label trial, one single-arm study and six observational studies met our inclusion criteria for assessment. These citations were comprised of 13 publications and 13 conference abstracts/posters. Primary reasons for study exclusion included use of interventions not in our scope, study population outside of our scope (e.g., patients with other hyperkinetic movement disorders), and small sample sizes ($n < 10$). Three additional references were included in our review for the safety assessment. Additional details of included references are described in Appendix F.

Valbenazine

Of the 26 identified references, three publications and six abstracts relating to two placebo-controlled randomized trials (KINECT 2 & KINECT 3), two open-label extensions (OLE) (KINECT OLE & KINECT 3 OLE), and one open label trial (KINECT 4) focused exclusively on the use of valbenazine in TD. We included evidence from two additional trials of valbenazine that had no publications or publicly-available conference presentations in our review. Data on one of the trials (NCT01393600) was obtained from clinicaltrials.gov, while the other one (NCT01688037 [KINECT]) was from the FDA medical review document.

Deutetrabenazine

Of the 26 identified references, two publications and seven abstracts relating to two placebo-controlled randomized trials (ARM-TD & AIM-TD), and one OLE (ARM-TD & AIM-TD OLE) focused exclusively on the use of deutetrabenazine in TD. Additionally, we included one reference on the use of deutetrabenazine in Huntington's disease for additional safety assessment.

Tetrabenazine

Of the 26 identified references, eight publications relating to one non-randomized comparative trial, one single-arm trial, and five observational studies focused exclusively on use of tetrabenazine in TD. Additionally, we included three references on the use of tetrabenazine in Huntington's disease for additional safety assessment.

Quality of Individual Studies

We rated all four RCT of valbenazine and deutetrabenazine to be of good or fair quality using criteria from the U.S. Preventive Services Task Force (USPSTF).⁶⁷ One good quality study of valbenazine had comparable study arms at baseline, did not show differential attrition, and used intent-to-treat analysis.⁴ The three fair-quality studies also had comparable study arms and did not demonstrate differential attrition, but used a modified intent-to-treat or per-protocol analysis.

Of the two tetrabenazine trials, only one was comparative.^{5,7,8} We judged this trial⁹ to be of poor quality due to very small sample size, lack of reliable or valid measurement instrument, and unblinded outcome assessment. All other tetrabenazine studies were single-arm studies. Consequently, we did not assign quality ratings to these individual references and instead highlight limitations, uncertainties, and gaps in the evidence in the Controversies and Uncertainties section. We also did not assign a quality rating to references that were obtained from grey literature sources (e.g., conference proceedings).

Comparability of Evidence Across VMAT2 Inhibitors

We did not include tetrabenazine in any quantitative or qualitative comparison involving the other VMAT2 inhibitors due to poor quality data resulting from a lack of controlled trials and other major differences in study designs (e.g., use of nonstandard clinical measures of outcome, very small sample sizes). We did not attempt to conduct a formal comparison of the other two VMAT2 inhibitors (valbenazine & deutetrabenazine) to each other, as the limited number of available studies, as well as differences in trial eligibility criteria, and trial duration precluded these comparisons (See Table 4.1.). There were also additional differences within the valbenazine and deutetrabenazine trials that are described below (See Table 4.2 & 4.7).

Table 4.1. Comparability of Valbenazine and Deutetrabenazine Trials*

	Valbenazine	Deutetrabenazine
Eligibility Criteria	<ul style="list-style-type: none"> • Moderate to severe TD based on qualitative assessment • Severity based on review of screening videos by multiple external raters 	<ul style="list-style-type: none"> • Moderate to severe TD based on AIMS score ≥ 6 • Severity criterion required at both screening and baseline assessments • AIMS score assessed by the investigator and confirmed by an independent movement disorder expert via central video rating
Duration of Trials	6 weeks	12 weeks

*see Table 4.2 & 4.7 for additional differences within the valbenazine and deutetrabenazine trials

Valbenazine

Data to inform our assessment of the clinical effectiveness of valbenazine (VBZ) were mainly drawn from two published RCT of valbenazine: one Phase II trial (KINECT 2 study) and a Phase III trial (KINECT 3 study).^{4,5} Both were six week, multicenter, parallel design double-blind, placebo-controlled randomized trials. The six-week KINECT 3 study was followed by a 42-week single-arm, long-term extension study period.⁶⁸

We identified three other unpublished trials of valbenazine that met our inclusion criteria, of which two were RCTs. The first RCT I was Phase II parallel arms study design with detailed results available in the FDA medical review document (KINECT study),⁶ while the other was a Phase II cross-over design RCT with limited results published on We identified three other unpublished trials of valbenazine that met our inclusion criteria, of which two were RCTs. The first RCT I was Phase II parallel arms study design with detailed results available in the FDA medical review document (KINECT study),⁶ while the other was a Phase II cross-over design RCT with limited results published on clinicaltrials.gov (NCT01393600). The six-week KINECT study was followed by a six-week single-arm, open-label extension phase. Results from the OLE phase were presented at a clinical conference.⁶⁹ The third unpublished trial was a 48-week open label trials with results presented in abstract form at a clinical conference.⁷⁰

All four RCTs enrolled patients 18 years and older with moderate to severe TD (for at least three months) and history of use of DRBAs for at least three months. Participants were required to have stable psychiatric status, and remain on stable doses of their concomitant medications, including DRBAs, for at least 30 days prior to study entry as well as during the study. There were slight differences in the eligible underlying conditions in each trial. Specifically, the KINECT 3 trial enrolled patients with a clinical diagnosis of schizophrenia/schizoaffective disorder or mood disorder with

neuroleptic-induced TD,⁴ while KINECT 2 enrolled patients with any DRBA-induced TD including patients with gastrointestinal disorders and metoclopramide-induced TD. Enrollment in the two unpublished Phase II trials were limited to patients with a clinical diagnosis of schizophrenia/schizoaffective disorder and neuroleptic-induced TD. See Table 4.2 for details of the four studies.

Table 4.2. Valbenazine RCTs

	Published Trials		Unpublished Trials	
	KINECT 3	KINECT 2	KINECT	NCT01393600
Study Type	Phase III RCT	Phase II RCT	Phase II RCT	Phase II RCT cross-over design
Total # of Patients	234	102	107	37
Baseline AIMS Score	10	8	15	NR
Mean Age (Years)	56.1	56.2	55.1	51.1
Mean TD Duration	NR	NR	NR	NR
Treatment Duration (Weeks)	6	6	6	Placebo: 2 Valbenazine: 2
Dose/ Day	40mg or 80mg	Starting dose (25mg), then every 2 weeks to max dose of 75mg/d.	50mg or 100mg for 2 weeks & 50mg for 4 weeks	Randomized to 12.5mg or 50mg VBZ after 2 weeks on placebo
Comorbid Psychiatric Condition (%)				
Schizophrenia/Schizoaffective	66.1	58	100	100
Bipolar Disorder/Depression	33.9	38	--	--
Gastrointestinal Disorder	--	4	--	--

NR: Not reported

Clinical Benefits of Valbenazine

The primary efficacy endpoint in the trials of valbenazine was the change from baseline in AIMS score at six weeks. The key secondary outcome was site investigator rated clinical global impression of change (CGIC) mean score. Other secondary outcomes included patient reported global impression of change (PGIC) mean score, and patients classified as responders based on AIMS score ($\geq 50\%$ AIMS improvement), CGIC score (“much improved” & “very much improved”), and PGIC score (“much improved” & “very much improved”).

The primary and key secondary endpoints were pre-specified to be analyzed in the intent-to-treat population (KINECT 3) or modified intent-to-treat population (KINECT 2 & KINECT).

Abnormal Involuntary Movement Scale (AIMS)

Published evidence from two trials showed statistically significant improvement in AIMS score for valbenazine compared to placebo. A greater percentage of patients receiving valbenazine achieved a reduction of 50% or more in the AIMS score at six weeks relative to those receiving placebo, resulting in numbers needed to treat of four to seven.

Both KINECT 2 and 3 reported the change in total AIMS score from baseline to week six as a primary outcome. The AIMS score was assessed by centrally performed video review and scoring using two blinded raters who were movement disorder specialists not otherwise involved in the KINECT 3 and KINECT 2 trials.^{4,5} In contrast, the unpublished KINECT study measured the change using on-site raters who differed from site to site and were not blinded to study visit number.⁶

In the KINECT 3 study (Phase III), the 40mg and 80mg doses of valbenazine resulted in a statistically significant greater reduction in AIMS score compared to placebo at six weeks (least squares [LS] mean change: -1.9 & -3.2 vs. -0.1; $p < 0.003$).⁴ Similarly, a statistically significant greater proportion of patients who were in the 40mg and 80mg valbenazine groups had an AIMS response (greater or equal to 50% reduction in AIMS score) compared to placebo (23.8% & 40% vs. 8.7%; $p < 0.03$).⁴ This resulted in a number needed to treat (NNT) of seven and four, respectively, compared with the placebo group. The KINECT 2 trial also showed a statistically significant greater reduction in the AIMS score and higher AIMS response in the valbenazine arm compared to placebo at six weeks (see Table 4.3). Subgroup analysis conducted by psychiatric diagnosis in both the KINECT 2 and 3 trials showed a statistically significant greater reduction in the AIMS score favoring valbenazine over placebo in both the mood disorder and schizophrenia subgroups. This pattern was consistent with the overall population (mood disorder and schizophrenia), although response to valbenazine in the schizophrenia group appears lower than in the mood disorder group (see Appendix Table F2).^{13,71,72}

Table 4.3. Valbenazine: AIMS Change and AIMS Response Across Trials at Six Weeks

Trials	Baseline AIMS Score (Mean)	AIMS Reduction from Baseline (LS Mean)	≥50% AIMS Improvement (%)	NNT Vs. Placebo
Kinect 3⁴				
Valbenazine 80mg/D	10.4	-3.2*	40.0*	4
Valbenazine 40mg/D	9.7	-1.9†	23.8†	7
Placebo	9.9	-0.1	8.7	--
Kinect 2⁵				
Valbenazine (Max 75mg/D)	8.0	-2.6*	48.9*	4
Placebo	7.0	-0.2	18.2	--
KINECT[‡] (Post-Hoc Analysis)⁶				
Valbenazine (50mg/D + 100mg/50mg)	14.6	-1.2	NR	--
Placebo	15.3	-0.2	NR	--

*p values≤0.001 vs. placebo; †p values≤0.05; ‡unpublished data from FDA Medical Review

The AIMS change observed with valbenazine in the RCT phase of the KINECT 3 trial persisted in the 48 week open-label extension study (Mean change: -3.0 & -4.8 for 40mg & 80mg valbenazine), with 28.3% and 52.4% of patients on 40mg valbenazine and 80mg valbenazine respectively classified as responders at 48 weeks.⁷³ Importantly, during a four-week washout period at the end of the study, an increase in AIMS score was observed, suggesting a return of TD symptoms following discontinuation of valbenazine. Similar findings were observed in the 48 week open label trial.⁷⁰

In contrast to the two published trials, the mean change from baseline in the unpublished Phase II trial (KINECT study) was not significantly different between treatment groups at week 6 (LS mean change: -3.3 vs. -2.5 for valbenazine vs. placebo).⁶ As mentioned previously, the primary endpoint in this trial was assessed by on-site raters who were not blinded to the study visit (baseline, two week or four week follow-up visit). A post-hoc analysis of the KINECT trial using blinded central video rating found a greater reduction in the valbenazine group, but this was still not statistically significant (LS Mean change: -1.2 vs. -0.2; p=0.066).⁶ In the other unpublished cross over study, the reduction in AIMS score after two weeks on 50mg valbenazine compared to the AIMS score at the end of a two week placebo period did not differ.⁷⁴ However, a post-hoc analysis that excluded one of 11 sites (reason for exclusion not provided) showed a significant difference after two weeks on valbenazine compared to the placebo period (Mean difference: -4.2; pvalue=0.0015).⁷⁴

Clinical Global Impression of Change (CGIC)

Evidence is mixed on improvement in TD symptoms as assessed by the CGIC score, with a statistically significant improvement noted for valbenazine over placebo in one trial but no differences observed in two other trials.

The investigator rated CGIC mean score at week 6 was a key secondary outcome in both KINECT 2 and 3. Results from the Phase III KINECT 3 study showed no significant differences between the valbenazine and placebo group on CGIC score and CGIC responders at week 6 in the intent-to-treat population.^{4,6} However, an analysis conducted in the KINECT 3 per protocol population (i.e. including only valbenazine treated patients who had a detectable level of valbenazine at week 6) showed significant differences in favor of valbenazine for CGIC score at week 6 (Mean score: 2.8 & 2.8 for 40mg & 80mg valbenazine groups vs. 3.2 for the placebo group; $p=0.011$).⁴ The unpublished Phase II KINECT study also did not show any differences on CGIC after six weeks.⁶

In contrast, the CGIC score in the KINECT 2 study showed a greater improvement in the valbenazine group compared with the placebo group in the modified intent-to-treat population (LS Mean: 2.2 vs. 3.1; $p<0.0001$).⁵ Furthermore, the percentage of patients classified as CGIC responders in KINECT 2 was higher in the valbenazine group, resulting in a NNT of two compared with placebo (Table 4.4).

Although statistical significance was not reported, results of the subgroup analysis conducted by psychiatric diagnosis in the KINECT 2 trial were consistent with the overall population (see Table 4.4), with a CGIC response of 61.5% vs. 14.8% in the schizophrenia/schizoaffective disorder subgroup, and 73.7% vs. 18.8% in the mood disorder subgroup (valbenazine vs. placebo, respectively).⁷²

Table 4.4. Valbenazine: CGIC Score and CGIC Response Across Trials at Six Weeks

Trials/ Arms	CGIC Score (LS Mean)	CGIC Responders (%)	NNT Vs. Placebo
Kinect 3⁴			
Valbenazine 40mg/D	2.9	31.7	NS
Valbenazine 80mg/D	2.9	31.4	NS
Placebo	3.2	20.3	--
Kinect 2⁵			
Valbenazine (Max 75mg/D)	2.2*	66.7*	2
Placebo	3.1	15.9	--
Kinect⁶			
Valbenazine (50mg/D + 100mg/50mg)	3.3	NR	--
Placebo	3.2	NR	--

*p values \leq 0.0001 vs. placebo; †unpublished data from FDA Medical Review

Patient Global Impression of Change (PGIC)

Evidence is mixed on improvement in TD symptoms as assessed by the PGIC score, with a statistically significant improvement noted for valbenazine over placebo in one trial but no differences observed in another trial and data indicating inferior performance to placebo in another study.

In the KINECT 2 trial, patients in the valbenazine treatment group had a greater perception of improvement on average, compared with the placebo group (LS Mean: 2.6 vs. 3.3; $p=0.0011$).⁵ The valbenazine group also had a greater proportion of patients classified as PGIC responders compared with the placebo group (57.8% vs. 31.8%, $p\leq 0.001$), resulting in a NNT of four.

Although listed as a secondary outcome in the KINECT 3 study, the PGIC outcome was not reported in the published trial results. However, data in the FDA medical review document showed that on average, patients in the valbenazine groups and placebo group did not differ in their report of TD symptom improvement in both the KINECT 3 and KINECT trials.⁶ In fact, a significantly lower proportion of patients were categorized as PGIC responders in the 80mg valbenazine group compared with the placebo group in the KINECT 3 study. An additional exploratory PGIC responder analysis was conducted to assess the underlying diagnostic categories, and the analysis showed that the difference between 80mg valbenazine group and the placebo group was driven mainly by subjects with schizophrenia or schizoaffective disorder.⁶

Table 4.5. Valbenazine: PGIC Score and PGIC Response Across Trials at Six Weeks

Trials/ Arms	PGIC Score (LS Mean)	PGIC Responders (%)	NNT Vs. Placebo
Kinect 3⁶			
Valbenazine 40mg/D	2.9	31.7	NS
Valbenazine 80mg/D	3	24.3*	
Placebo	2.7	42.0	--
Kinect 2⁵			
Valbenazine (Max 75mg/D)	2.6*	57.8*	4
Placebo	3.3	31.8	--
Kinect^{†6}			
Valbenazine (50mg/D + 100mg/50mg)	3.2	24.5	--
Placebo	3.1	30.0	--

* p values ≤ 0.001 vs. placebo; †unpublished data from FDA Medical Review

Harms: Valbenazine

The most common side effects of valbenazine were somnolence, fatigue, headache, decreased appetite, akathisia, nausea, vomiting and dry mouth. There was no indication of increased rates of depression and suicidal ideation with valbenazine at six weeks.

In the pooled analysis of the KINECT 2 and KINECT 3 trials, the incidence of serious AEs was 6.6% in the valbenazine arm versus 3.9% in the placebo arm. All serious AEs were considered not to be treatment related. There was one death in the valbenazine group, which was considered to be unrelated to treatment.

The most common AE with valbenazine at six weeks was somnolence, occurring in $\geq 5\%$ of patients and with a higher incidence than in the placebo group.^{4,5} Other common AEs with incidence $\geq 3\%$, and with higher incidence in the valbenazine group compared with placebo group were fatigue, headache, decreased appetite, akathisia (agitation/restlessness), nausea, vomiting and dry mouth. Data from the two 48-week long open label studies obtained from a conference abstract showed similar pattern of common AEs.^{13,70}

Based on similar mechanisms of action and multiple overlapping metabolites of valbenazine and tetrabenazine, and the inclusion of a boxed warning for the risks of depression and suicidality for tetrabenazine's use in Huntington's disease, the FDA's safety review of valbenazine paid particular attention to signals of depression and suicidal ideation.⁶ Although, there was one case of suicide attempt in the six-week KINECT 3 study, findings from both KINECT 2 and KINECT 3 studies showed that the occurrence of depression and suicidal ideation in the valbenazine groups was not significantly different from the placebo-treated patients.⁴⁻⁶ Although, there was one case of suicide attempt in the 6-week KINECT 3 study, findings from both KINECT 2 and KINECT 3 studies showed that the occurrence of depression and suicidal ideation in the valbenazine groups was not significantly different from the placebo-treated patients.^{4,5} Furthermore, psychiatric scale assessments indicated no worsening of symptoms in patients with schizophrenia/schizoaffective disorder or mood disorder during long-term valbenazine treatment (see Appendix Table F3-F4).¹³

The pooled discontinuation rate due to adverse events at six weeks from KINECT 2 and KINECT 3 was 4.5% in the valbenazine group, compared with 3.2% in the placebo group (statistical significance not assessed; see Table 4.6). At 48 weeks of follow-up in the KINECT 3 extension study, discontinuation rates due to adverse events in the 40mg and 80mg valbenazine groups were 14% and 18%, respectively.¹³

Table 4.6. Valbenazine: Adverse Events at Six Weeks and 48 Weeks

	Any AE≥1 (%)	SAEs≥1 (%)	Discontinuation Due to AE (%)	Somnolence (%)	Fatigue (%)	Depression (%)	Suicidal Ideation (%)
6 Week Placebo Controlled Studies (Pooled KINECT 2 & KINECT 3)^{4,5}							
VBZ (40mg - 80mg)	45.0	6.6	4.5	6.4	4.0	1.3	2.6
Placebo	39.2	3.9	3.2	4.0	2.4	2.6	5.3
48 Week Long Term Extension Study¹³							
VBZ 40mg	61.9	13.4	13.4	4.0	NR	6.2	5.0
VBZ 80mg	76.2	15.8	17.8	3.1	NR	2.0	5.2

SAE: serious adverse event

Deutetrabenazine

We identified two clinical trials evaluating the effect of deutetrabenazine (DTBZ) on TD: a Phase III trial (AIM-TD) and a Phase II/III trial (ARM-TD).^{7,8} Both were 12-week, multicenter, parallel design, double-blind, placebo-controlled randomized trials. The two trials had similar inclusion criteria, enrolling adult patients 18-80 year of age, having an AIMS score ≥ 6 at screening and baseline, a clinical diagnosis of TD for at least three months before screening with stable psychiatric illness, and history of DRBA use for at least three months (at least one month for patients 60 years of age or older). See Table 4.7 for study characteristics. Both trials were rolled over into the same single-arm, open-label long term extension (OLE) study after a one week washout (54-week data available in conference abstract).^{75,76}

Table 4.7. Deutetrabenazine Trials

	AIM-TD	ARM-TD
Study Type	Phase III RCT	Phase II/III RCT
Total # of Patients	293	117
Baseline AIMS Score	9.7	9.6
Mean Age (Years)	56.4	54.6
Mean TD Duration (Years)	5.6	6.2
Treatment Duration (Weeks)	12	12
Dose/Day (2 Divided Doses)	Randomized To 12mg, 24mg, or 36mg (Initial Total Dose Of 12mg, Then Titrated Weekly For 4 Weeks Until Randomized Dose	Initial Dose Of 12mg, Then Titrated Weekly For 6 Weeks to Max. Dose Of 48mg/Day or A Significant AE Occurred.
Comorbid Psychiatric Condition (%)*		
Schizophrenia/Schizoaffective Disorder	60	68.4
Bipolar Disorder	17	23.1
Depression	19	25.6
Others	4	--

*The percentages add up to a value greater than 100% in the ARM-TD trial. This is likely because patients could be categorized as having 1 or more comorbid psychiatric condition.

Clinical Benefits of Deutetrabenazine

The primary efficacy endpoint in the trials of deutetrabenazine was the change from baseline in AIMS score. The secondary outcomes were percentage of patients classified as responders based on AIMS score ($\geq 50\%$ AIMS improvement), CGIC score (“much improved” & “very much improved”), and PGIC score (“much improved” & “very much improved”). Additionally, change in modified Craniocervical Dystonia Questionnaire (mCDQ)-24 score was assessed as a secondary endpoint. All outcomes were assessed at 12 weeks.

The efficacy analysis of all outcomes was performed in the modified intent-to-treat population (mITT) who received at least one dose of deutetrabenazine.

Abnormal Involuntary Movement Scale (AIMS)

Published evidence from two trials showed statistically significant improvement in AIMS score for deutetrabenazine compared to placebo. A greater percentage of patients receiving deutetrabenazine achieved a reduction of 50% or more in the AIMS score at 12 weeks, resulting in numbers needed to treat of five compared to placebo.

Table 4.8 presents AIMS score outcomes. In the Phase III AIM-TD trial, the 24mg and 36mg doses of deutetrabenazine resulted in a statistically significant greater improvement in the AIMS score

compared to placebo at week 12 (LS Mean change: -3.2 & -3.3 vs. -1.4, $p<0.003$).⁷ In addition, significantly more patients in the 24mg and 36mg deutetrabenazine groups had a 50% or more reduction in the AIMS score at 12 weeks compared to the placebo group (35% & 33% vs. 12%; $p\leq 0.05$; NNT=5). The ARM-TD trial also showed statistically significant greater improvement in the AIMS score in the deutetrabenazine arm compared to placebo at 12 weeks (see Table 4.8). At 54 weeks in the OLE study, there was further improvement in AIMS score reduction (Mean change: -5.1).⁷⁵

We identified no subgroup analysis by underlying psychiatric condition. Subgroup analysis by ongoing use of DRBAs in the AIM-TD trial showed a statistically significant greater improvement in the AIMS score favoring deutetrabenazine over placebo in both subgroups of patients currently on DRBAs and patients not on DRBA therapy (See Appendix Table F5).⁷⁷

Table 4.8. Deutetrabenazine: AIMS Change and AIMS Response Across Trials at 12 Weeks

Trials	Baseline AIMS Score (Mean)	AIMS Reduction from Baseline (LS Mean)	$\geq 50\%$ AIMS Improvement (%)	NNT vs. Placebo
AIM-TD⁷				
DTBZ 12mg/D	9.6	-2.1	13	NS
DTBZ 24mg/D	9.4	-3.2 [†]	35 [†]	5
DTBZ 36mg/D	10.1	-3.3 [*]	33 [†]	5
Placebo	9.5	-1.4	12	--
ARM-TD⁸				
DTBZ	9.6	-3.0 [†]	--	--
Placebo	9.6	-1.6	--	--

*p values ≤ 0.001 vs. placebo; †p values ≤ 0.05 ; NS: not significant

Clinical Global Impression of Change (CGIC)

Evidence is mixed on the impact of deutetrabenazine on the CGIC measure, with differences observed in one of three active treatment arms of one trial, and no differences observed in the other trial.

In the AIM-TD study, a statistically significant increase in treatment success on the CGIC was seen in patients receiving deutetrabenazine, but only in the 24 mg/day group (49% vs. 26% for placebo; $p=0.014$).⁷ The 36 mg/day and 12 mg/day groups did not differ from placebo.⁷ Similarly, there was no statistically significant difference between the proportion of patients achieving CGIC treatment success in the deutetrabenazine arm and the placebo arm at week 12 in the ARM-TD trial (see Table 4.9).⁸

An additional post-hoc analysis which in the ARM-TD trial was performed in patients with AIMS ≥ 6 at both screening and baseline (and included 85.8% of the overall population) resulted in a greater difference between the two arms (52.1% vs. 34.7%), although statistical significance was still not reached.⁸ However, in a pooled analysis of both AIM-TD (using the AIMS cutoff of the post-hoc analysis) and ARM-TD (24mg/day and 36mg/day groups only), a significantly higher percentage of patients treated with deutetrabenazine achieved treatment success compared with the placebo group (48% vs. 30%; $p=0.005$).⁷⁸

Furthermore, in a subgroup analysis of AIM-TD stratified by ongoing DRBA use, CGIC response with deutetrabenazine was statistically better than placebo only in the group not receiving DRBA therapy (See Appendix Table F5).⁷⁷

Table 4.9. Deutetrabenazine: CGIC Treatment Success Across Trials at 12 weeks

Trials	CGIC Treatment Success (%)	NNT vs. Placebo
AIM-TD⁷		
DTBZ 12mg/Day	28	NS
DTBZ 24mg/Day	49 [†]	5
DTBZ 36mg/Day	44	NS
Placebo	26	--
ARM-TD⁸		
DTBZ	48.2	NS
Placebo	40.4	--
Pooled ARM-TD & AIM-TD⁷⁸		
DTBZ	48 ^{†‡}	6
Placebo	30 [‡]	--

[†]p values ≤ 0.05 vs. placebo; [‡]unpublished data presented in conference abstract; NS: not significant

Patient Global Impression of Change (PGIC)

Results from two trials showed no significant differences between deutetrabenazine and placebo in the likelihood of achieving treatment success in patients based on the PGIC scale.

In the AIM-TD trial, although there were more patients in the 24mg/ day and 36mg/day deutetrabenazine arms classified as having treatment success compared to the placebo arm, the differences were not statistically significant and patients in the 12mg/day group had a slightly lower response rate than placebo.⁷ Similarly, the percentage of patients achieving PGIC treatment success favored the deutetrabenazine arm in the ARM-TD trial, but the difference was not statistically significant (see Table 4.10).⁸

However, in a pooled analysis of data from both the AIM-TD (24mg and 36mg per day groups) and ARM-TD trials, the deutetrabenazine group had a statistically significantly greater proportion of

patients with PGIC treatment success compared to the placebo group (43% vs. 30%; $p=0.026$).⁷⁹ Additionally, a subgroup analysis based on the underlying psychiatric condition was performed on the pooled population. The direction of results in both the mood disorder subgroup (deutetrabenazine vs. placebo: 47% vs. 26%) and psychotic disorder subgroup (41% vs. 32%) were consistent with the overall pooled population. However, results were statistically significant only in the mood disorder subgroup ($p=0.026$).⁷⁹

Table 4.10. Deutetrabenazine: PGIC Treatment Success Across Trials at 12 weeks

Trials	PGIC-TD Treatment Success (%)	NNT vs. Placebo
AIM-TD⁷		
DTBZ 12mg/Day	23	NS
DTBZ 24mg/Day	45	NS
DTBZ 36mg/Day	40	NS
PBO	31	--
ARM-TD⁷⁸		
DTBZ	42.9	NS
PBO	29.8	--
Pooled Analysis (AIM-TD & ARM-TD)⁷⁹		
DTBZ (N=152)	43	8
PBO (N=107)	30	--

NS: not significant

Modified Craniocervical Dystonia Questionnaire (mCDQ-24)

Results showed no significant differences in mCDQ-24 scores in the ARM-TD and AIM-TD trials at 12 weeks.

Although patients receiving 24mg/day and 36mg/day of deutetrabenazine in the AIM-TD trial had greater LS mean reduction from baseline on the mCDQ-24 score compared to placebo, differences were not statistically significant.⁷ Patients treated with deutetrabenazine in the ARM-TD trial also had a greater improvement on the mCDQ-24 compared to the placebo group, but these differences were also not significant (See Appendix Table F7). Result of the subgroup analysis from AIM-TD trial was consistent with overall findings.

Harms: Deutetrabenazine

Somnolence, headache, diarrhea, fatigue, insomnia, anxiety, and nasopharyngitis were the most common side effects reported for deutetrabenazine. There was no indication of increased rates of depression and suicidal ideation with deutetrabenazine at 12 weeks.

At 12 weeks, the incidence of adverse events was similar between patients in the deutetrabenazine and placebo groups in both AIM-TD and ARM-TD trials. In the pooled analysis of both trials, the incidence of serious AEs was 6.3% in the deutetrabenazine arm versus 6.9% in the placebo arm. Of the 13 cases of serious AE occurring in the deutetrabenazine group, only one (suicidal ideation) was considered to be possibly related to treatment. There were two deaths in the deutetrabenazine group, and both were not considered to be related to treatment.

Table 4.11 presents the most common AEs and other AEs of interest. At 12 weeks, the most common AE occurring in $\geq 5\%$ of patients and with higher incidence than in the placebo group were somnolence, headache & diarrhea. Other common AEs that occurred in $\geq 3\%$ of patients in the deutetrabenazine groups were fatigue, anxiety, nasopharyngitis & insomnia. The incidence of depression and suicidal ideation was similar between treatment groups, and did not show a dose-response relationship. Results from 54-week long-term extension study showed deutetrabenazine was generally well tolerated, with a 5.9% incidence of discontinuation due to adverse events. There was no evidence of increased depression, anxiety, suicidality, restlessness, somnolence and sedation, or Parkinsonism resulting from long-term exposure.

Additional safety information obtained from a 12-week RCT assessing the effect of deutetrabenazine in patients with Huntington's disease (HD) that used a dosing regimen similar to the ARM-TD trial showed a similar side effect profile.⁸⁰ The incidence of depression and suicidal ideation was similar between treatment groups in the HD trial (see Table 4.11). However, a generally high rate of depression and suicidality in HD makes it difficult to assess if deutetrabenazine adds to this risk, and because of its chemical similarity to tetrabenazine, a boxed warning for depression and suicidality was added to the deutetrabenazine labeling for HD (see tetrabenazine harms below).^{17,81}

Table 4.11. Deutetrabenazine: Adverse Events at Six Weeks and 48 Weeks

	Any AE≥1 (%)	SAEs≥1 (%)	Discontinuation Due to AE (%)	Somnolence (%)	Headache (%)	Depression (%)	Suicidal Ideation (%)
12 Week Placebo Controlled Studies in TD (Pooled AIM-TD & ARM-TD)							
DTBZ	54	6.3	2.9	5.9	4.9	2	1.5
Placebo	53.4	6.9	3.1	6.9	7.6	0.8	0.8
54 Week Long Term Extension Study In TD							
DTBZ	59.5	9.5	5.9	7.2	6.9	7.2	1.6
12 Week Placebo Controlled Study In HD							
DTBZ				11.1	NR	4.4	2.2
Placebo				4.4	NR	6.7	2.2

SAE: serious adverse event

Tetrabenazine

We identified eight tetrabenazine studies,^{9-12,82-85} of which only one was comparative.⁹ The others were either retrospective or prospective single-arm studies. Tetrabenazine was compared with placebo in a non-randomized cross-over fashion in the comparative study. Unlike the valbenazine and deutetrabenazine trials that required patients to be on a stable DRBA during the study period, patients enrolled in the tetrabenazine trial were required to stop neuroleptic medication at least four weeks before the initiation of tetrabenazine. Furthermore, the tetrabenazine trial was small (n=24), was performed 45 years ago, and used different outcome measures than those used in the valbenazine and deutetrabenazine trials. The majority of the non-comparative trials of tetrabenazine also used a number of different non-standard measures of clinical improvement that make comparing results among these studies problematic.

Clinical Benefit of Tetrabenazine

Tetrabenazine may reduce the symptoms of TD. However, the lack of randomized controlled trials, use of non-standard and variable clinical measures, and other study design limitations (e.g., stopping neuroleptic medications during trial) severely limits any inferences that can be drawn from the available evidence, and precludes any possibility of even qualitative comparisons to the other VMAT2 inhibitors.

In the tetrabenazine cross-over study, 24 patients with clear signs of oral TD were given placebo for four weeks followed by 50mg to 100mg doses of tetrabenazine per day over six weeks in a non-randomized fashion.⁹ The goal of the study was to assess the effect of tetrabenazine on TD by measuring the changes in the frequency of dyskinetic movement in the oral region (e.g. chewing,

licking, puffing, pursing of lips, protrusion of tongue) per minute. After six weeks on tetrabenazine, dyskinesia had disappeared completely in eight patients (33%), and reduced significantly in six patients (25%), resulting in a mean oral dyskinesia frequency of 11 per minute in the tetrabenazine group compared to 30 per minute at the end of the placebo period ($p<0.0005$).⁹

We identified only one tetrabenazine study that used the AIMS score as an outcome measure.¹⁰ This was a 20-week, open label single-arm study conducted in 20 patients with TD (mean duration of TD: 40 months) who had failed to respond to previous treatment. Patients were placed on a tetrabenazine dose of 25mg to 150mg per day (mean dose: 57.9mg/day) and were followed prospectively. All patients were required to stop taking the DRBAs four weeks prior to the start of the study, and were videotaped before and after tetrabenazine treatment. At approximately 20 weeks follow up, the mean AIMS score as determined by blinded video raters had improved by 9.7 points from baseline (Mean of 17.9 and 8.2 at baseline and 20 weeks respectively; $p<0.001$).¹⁰

We identified six other single-arm retrospective studies of tetrabenazine conducted in patients with varying hyperkinetic movement disorders including TD where outcomes were separately reported for the underlying disorder (see Appendix Table F8). Response to tetrabenazine therapy was assessed with varying scales of global improvement. In the majority of the studies, the scoring was a composite of patient and caregiver assessment, along with the investigator's examination. Results showed a wide range of improvement in the study populations, ranging from 41% to 93% with moderate to marked improvement^{11,12} Study descriptions and findings are available in Appendix Table F8.

Harms: Tetrabenazine

The most common side effects of tetrabenazine were somnolence, fatigue, insomnia, fall, depression, agitation, parkinsonism, akathisia, and anxiety. Although statistical significance was not reported, tetrabenazine resulted in substantially greater incidence of depression compared to placebo group in the trial of Huntington's disease.

There were no harms data presented in the comparative study of tetrabenazine for TD. Comparative tetrabenazine safety information was primarily informed by two studies (12-week RCT & 80 week open label study) conducted in patients with Huntington's disease, an indication for which tetrabenazine is approved (see Table F8 in Appendix).^{14,15} The first study was a 12-week double blind, placebo controlled trial conducted in 84 patients with Huntington's disease.¹⁴ In this study, tetrabenazine was initiated at a dose of 12.5mg/day and titrated in blinded fashion to a maximum dose of 100mg/day or until the desired antichoreic effect or intolerable adverse effect occurred. The most common AEs occurring in $\geq 5\%$ of patients and with greater incidence in the tetrabenazine group compared with the placebo group were somnolence, fatigue, insomnia, fall, depression, agitation, and anxiety.¹⁴ Many of the common AEs, including somnolence and

depression, and less common ones, including akathisia and Parkinsonism, were dose limiting, and were managed by dose reductions during the trial.

Notably, the incidence of depression in the tetrabenazine treated patients was substantially greater than in the placebo group (15% vs. 0%).¹⁴ Data from the long term extension study showed that the incidence of depression had risen to 23% at 80-week follow-up.¹⁵ Additionally, there was one case of suicide occurring in a patient with undetected depression during the RCT phase, and one case of a suicide attempt during the long term extension study.^{14,15} Based upon the findings from these studies, tetrabenazine was given a black box warning for the risks of depression and suicidality, noting that “tetrabenazine increases the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington’s disease. Anyone considering the use of tetrabenazine must balance the risks of depression and suicidality with the clinical need for control of choreiform movements. Close observation of patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior should accompany therapy with tetrabenazine. Tetrabenazine is contraindicated in patients who are actively suicidal, and in patients with untreated or inadequately treated depression.”¹⁶

Review of safety information from the on- and off-label use of tetrabenazine for various hyperkinetic disorders (including TD) in observational studies is summarized in F10 in the Appendix. Adverse events (AEs) that occurred in ≥ 5% of patients in these studies include somnolence, fatigue, parkinsonism, depression, insomnia, nervousness/anxiety, akathisia, and nausea/vomiting.

Controversies and Uncertainties

Ideally, clinical effectiveness of drugs or medical interventions is best informed by evidence from large, high quality, randomized controlled trials. Unfortunately, we did not identify any randomized controlled trials of tetrabenazine for patients with TD. Therefore, our assessment of the use of tetrabenazine in TD was limited and qualitative in nature. We identified four placebo-controlled randomized controlled trials assessing valbenazine and deutetrabenazine, but there were no studies directly comparing these two agents. This is not surprising given that these drugs were approved for use in TD in April and August of 2017. We also did not identify any trials comparing VMAT2 inhibitors to other agents that have been used to treat TD. As a result, we could only compare the benefits and harms of VMAT2 inhibitors to placebo. We considered performing a network meta-analysis, but the absence of such head-to-head evidence, the limited number of available studies, as well as major differences in study populations, and duration of treatment precluded such comparisons.

Another major limitation of our evidence base is the lack of outcome measures that directly reflect the burden of TD in affected individuals. Patients and advocacy organizations described the burden of the symptoms of TD on all aspects of a patient’s life, including overall quality of life. In addition

to physical impairment, TD can affect employment, interpersonal relationships, and have an impact on other day-to-day activities. The primary outcome in the clinical trials (AIMS scale) was provider-measured, and its measurement was based on office video recordings that may not reflect TD in routine settings. The AIMS scale, though commonly used in research and clinical studies, has well-recognized limitations, including the summation of severity scores across body regions that may not accurately reflect the overall burden of TD symptoms. The need for central, blinded, expert review of video recorded patient assessments highlight the practical challenge in performing such assessments as part of routine care. Moreover, studies demonstrated that assessments done by local investigators who were not blinded to the order of the videos resulted in different outcomes than those from central, blinded reviews.¹⁷

It is also unclear that the score from AIMS items 1-7 provides an accurate assessment of the overall severity of symptoms. For example, patients with severe facial symptoms that are quite impairing may have the same AIMS score as someone with minimal symptoms in four different body locations, but may feel a much greater burden from facial symptoms because of their place of employment or education. However, none of the trials reported data on the global severity ratings that are included in the AIMS (items 8 -10). Finally, while the statistical significance of changes in AIMS scores were assessed in these trials, and a pooled analysis of valbenazine trials suggested a change of 2-3 points in the AIMS score corresponded to improvement on the clinical global impression of change (CGIC) scale,³ the threshold for what constitutes a clinically-important difference remains to be established.

Given the impact of TD on quality of life, patient reported measures were included as secondary outcomes in both the valbenazine and deutetrabenazine trials. However, patient reported outcomes comparing valbenazine or deutetrabenazine to placebo generally did not demonstrate a beneficial impact of active treatment, even though TD symptoms were rated as significantly improved by blinded central raters. It is not clear why provider-based and patient-reported measures of success differed. Patients may not have appreciated the amount of benefit that was observed on video reviews. Some experts have suggested that patients with underlying psychotic disorders (e.g., schizophrenia/schizoaffective disorder) may be unaware of their own dyskinetic movements, or their severity, and thus unable to assess the impact of TD on their quality of life.^{86,87} Indeed, while results were not definitive, greater improvement in TD symptoms was recorded in some of these studies among patients with mood disorders than in those with schizophrenia. However, as a result of these limitations in measuring the quality of life in patients with TD and how it may change with treatment, there is uncertainty regarding the magnitude of benefit for treatments of TD on patients' overall quality of life. It remains important to develop a patient-based rating scale that can sufficiently capture the individual burden of the disorder in all affected patients.

The side effect profile of the VMAT2 inhibitors is another area of uncertainty. Although, the risk of depression and suicidality was similar between treatment groups in the trials of deutetrabenazine in patients with Huntington's disease (HD), a boxed warning for depression and suicidality was added to its label for use in patients with HD (in all likelihood because of its chemical similarity to tetrabenazine). The current clinical trials of valbenazine and deutetrabenazine in patients with TD are limited to only a few weeks' duration. These trials are not sufficiently long enough to conclude that their side effect profiles are similar or superior to that of tetrabenazine. However, both valbenazine and deutetrabenazine appear to be well tolerated in the TD clinical trials. Nevertheless, given the similar mechanism of action and multiple overlapping metabolites with tetrabenazine, the long-term safety of these drugs remains to be determined.

We have heard from patients and their advocates about the concerns of maintaining effective antipsychotic therapy while managing the symptoms of TD. For example, antipsychotic dose reduction by the treating clinician has been used as a strategy to treat or minimize the risk of developing TD and other extrapyramidal symptoms (muscle/posture related side effects of DRBAs including TD). In addition, evidence from the published literature has shown that numerous antipsychotic side effects including TD can lead to non-adherence with therapy.⁸⁸ Sub-optimal adherence or deliberate dose-reduction have been shown to increase the risks of psychotic exacerbation and relapse.⁸⁹⁻⁹¹ Hence, some stakeholders have suggested that the new VMAT2 inhibitors could have a significant impact on controlling the underlying psychiatric conditions. This is based on the assumption that better TD management will increase adherence to antipsychotics and reduce the use of underlying psychiatric agent modification as a treatment strategy. While this is a plausible concept, it has not been evaluated in clinical studies to date, and so real-world data will be needed to assess these effects.

Finally, while the development of the new VMAT2 inhibitors is a step forward in the management of TD, there are still several unanswered questions regarding the use of this class of drugs in clinical practice. Future studies should evaluate the patient or clinical factors (e.g. age, TD symptoms, baseline AIMS score, TD duration, ongoing use of DRBAs) that predict the likelihood of response to VMAT2 inhibitors. In addition, pragmatic clinical trials that include patients with other comorbid conditions or severe mental disorders encountered in routine clinical practice will be helpful. Furthermore, future studies should evaluate not only the short-term effect of these drugs but also the factors that will predict the durability of these effects and long term functional improvement.

Summary

We reviewed data on use of VMAT2 inhibitors for the treatment of adults aged 18 and older with symptoms of TD for at least three months and history of use of DRBAs. Using the ICER Evidence Matrix, we assigned evidence ratings independently for each of the VMAT2 inhibitors compared to placebo.

Table 4.12. ICER Evidence Ratings

VMAT2 Inhibitors	ICER Evidence Rating
Valbenazine	P/I
Deutetrabenazine	P/I
Tetrabenazine	I

Valbenazine

- Treatment with valbenazine resulted in a greater reduction in AIMS scores and more patients with a substantial improvement in AIMS scores compared to placebo.
- Despite improvements in AIMS scores, treatment with valbenazine did not consistently result in improvement on Clinical Global Impression of Change (CGIC) scores. Additionally, currently available data on patient reported outcome (PGIC scores) do not demonstrate a benefit for valbenazine over placebo.
- Although valbenazine was generally well tolerated in the six-week trials, this is a new therapy that requires ongoing use, and important adverse effects could become apparent over time in larger patient populations.

For adults with TD for at least three months and history of use of DRBAs, we have moderate certainty that valbenazine provides a comparable, small, or substantial net health benefit. However, because of the lack of clear benefit on CGIC scores and the patient reported PGIC scores, as well as the absence of long-term safety data compared to usual care, we cannot definitively rule out the possibility of a small net harm. Therefore, we consider the evidence on valbenazine to be “promising but inconclusive” (P/I).

Deutetrabenazine

- Treatment with deutetrabenazine resulted in a greater reduction in AIMS scores, and more patients with a substantial improvement in AIMS scale compared to placebo.
- Despite improvements on AIMS score, treatment with deutetrabenazine did not result in improvement on CGIC scores. Additionally, currently available data on patient reported outcome (PGIC scores) do not demonstrate a benefit for deutetrabenazine over placebo.

- Although deutetrabenazine was generally well tolerated in the 12-week trials, this is a new therapy that requires ongoing use, and important adverse effects could become apparent over time.

For adults with TD for at least three months and history of use of DRBAs, we have moderate certainty that deutetrabenazine provides a comparable, small, or substantial net health benefit. However, because of the lack of clear benefit on the clinician assessed CGIC scores and the patient reported PGIC scores, as well as the absence of long-term safety data relative to usual care, we cannot definitively rule out the possibility of a small net harm. Therefore, we consider the evidence on deutetrabenazine to be “promising but inconclusive” (P/I).

Tetrabenazine

- No high-quality comparative studies were identified on the use of tetrabenazine in adults with TD and history of use of DRBAs.
- Currently available evidence on tetrabenazine suggest a possible benefit for the use of tetrabenazine in improving symptoms of TD; however, the use of various non-standard clinical measures assessed over variable periods of time and without concurrent comparators makes interpretation of results extremely problematic.
- The tolerability profile of tetrabenazine was reported in a clinical trial of patients with Huntington’s disease. Using doses similar to that in TD, tetrabenazine resulted in more patients with adverse events (e.g., somnolence and insomnia), including some serious adverse events (e.g., depression) compared to placebo. However, many of these events were dose related and managed by dose adjustments without discontinuing tetrabenazine.

Although tetrabenazine appears to have some potential benefit, we cannot be certain whether tetrabenazine is comparable, or possibly even inferior to placebo or other therapies due to the lack of direct comparative evidence in patients with TD and the potential unfavorable safety profile. We therefore consider the evidence for tetrabenazine in adults with TD for at least three months and history of use of DRBAs to be “insufficient” (I).

5. Long-Term Cost-Effectiveness

5.1 Overview

We conducted a lifetime cost-effectiveness analysis using a simulation model of the two FDA-approved VMAT2 inhibitors, valbenazine and deutetrabenazine, for treating the symptoms of moderate-to-severe TD compared to placebo in adult patients with underlying schizophrenia/schizoaffective disorders and bipolar and major depressive disorders (hereafter referred to as "other affective disorders"). As noted in Section 4.3, differences in trial design, entry criteria, and outcome measurement precluded explicit comparisons between these two agents, and so the cost-effectiveness of each was separately compared to placebo.

While other drug and non-drug treatments are used off-label for managing TD symptoms, these were not included in our analyses, as the quality of evidence supporting their use in TD was poor.²⁶ Other treatment strategies, such as altering the dose of the medication thought to be causing TD symptoms, also were not included because of similar concerns of low-quality or insufficient evidence, and because such changes were not allowed in the study protocols for valbenazine and deutetrabenazine. We included model parameters such as the probability of TD symptom improvement, utility gain from symptom improvement, treatment discontinuation rates, mortality rates, treatment costs, and other health care costs. We incorporated clinical parameters based on applicable clinical trial data. Utilities, mortality rates, and treatment costs were obtained from drug manufacturers and published literature identified through the systematic review. Health care costs related to TD treatment were unavailable in the literature and were estimated based on expert opinion.

The primary outcomes of the model included discounted total payer costs, life years, quality-adjusted life years (QALYs) gained, and incremental cost-effectiveness ratios, using a health-care system perspective over a lifetime horizon. A scenario analysis using a modified societal perspective including productivity costs was also conducted.

5.2 Cost-Effectiveness Model: Methods

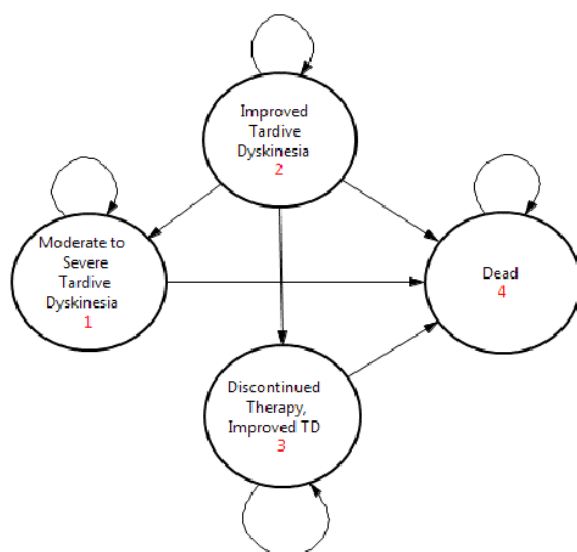
Model Structure

We developed a new semi-Markov model with time-dependent mortality and discontinuation rates for this evaluation. There were four health states in the base-case model for the treatment arms: improved TD (where patients remained on treatment for TD), moderate to severe TD (where

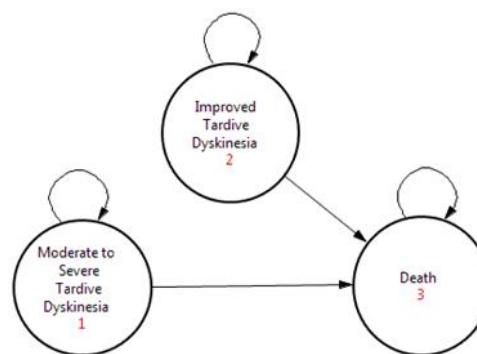
patients had discontinued TD therapy, either after an initial one-month trial or at a later time due to adverse events or lack of efficacy), discontinued therapy with improved TD (patients had improved TD symptoms despite discontinuing therapy), and death (Figure 5.1). Because there is no discontinuation of treatment in the placebo arm, three health states were used to define the model as follows: moderate to severe TD, improved TD, and death (Figure 5.1). Note that, because treatment effects were observed rapidly in the clinical trials, they are modelled ahead of the start of the annual cycles in the model; because of this, patients cannot move from moderate to severe TD to improved TD after the model has begun. For the base case, patient responses to valbenazine and deutetrabenazine were defined as 50% improvement in the Abnormal Involuntary Movement Scale (AIMS) scores observed in clinical trials. The models were built using Microsoft Excel 2013 (Redmond, WA).

Figure 5.1. Base Case Model Structures

Treated Patients



Placebo Patients



Key Model Characteristics

The base case model used a U.S. health care system perspective (i.e., focused only on direct medical care costs), and employed annual cycles over a lifetime horizon.

Prior to entering the first cycle of the model, all patients in the treatment arm were modelled as receiving one month of treatment. Patients initiating therapy would have a trial period of the medications resulting in either response and continuation of treatment or non-response and

discontinuation, after which they entered into the model and cycled through the four health states based on annual transition probabilities, until all but 0.1% of patients had transitioned to death. For the placebo model, patients entered the model based on placebo response rates. Mortality was modeled using age-adjusted mortality rates from CDC/NCHS National Vital Statistics System. In addition, the model incorporated the “life-table” method of half-cycle adjustment, which is similar to the original half-cycle correction method but more robust.⁹² Costs and quality adjusted life years were discounted at an annual rate of 3%, beginning with the second model cycle.

Target Population

A review of the literature was conducted, separate from the clinical review described above, to identify model inputs for demographic characteristics of patients with TD and patients with schizophrenia, schizoaffective, and affective disorders taking medications known to cause TD. From the identified papers, those best representing the intended modeled population were selected for the model inputs.

The underlying proportion of patients receiving antipsychotic medications were obtained from Domino et al, which characterized new users of antipsychotic medications using the Medical Expenditure Panel Survey (MEPS) from 1996 to 2005.⁹³ In the base case model, the proportion of patients with schizophrenia/schizoaffective disorders was set at 70.2% and the proportion with bipolar and other affective disorders was set at 29.8%.

Patient age and gender was necessary to estimate mortality risk for the modeled population. Data was obtained from two separate studies characterizing the population aged 18-64 years with schizophrenia/schizoaffective disorder²⁰ and affective disorders.²¹ In these studies, patients with schizophrenia/schizoaffective disorders had a mean age of 38 years and were 52.5% female²⁰ while patients with affective disorders had a mean age of 40 years and were 64.8% female.²¹ Using these population estimates resulted in a modeled population with an expected average age of 39 years.

The resulting modeled population represented U.S. adults ages 18-64 years with TD and the underlying conditions of schizophrenia/schizoaffective disorders or affective disorders, and on medications that cause TD (as a proxy for patients with moderate to severe TD).

Key Model Assumptions

Table 5.1 contains a list of key model assumptions along with the rationale for each assumption.

Table 5.1. Key Model Assumptions and Rationale

Assumptions	Rationale
Patients receiving metoclopramide for gastrointestinal conditions and developing tardive dyskinesia were not modeled in this analysis.	Patients receiving metoclopramide were excluded from most of the primary trials involving valbenazine or deutetrabenazine. Furthermore, there is insufficient data regarding the demographics of patients receiving metoclopramide and developing TD to accurately depict this population in the model.
Before entering the model, all patients received one month of treatment and incurred one month of treatment costs as an initial cost.	Patients initiating therapy would have a trial period of the medications. Medications are usually dispensed in one-month increments.
Patient response to the first month of treatment was reflected in their initial health states.	This prevented a lag in response to therapy that would occur if all patients were started in the “moderate to severe tardive dyskinesia” state. Additionally, patient response to therapy was quite rapid in the clinical trials. ^{18,19}
Patients not responding to treatment with valbenazine or deutetrabenazine discontinued their treatment.	Patients not responding will not see benefits of therapy and should have no ongoing TD treatment costs.
Response to treatment remained constant for all responders. Patients did not improve or decline beyond their initial response to therapy while remaining in the “improved TD” state.	There is limited information on the individual change in response to therapy over time. Furthermore, there is no information available on the impact of TD severity on quality of life.
Long-term discontinuation rates were modeled from open-labeled studies with less than one year of observation.^{18,22} Following the first cycle, discontinuation rates were modeled as being 50% of that observed in the first cycle.	There is no information regarding discontinuation rates of therapies beyond the clinical trial extensions. We lowered the discontinuation rate by 50% following the first year because for most therapies, patients typically discontinue their medications at a higher rate in the first year of treatment.
Patients who responded to treatment were assumed to have no added primary care and neurologist visit costs related to TD. Patients not responding to treatment were assumed to have two additional primary care and two additional neurologist visits per year.	There is currently no data on the costs associated with treating TD. It is likely that patients whose TD has improved will incur fewer office visits.
TD treatments do not have a direct effect on mortality.	We identified no studies demonstrating an impact of VMAT2 inhibitors on mortality in patients with TD.
Treatment of TD has no effect on the outcomes or costs of treating the underlying conditions.	We identified no studies that demonstrate valbenazine or deutetrabenazine improve the management of underlying conditions.

Interventions

Interventions assessed in this model included the two FDA-approved VMAT2 inhibitors, valbenazine and deutetrabenazine, both compared with placebo. Patients not receiving active treatment for TD symptoms were modeled using outcomes associated with the placebo arms from the relevant clinical trials.⁷ For valbenazine, we modeled the effects and costs of the 80mg dose. For deutetrabenazine, we modeled effects and costs for the 36mg dose (two 9mg tablets twice daily), although the information for prescribers states that patients can be titrated up to 48mg per day.⁸¹ We used the effectiveness for the 36mg dose for two reasons i) the lack of effectiveness data on using the 48mg dose and ii) mean daily dose of deutetrabenazine at the end of the treatment period was approximately 38mg in the trial.⁷ All patients were assumed to have received one month of therapy prior to entering the model.

Initial State Probabilities

Patients entered the model as having improved or not, following the first month of therapy. Those who improved on treatment entered the model in the “improved TD” state. Those who had not improved began the model in the “moderate to severe TD” state.^{18,19} The proportion of patients starting in the “improved TD” state were abstracted from the Phase III clinical trials evaluating response to valbenazine and deutetrabenazine compared with placebo (Table 5.2). The effectiveness of valbenazine and deutetrabenazine was based on the proportion of patients that experienced a $\geq 50\%$ improvement in the AIMS score at the maximal tolerated dose in the clinical trials (80mg for valbenazine and 36mg for deutetrabenazine). The $\geq 50\%$ improvement was chosen because it was consistently reported for both therapies, and as a balance between the available utility gains in the literature based on “full improvement” and the goals of the clinical trials.

Table 5.2. Key Model Inputs: Probabilities

Parameters	Valbenazine		Deutetrabenazine	
	Value	Reference	Value	Reference
Proportion of PLACEBO Responders with $\geq 50\%$ Reduction in AIMS	8.7%	Hauser 2017 ¹⁸	12.0%	Anderson 2017 ⁷
Proportion of TREATMENT Responders with $\geq 50\%$ Reduction in AIMS	40.0%	Hauser 2017 ¹⁸	33%	Anderson 2017 ⁷
Annual Discontinuation Rate (First Year)	17.6%	Remington 2016 ⁹⁴ Hauser 2017 ⁴	13.0%	Anderson 2017 ⁹⁵
Annual Discontinuation Rate (Year 2+)	8.8%	Calculation*	6.5%	Calculation*

*Assumed 50% decrease after 1st year

Transition Probabilities

Adverse Events and Medication Discontinuation

In clinical trials, serious adverse events were uncommon and occurred at a rate similar to what was observed in the placebo arm. Hence the model did not directly incorporate the impact of adverse events in either arm. The model did incorporate discontinuation rates, however. As discussed above, the initial state included responders and non-responders, and non-responders are assumed to discontinue their TD treatment permanently and start out in the “moderate to severe TD” state. Following the initial state, discontinuation rates in the treatment arm are applied to the responders who start in the “improved TD” state, based on the longest follow-up data available corresponding to the first year within the model. Specifically, the discontinuation probability for the first year of valbenazine was calculated based on the discontinuation rate from the longest reported observation period from open label studies, subtracting the discontinuation rate from the clinical trial, and then extrapolating to one year.^{18,94} The discontinuation probability for the first year of deutetrabenazine was equal to the exposure-adjusted incidence rate reported in Anderson et al.,

which only included discontinuations after a washout period.²² For both drugs, we assumed a 50% decrease in discontinuation rate after the first year for all subsequent years.

Among initial responders who subsequently discontinued, a portion of patients entered the “discontinued therapy, improved TD” state and the remainder entered the “moderate to severe TD” state, where it was assumed that those responding to treatment would include all those that would have been placebo responders in the absence of treatment and that those who would not have been placebo responders would return to the moderate to severe TD state upon treatment discontinuation. For example, if all patients discontinued their TD therapy, then the resulting proportion in the moderate to severe TD state would be the same as the placebo response rate. Therefore, patients discontinuing therapy and continuing to have improved TD with no treatment was calculated using the following conditional probability:

$$(Proportion\ with\ placebo\ response) / (Proportion\ of\ treatment\ responders).$$

The remainder of patients that discontinued therapy cycled back into the moderate to severe TD state.

Mortality

Mortality was modeled using age- and gender-adjusted mortality estimates for the general population. Mortality estimates were obtained from the CDC/NCHS National Vital Statistics System, and further adjusted to reflect mortality rates in the underlying populations of schizophrenia/schizoaffective disorders and other affective disorders. The multipliers used to adjust population mortality rates were derived from the published literature, and were 3.70 and 2.05 for schizophrenia/schizoaffective and other affective disorders, respectively (Appendix Table H5).^{27,28} We assumed that TD and TD-related therapies did not affect mortality.¹³

Cost Inputs

Costs associated with caring for TD were included in the model (Appendix Tables H1-H3). Specifically, medication costs and primary care/specialist visits to manage TD were considered. Annual drug acquisition costs for valbenazine (80mg per day) and deutetrabenazine (36mg per day) were used in the model. Since both drugs were only recently approved by the FDA, information on their net sales volume and revenue was not available. We applied the industry-wide average discount rate of 27% for branded drugs²⁹ to the wholesale acquisition cost (WAC) of the deutetrabenazine 9mg tablets to arrive at an annual net price of approximately \$65,800 and to the valbenazine 80mg capsules to arrive at an annual net price at approximately \$55,300.

Patients with moderate to severe TD were assumed to require additional neurologist and primary care visit costs. Specifically, having moderate to severe TD was assumed to necessitate two

additional primary care and two additional neurologist visits per year. Costs for these visits were derived from the 2017 Medicare Physician Final Fee Schedule (approximately \$365) (Appendix Table H3).⁹⁶ There were no additional costs associated with death.

Utilities

Gains in utility from improvement in TD symptoms were modeled using utility estimates available in the literature for moderate to severe TD versus no TD (Appendix Table H4). The mean utility for the modeled population with improved TD was 0.82, which in part reflects utility scores associated with the underlying conditions.^{23,24} To this utility, we applied a utility decrement of 0.095 to those patients with moderate to severe TD.²⁵ The utility gained from improvement in TD was assumed to be independent of any other underlying condition(s). We chose this utility decrement for TD because it was the only available utility estimate that directly assessed the impact of TD. The estimate was based on standard gamble utilities from subjects rating TD relative to perfect health and was directly elicited from healthy individuals upon viewing the symptoms of moderate to severe TD, independent of any underlying conditions. Limitations of soliciting utilities from healthy volunteers include that the final utility depends on the accuracy of the scenarios presented.⁹⁷ However, patients who have the condition in question often adapt to their conditions and frequently report utilities that are higher (or decrements that are smaller) than those reported from healthy volunteers. Because of the uncertainty associated with this utility decrement estimate for TD, we also compared this decrement with those for other better-studied mental health and non-mental health conditions, which ranged from 0.011 for drug dependency to 0.159 for new-onset depression.⁹⁸ Long term depression was associated with a utility decrement of 0.118 and generalized anxiety disorder with a decrement of 0.081. In another study, the only diabetes complications with decrements over 0.10 were painful neuropathy and amputation.⁹⁹ This led us to believe that the utility decrement we applied was likely a reasonable estimate for the impact of TD on patient health-related quality of life. We nevertheless varied our estimate across a broad range in sensitivity analyses.

Patients in the “improved TD” or “discontinued therapy, improved TD” states did not incur the disutility. Due to the uncertainty surrounding the TD utility decrement, we chose a conservative approach to estimating the benefits of the VMAT2 inhibitors, in that it allocates a benefit associated with the complete removal of TD to patients with a 50% or higher decrease in the AIMS score, biasing the model results in favor of the therapies.

Sensitivity Analyses

One-Way Sensitivity Analyses

All model parameters were subjected to one-way sensitivity analysis. In addition to one-way sensitivity analyses, threshold analyses were conducted varying the discontinuation rate or the annual acquisition costs of valbenazine and deutetrabenazine until (when possible) there was a projected incremental cost effectiveness ratio of \$150,000/QALY gained.

Two-Way Sensitivity Analysis

Due to the uncertainty and discussion surrounding the benefits of therapies on utility decrements of TD and proportion of patients receiving significant benefit, which was defined as a 50% reduction in the AIMS score, we conducted a two-way sensitivity analysis showing the impact of varying the utility decrement and proportion of patients responding on incremental cost-effectiveness ratios.

Probabilistic Sensitivity Analysis

A Monte Carlo probabilistic sensitivity analysis was conducted using 10,000 simulations. Distributions were assigned based on available data. Beta distributions were assigned for probabilities and for disutility associated with TD.¹⁰⁰ Parameters for specifying beta distributions were obtained from literature values using the number of occurrences of the event in question and the overall sample size. The disutility of TD symptoms also used a beta distribution with a mean score equal to the base case, to provide a relatively large variance that was also bounded between zero and one. Distributions describing drug costs and the medical costs of managing TD were unavailable. Given this absence of information, uniform distributions were used, with costs being varied between 50% and 150% of the base case values. All probabilistic sensitivity analysis distributions and parameters are shown in Appendix Table H5.

Scenario Analyses

Because utility measures evaluating different severity levels of TD were not available, and there was considerable uncertainty surrounding the impact of VMAT2 inhibitors on utilities, results were also presented using TD symptom-reduced years (i.e., proportion of patients with a 50% reduction in TD symptoms each model cycle). This measure encompassed the additional average number of years individuals could expect to live with reduced symptoms of TD while on therapy compared with placebo. To produce these estimates, all patients with improved TD received a value of 1 and all patients with moderate to severe TD received a value of 0. The model was then run and the cost per TD symptom-reduced year calculated.

In addition to varying base-case model parameters, an analysis from a modified societal perspective was undertaken, varying the annual lost productivity due to TD from \$0 to \$2,252. The \$2,252 value was based on employment differences observed in a single study that included patients with schizophrenia and TD.¹⁰¹ In this study, 22.9% of patients without TD were employed, while 17.8% with TD were employed. The median 2016 US salary (\$44,148) was used to estimate an upper bound for productivity benefits resulting from improved TD [calculated as a 5.1% difference in proportion of patients who worked and median annual US income (i.e. $0.05 * \$44,148 = \$2,252$)].

Currently, there is little agreement on the best measure for assessing patient TD symptoms or improvement. In addition to the AIMS, clinical trials involving valbenazine and deutetrabenazine included the clinician-rated CGIC scale. A beneficial response to therapy was stated as being either a ≤ 2 -point improvement in the valbenazine trials or a response of “improved” or “very much improved” in the deutetrabenazine trials (See Section 2.5). Scenario analyses were conducted evaluating the impact of VMAT2 inhibitors on the proportion of responders when using the CGIC scale. Results were presented as cost/QALY gained and as cost per TD symptom-reduced year.

Finally, scenario analyses were also undertaken to account for potential indirect effects of valbenazine and deutetrabenazine on the underlying conditions of the patients. Separate models were developed for patients with schizophrenia/schizoaffective disorders and bipolar disorders. The models incorporated well-controlled and poorly-controlled mental health states for the underlying conditions, to reflect a proportion of patients with TD becoming non-adherent to their antipsychotic medication. For this scenario, it was assumed that 10% of patients with symptomatic TD (in non-responders to treatments or placebo) and well-controlled mental health for the underlying condition would become poorly controlled for one cycle. This was intended as a rough approximation of the potential impact of non-adherence related to TD symptoms. Further, as there is no data for this potential impact, the probability of having poor control was also varied between 0% and 100% in this scenario analysis. Further details on the structure, health states, assumptions, and additional parameter inputs for this analysis are available in Appendix H.

5.3 Cost-Effectiveness Model: Results

Base-Case Results

The main results are summarized in Tables 5.3-5.5. The total discounted lifetime costs for valbenazine and the placebo comparator were approximately \$185,200 and \$6,900, respectively (Table 5.3). The total discounted quality-adjusted life years (QALYs) for valbenazine and placebo were 15.35 and 15.12, respectively. Deutetrabenazine and its placebo comparator had lifetime discounted costs of approximately \$220,400 and \$6,600 and lifetime discounted QALYs of 15.37 and

15.18, respectively. The incremental cost-effectiveness ratios over a lifetime horizon were approximately \$752,000 per QALY for valbenazine and approximately \$1.1 million per QALY for deutetrabenazine (Table 5.4).

Table 5.3. Base-Case Discounted Costs and Outcomes

Treatment Arm	Total Costs	Total QALYs
Valbenazine	\$185,167	15.35
Placebo (Valbenazine Comparison)	\$6,876	15.12
Deutetrabenazine	\$220,423	15.37
Placebo (Deutetrabenazine Comparison)	\$6,627	15.18

Table 5.4. Pairwise Results for VMAT2 Inhibitors Compared to Placebo

Regimen	Incremental Costs	Incremental QALYs	Incremental Cost-Effectiveness Ratios vs. Placebo
Valbenazine	\$178,291	0.24	\$752,080
Deutetrabenazine	\$213,795	0.19	\$1,100,773

Costs per TD symptom-reduced year were approximately \$71,000 and \$105,000 for valbenazine and deutetrabenazine versus placebo respectively (Table 5.5). It is difficult to judge the importance of these results, however, as there are no clear benchmarks of cost per TD symptom-reduced year for comparison.

Table 5.5. Cost per TD Symptom-Reduced Year

Treatment	Cost per TD Symptom-Reduced Year
Valbenazine vs. Placebo	\$71,448
Deutetrabenazine vs. Placebo	\$104,573

Sensitivity Analyses over Different Time Horizons

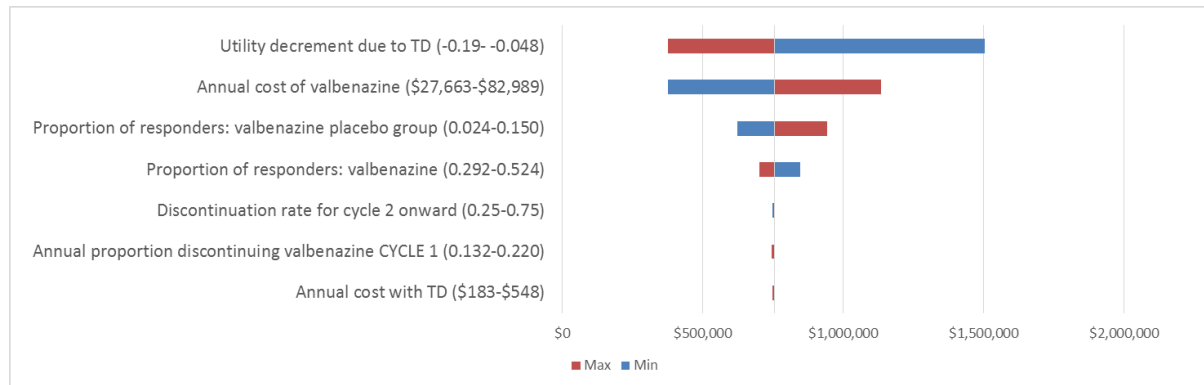
The estimated incremental cost-effectiveness ratios were higher over shorter time horizons and all surpassed commonly utilized thresholds of \$100,000 or \$150,000 per QALY in the base case analysis. The full results for these sensitivity analyses are reported in Appendix H7.

One-Way Sensitivity Analyses

Results of the one-way sensitivity analyses are shown in Tables 5.6 and 5.7. Altering the proportion of responders in either treatment or placebo group across calculated 95% confidence intervals did not result in an incremental cost effectiveness ratio below the \$150,000 per QALY gained threshold. Similarly, one-way changes in discontinuation rates, drug costs, cost of TD, and disutility across

reasonable bounds resulted in incremental cost effectiveness ratios that were consistently above the \$150,000 per QALY gained threshold.

Figure 5.2. Tornado Diagram for Valbenazine One-Way Sensitivity Analyses

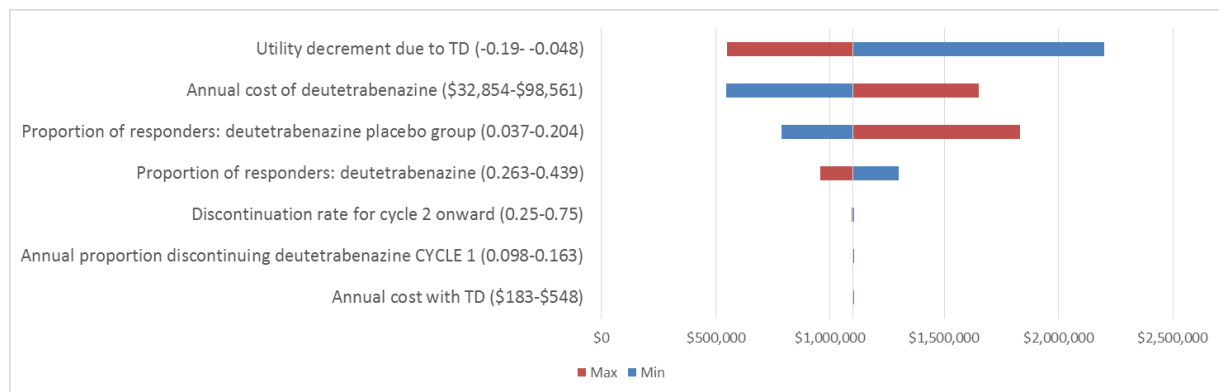


Base-Case Incremental Cost-Effectiveness Ratio: \$752,080 per QALY gained

Table 5.6. One-Way Sensitivity Analyses: Valbenazine

Parameters	Base Case Value	Sensitivity Analysis Value		Incremental Cost per QALY	
		Min	Max	At Input Min	At Input Max
Proportion of Responders: Placebo	0.087	0.024	0.150	\$624,754	\$942,574
Proportion of Responders: Valbenazine (80mg)	0.400	0.292	0.524	\$846,715	\$701,109
Annual Discontinuation*	0.176	0.132	0.220	\$750,100	\$745,151
Discontinuation rate for cycle 2 to end of time horizon	50% of first cycle	25% of first cycle	75% of first cycle	\$748,933	\$755,000
Annual Cost of Valbenazine	\$55,326	\$27,663	\$82,989	\$374,116	\$1,130,039
Annual Cost of TD Care	\$365	\$183	\$548	\$754,000	\$750,158
Utility Decrement due to TD	-0.095	-0.19	-0.048	\$376,040	\$1,504,160

Figure 5.3. Tornado Diagram for Deutetrabenazine One-Way Sensitivity Analyses



Base-Case Incremental Cost-Effectiveness Ratio: \$1,100,773 per QALY gained

Table 5.7. One-Way Sensitivity Analyses: Deutetrabenazine

Parameters	Base Case Value	Sensitivity Analysis Value		Incremental Cost per QALY	
		Min	Max	At Input Min	At Input Max
Proportion of Responders: Placebo	0.12	0.037	0.204	\$788,925	\$1,831,387
Proportion of Responders: Deutetrabenazine	0.330	0.263	0.439	\$1,299,756	\$959,104
Annual Discontinuation*	0.130	0.098	0.163	\$1,098,071	\$1,103,676
Discontinuation rate for cycle 2 to end of time horizon	50% of first cycle	25% of first cycle	75% of first cycle	\$1,096,311	\$1,105,106
Annual Cost of Deutetrabenazine	\$65,752	\$32,876	\$98,628	\$548,467	\$1,653,094
Annual Cost of TD Care	\$365	\$183	\$548	\$1,102,692	\$1,098,851
Utility Decrement due to TD	-0.095	-0.19	-0.048	\$550,386	\$2,201,547

*Note that the model assumes annual discontinuation rates in cycles 2 and beyond are 50% of first-year rates

The incremental cost-effectiveness ratios were driven primarily by the utility decrement due to TD, followed by the cost of TD medication. Lower discontinuation rates and higher treatment effects resulted in lower incremental cost effectiveness ratios. However, neither lowering annual

discontinuation probabilities to 0% nor increasing the proportion of treatment responders to 100% in one-way sensitivity analyses resulted in incremental cost effectiveness ratios below the \$150,000 per QALY threshold. Utility gains from treatment of TD would need to reach 0.47 for valbenzazine and 0.70 for deutetrabenazine (base case = 0.095) to reach a cost-effectiveness threshold of \$150,000 per QALY gained.

Two-Way Sensitivity Analysis

The results of the two-way sensitivity analyses are shown in Figures 5.4 and 5.5. Utility decrements of 0.15 with these effects occurring in up to 60% of patients with TD did not result in incremental cost-effectiveness ratios below the willingness to pay threshold of \$150,000 per QALY for either therapy compared with placebo.

Figure 5.4. Two-Way Sensitivity Analysis for the Utility Decrement for TD and the Proportion of Patients to Which the Decrement was Applied: Valbenzazine versus Placebo

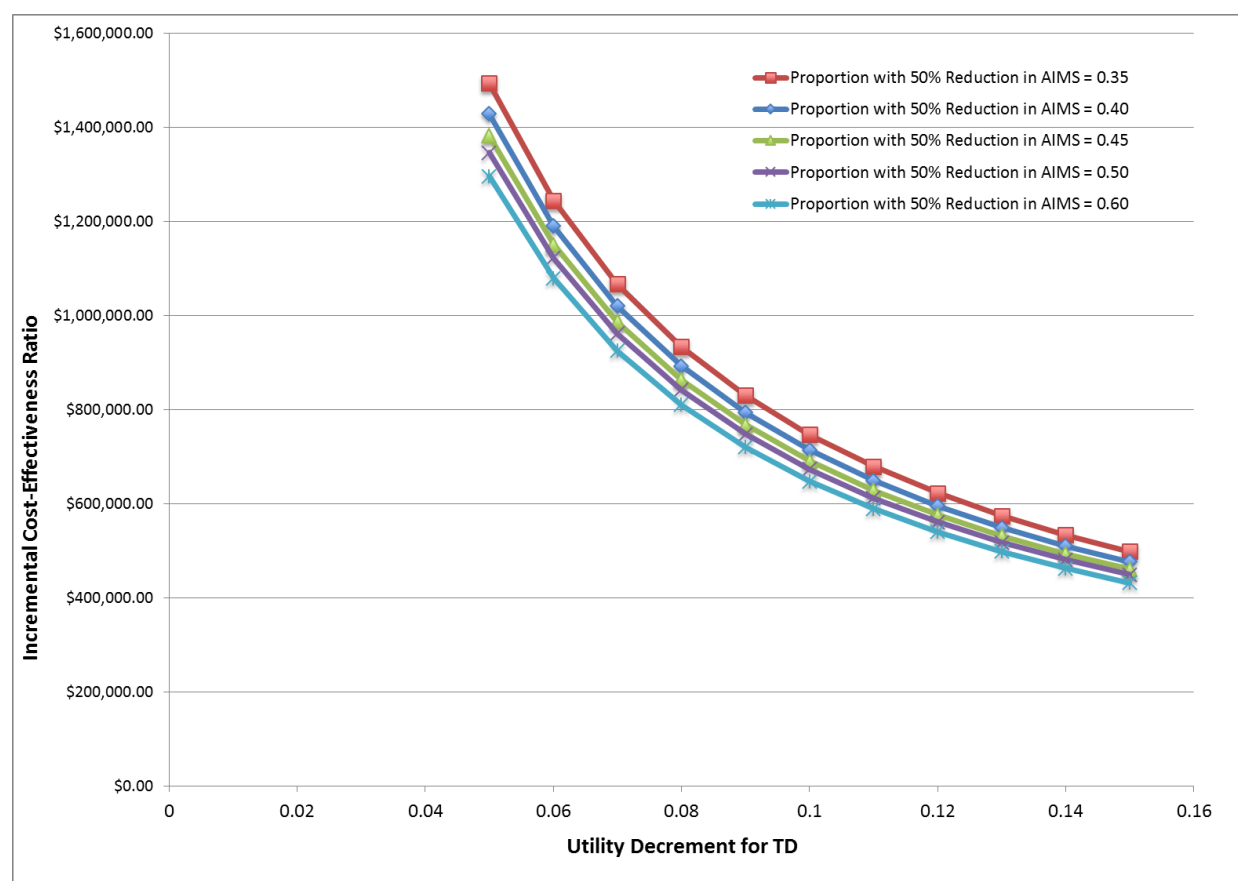
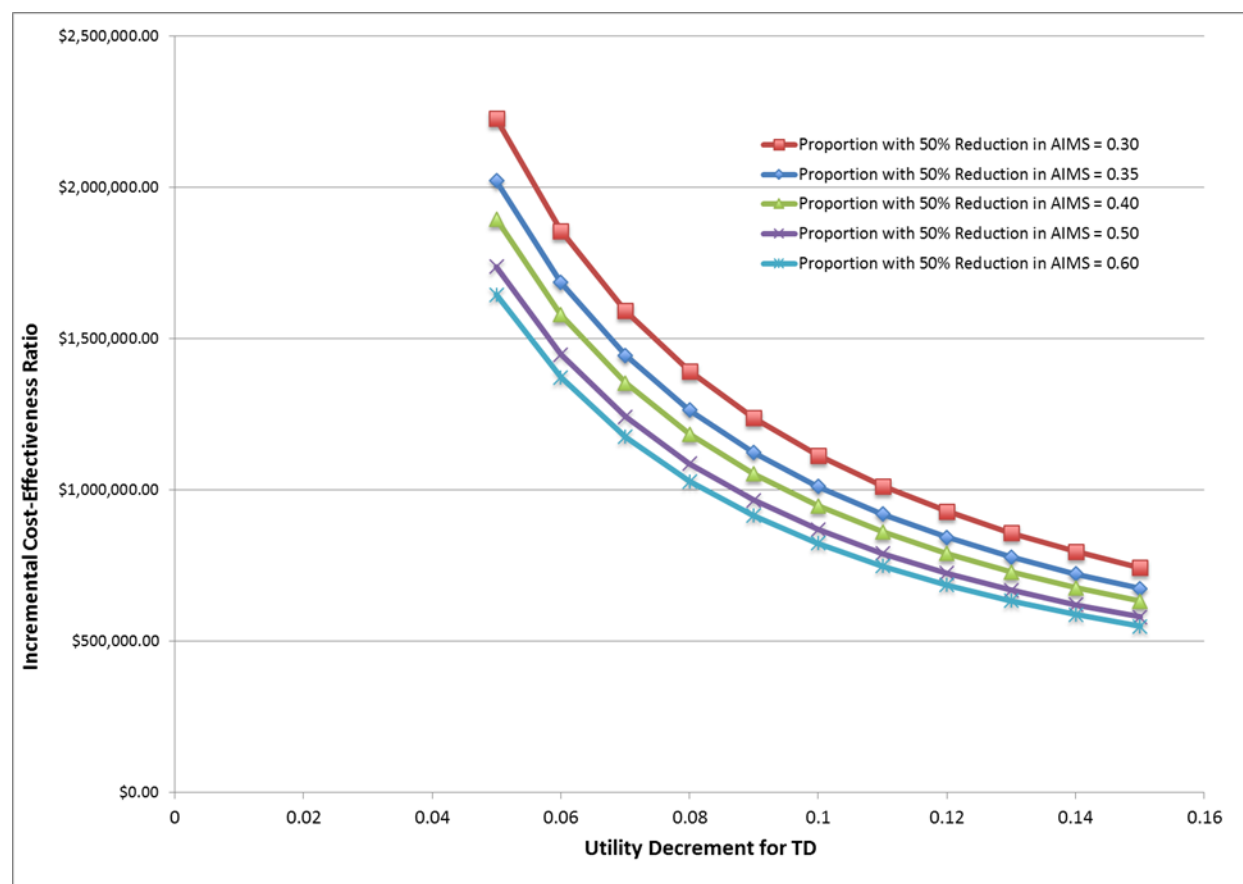


Figure 5.5. Two-Way Sensitivity Analysis for the Utility Decrement for TD and the Proportion of Patients to Which the Decrement was Applied: Deutetrabenazine versus Placebo.



Probabilistic Sensitivity Analysis

The results of the probabilistic sensitivity analyses are summarized in Appendix H5. At willingness to pay thresholds of \$150,000 per QALY or lower, zero percent of the simulations reach these thresholds for valbenazine or deutetrabenazine relative to placebo.

Threshold Analysis

In single-input threshold analyses, prices for each drug to achieve commonly-cited cost-effectiveness thresholds ranging from \$50,000 to \$150,000 per QALY gained are presented in Table 5.8.

Table 5.8. Threshold Analysis Results for Valbenazine and Deutetrabenazine

	Annual WAC	Annual Price to Achieve \$50,000 Per QALY	Annual Price to Achieve \$100,000 Per QALY	Annual Price to Achieve \$150,000 Per QALY
Valbenazine 80mg capsules (dose = 80 mg per day)	\$75,789	\$3,941	\$7,600	\$11,260
Deutetrabenazine 9 mg tablets (dose = 36 mg per day)	\$90,071	\$3,205	\$6,181	\$9,158

Scenario Analyses

Including productivity gains from improved TD in the model, with all else remaining equal, resulted in only small improvements in the cost-effectiveness ratios for the two agents (\$728,000 per QALY gained for valbenazine and \$1.077 million per QALY gained for deutetrabenazine). Two additional scenario analyses attempted to account for potential but unproven benefits of TD treatment in improved maintenance and medication adherence for patients' underlying conditions of schizophrenia/schizoaffective disorders and bipolar disorders. The incremental cost effectiveness ratios for these scenario analyses were predictably lower compared with the base case analysis (Table 5.9), but also remained well above commonly-cited thresholds. In patients with the underlying condition of schizophrenia/ schizoaffective disorders, the estimated incremental cost effectiveness ratios were \$553,000 per QALY gained for valbenazine and \$779,000 per QALY gained for deutetrabenazine. For patients with bipolar disorder, the incremental cost effectiveness ratios for valbenazine and deutetrabenazine were \$605,000 and \$875,000 per QALY gained, respectively. Varying the probability of non-adherence resulting in poorly-controlled schizophrenia or bipolar disorder to 100% (a highly unlikely scenario) resulted in cost-effectiveness ratios that still exceeded \$150,000 per QALY (see model structure and inputs in Appendix H, Figure H3 and Table H6).

Table 5.9. Scenario Analyses of Control Benefit from Improved Adherence

Base Case vs. Placebo	Underlying Condition	Incremental Cost Per QALY
Valbenazine	Schizophrenia/Schizoaffective Disorders	\$552,589
Deutetrabenazine	Schizophrenia/Schizoaffective Disorders	\$779,342
Valbenazine	Bipolar Disorder	\$604,568
Deutetrabenazine	Bipolar Disorder	\$874,934

Model Validation and Prior Published Evidence on Costs and Cost-Effectiveness

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model produced findings consistent with expectations. Three independent modelers tested the mathematical functions in the model as well as the therapy-specific inputs and corresponding outputs.

We also compared the ICER model to previously published models. We searched the literature to identify models that were similar to our own, with comparable populations, settings, perspective, and treatments. In our review of the literature, we found only one model that was relevant as a comparison to our model.

A model was developed by Rosenheck to assess the cost-effectiveness of second-generation antipsychotics in reducing the risk of TD in adults with schizophrenia.³¹ Reported incremental cost-effectiveness ratios at one year ranged from approximately \$660,000 per QALY gained using any one of four second-generation antipsychotics relative to perphenazine, a first-generation antipsychotic, to approximately \$1.7 million per QALY gained when using risperidone relative to perphenazine, a first-generation antipsychotic. Extending the model time-horizon to five years for the same interventions and comparator decreased the incremental results to approximately \$264,000 and \$684,000 per QALY gained, respectively. The interventions, comparators, associated costs, and effectiveness in reducing TD were different between the ICER and Rosenheck models; therefore, results cannot directly be compared. However, comparison from a structural perspective revealed other key differences between the two models: 1) a life-time horizon in the ICER model versus a maximum five-year time horizon in the Rosenheck model; 2) 3% discounting applied to costs and consequences in the ICER model versus no discounting in the Rosenheck model; and 3) population with approximately 70% with schizophrenia in the ICER model versus only patients with schizophrenia in Rosenheck. We also note that the Rosenheck model employed a different measure to assess improvement in TD symptoms.

5.4 Potential Budget Impact

We used the cost-effectiveness model to estimate the potential total budgetary impact of valbenazine and deutetrabenazine for patients with TD resulting from use of antipsychotics. We used the wholesale acquisition cost (WAC), an estimate of discounted WAC, and the three cost-effectiveness threshold prices for each drug in our estimates of budget impact.

Potential Budget Impact Model: Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using a new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon. The five-year time frame was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

The potential budget impact analysis included the entire candidate population for treatment, which consisted of adult patients with TD resulting from use of antipsychotic drugs used to treat underlying disease. Dhir et al. estimated the prevalence of TD using US population estimates from 2016 with epidemiological data on the prevalence and use of antipsychotic drugs to treat underlying schizophrenia, bipolar disease and major depressive disorder (MDD).¹⁰² The estimated prevalence of TD in 2016 was 573,000 patients in the US, of which 359,000 had moderate-to-severe TD. The authors also reported projected total prevalence and prevalence by severity of TD up to 2025. For our budget impact analysis, we used the projected prevalence of moderate-to-severe TD between 2017 (359,000 patients) and 2021 (361,000 patients) to arrive at an average prevalence estimate of 360,000 patients, with assumed uptake of the new therapies when analyzed individually, at 72,000 patients per year over five years.

ICER's methods for estimating potential budget impact and calculating value-based benchmark prices are described in detail [here](#) and have recently been updated. The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Briefly, we evaluate a new drug that would take market share from one or more drugs, and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. In this analysis, we assumed that each of the VMAT2 inhibitors would only replace the cost of disease management with non-specific therapy since there have been no FDA-approved therapies for TD prior to the approval of the two reviewed VMAT2 inhibitors.

Using this approach to estimate potential budget impact, we then compared our estimates to a budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in [ICER's methods presentation](#), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA each year, and the contribution of spending on retail and facility-based drugs to total health care spending. Calculations are performed as shown in Table 5.10.

For 2017-18, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage affordability is calculated to total approximately \$915 million per year for new drugs.

Table 5.10. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2017 (est.) +1%	3.20%	World Bank, 2016
2	Total health care spending, 2016 (\$)	\$2.71 trillion	CMS NHE, 2014
3	Contribution of drug spending to total health care spending (%)	17.7%	CMS National Health Expenditures (NHE), 2016; Altarum Institute, 2014
4	Contribution of drug spending to total health care spending (\$) (Row 2 x Row 3)	\$479 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	\$15.3 billion	Calculation
6	Average annual number of new molecular entity approvals, 2013-2014	33.5	FDA, 2016
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	\$457.5 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	\$915 million	Calculation

Potential Budget Impact Model: Results

Table 5.11 and 5.12 illustrate the per-patient budget impact calculations in more detail, based on WAC, discounted WAC and the prices to reach \$150,000, \$100,000, and \$50,000 per QALY for valbenazine and deutetrabenazine compared to usual care. Note that annual estimated budget impact is substantially lower than the annual WAC for both drugs given rates of non-response and discontinuation seen in clinical trials.

Table 5.11. Per-Patient Budget Impact Calculations for Valbenazine Over a Five-year Time Horizon

Average Annual Per Patient Budget Impact					
	WAC	Discounted WAC	\$150,000/QALY	\$100,000/QALY	\$50,000/QALY
Valbenazine	\$30,495	\$22,325	\$4,313	\$3,281	\$1,816
Usual Care	\$345				
Difference	\$30,150	\$21,980	\$4,001	\$2,936	\$1,471

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

Table 5.12. Per-Patient Budget Impact Calculations for Deutetrabenazine Over a Five-year Time Horizon

Average Annual Per Patient Budget Impact					
	WAC	Discounted WAC	\$150,000/QALY	\$100,000/QALY	\$50,000/QALY
Deutetrabenazine	\$31,307	\$22,924	\$3,428	\$2,398	\$1,368
Usual Care	\$333				
Difference	\$30,974	\$22,591	\$3,095	\$2,065	\$1,035

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

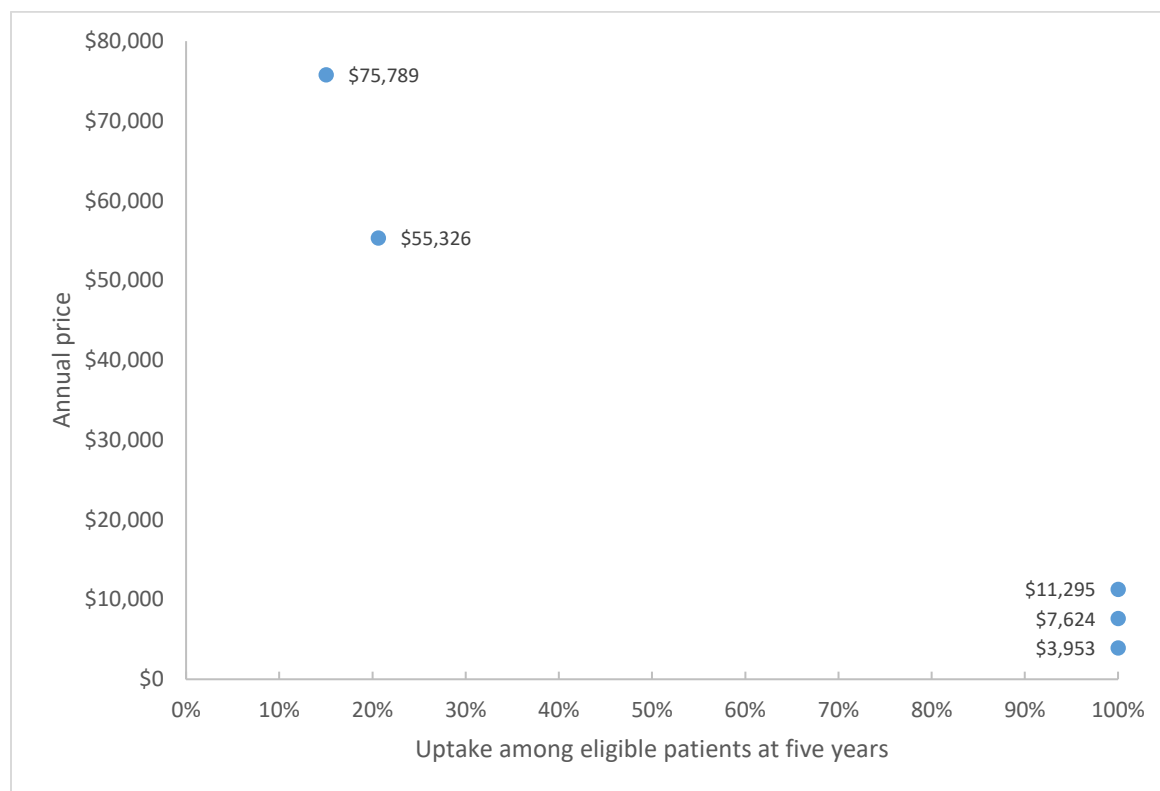
Valbenazine

The average potential budgetary impact when using the annual WAC (\$75,789) was an additional per-patient cost of approximately \$30,100, and approximately \$22,000 using the annual discounted WAC (\$55,326). Average potential budgetary impact at the three cost-effectiveness threshold prices for the drug ranged from approximately \$4,000 per patient using the annual price (\$11,295) to achieve \$150,000 per QALY to approximately \$1,500 using the annual price (\$3,953) to achieve a \$50,000 per QALY cost-effectiveness threshold.

As shown in Figure 5.6, approximately 15% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of \$915 million at WAC (\$75,789) and approximately 21% of patients at the discounted WAC (\$55,326). The entire eligible cohort could

be treated without crossing the ICER annual budget impact threshold of \$915 million at the three threshold prices.

Figure 5.6. Valbenazine Pricing and Uptake Relative to Annual Budget Impact Threshold

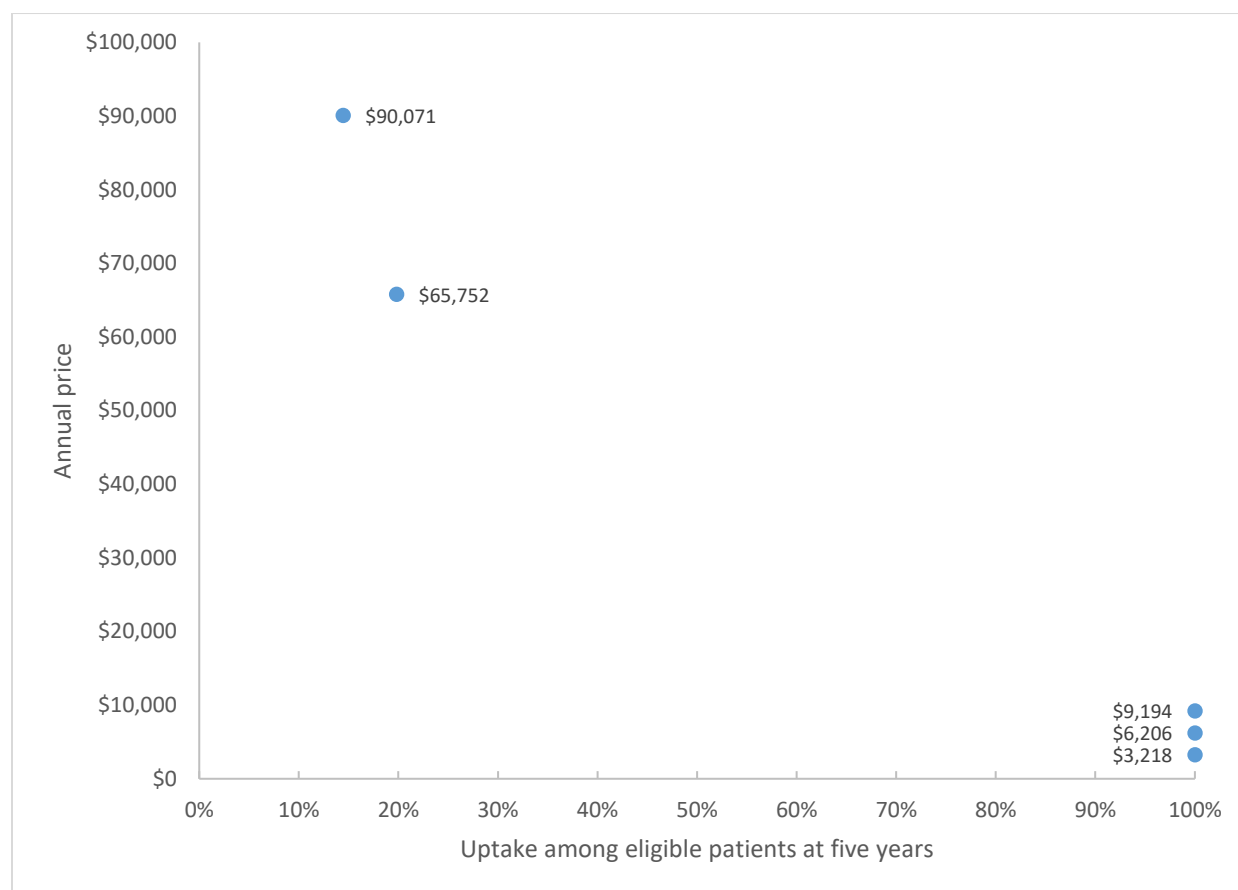


Deutetrabenazine

The average potential budgetary impact when using the annual WAC (\$90,071) was an additional per-patient cost of approximately \$31,000, and approximately \$22,600 using the annual discounted WAC (\$65,752). Average potential budgetary impact at the three cost-effectiveness threshold prices for the drug ranged from approximately \$3,100 per patient using the annual price (\$9,194) to achieve \$150,000 per QALY to approximately \$1,000 using the annual price (\$3,218) to achieve a \$50,000 per QALY cost-effectiveness threshold.

As shown in Figure 5.7, approximately 14% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of \$915 million at WAC (\$90,071) and approximately 20% of patients at the discounted WAC (\$65,752). The entire eligible cohort could be treated without crossing the ICER annual budget impact threshold of \$915 million at the three threshold prices.

Figure 5.7. Deutetrabenazine Pricing and Uptake Relative to Annual Budget Impact Threshold



5.5 Value-Based Benchmark Prices

Our value-based benchmark annual prices for valbenazine and deutetrabenazine are presented in Table 5.13. As noted in the initial ICER methods document (<http://icer-review.org/wpcontent/uploads/2016/02/Value-Assessment-Framework-slides-for-July-29-webinar-FINALcorrected-8-22-1.pdf>), the value-based benchmark price for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between \$100,000 and \$150,000 per QALY gained. For both drugs, the discounts required to meet both threshold prices are greater than the currently assumed discount from WAC.

Table 5.13. Value-Based Benchmark Prices for Valbenazine and Deutetrabenazine for the Treatment of Moderate to Severe Tardive Dyskinesia

	Annual WAC	Annual Price to Achieve \$100,000 Per QALY	Annual Price to Achieve \$150,000 Per QALY	Discount from WAC To Reach Thresholds
Valbenazine 80mg capsules (dose = 80 mg per day)	\$75,789	\$7,600	\$11,260	85%-90%
Deutetrabenazine 9 mg tablets (dose = 36 mg per day)	\$90,071	\$6,181	\$9,158	90%-93%

5.6 Summary and Comment

We estimated the cost-effectiveness of the two recently-approved VMAT2 inhibitors compared to placebo in patients with TD. In the base case, the incremental cost effectiveness ratios for valbenazine and deutetrabenazine versus placebo far exceeded commonly utilized cost-effectiveness thresholds. When model inputs were varied between reasonable ranges in one-way sensitivity analyses, none of the resulting estimates approached thresholds of \$150,000 per QALY. Further, the probabilistic sensitivity analyses resulted in acceptability curves suggesting an extremely low likelihood that the treatments will reach these thresholds.

There were several limitations of this analysis. First, the effectiveness of the TD treatments was based on limited intermediate measures from the clinical trials. Furthermore, current measures for assessing TD severity may not accurately reflect the global impact of TD on patients' lives or the impact of TD severity on overall quality of life. As a result, the impact of improvement from the treatment of TD on utility was not available in the literature. We attempted to address this limitation by generously applying the reported difference in utility between moderate-to-severe TD and no TD for responders in our analysis, based on a 50% reduction in the AIMS score. In addition, the model applies to an average TD patient, but may not reflect particular sub-populations or individuals. However, our reporting is consistent with guidelines for assessing and reporting cost-effectiveness analyses and, as noted in Section 4, findings for treatment effect were generally consistent across subgroups identified in the clinical trials.

Another limitation to this model was a lack of data on discontinuation of TD medication due to adverse events beyond the first year. We acknowledge that this input influences model results and hence had to make assumptions on post-year one discontinuation rates. Finally, due to a paucity of information available in the literature, an important limitation was that expert opinion was used for estimating the annual non-drug medical costs of treating TD. However, the model was insensitive

to this input, requiring an input of over 250 times the base case value (of ~\$262) to achieve commonly-cited cost-effectiveness thresholds.

Finally, our budget impact analyses for the use of VMAT2 inhibitors at net prices in place of no TD-focused treatment indicated that only 21% and 20% of the entire eligible TD cohort could be treated with valbenazine and deutetrabenazine, respectively, before crossing the budget threshold of \$915 million per year.

In summary, our analyses suggest that the clinical benefits associated with valbenazine and deutetrabenazine will lead to increased quality-adjusted life expectancy over no specific treatment for TD symptoms (i.e., placebo). At current pricing levels, however, the estimate lifetime cost-effectiveness of these agents far exceeds commonly-cited cost-effectiveness thresholds.

6. Additional Considerations

Our reviews seek to provide information on other benefits offered by VMAT2 inhibitors to the individual patient, caregivers, the delivery system, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below.

Table 6.1. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Additional Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to “usual care,” there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to “usual care,” there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

The review of available comparative clinical evidence on the use of VMAT2 inhibitors for TD due to DRBAs highlights key gaps in knowledge that may limit the ability to assess the potential benefit of these drugs. For example, because of the challenges of capturing the social impact of TD on individual patients, patients and patient groups expressed concern that the outcome measures reported in clinical literature may underestimate the magnitude of the impact of these drugs. We heard from several patients about the significant impact TD can have on ability to work. Although

data are lacking on the effectiveness of VMAT2 inhibitors on work-related outcomes, there is reason to believe that for some patients with TD, VMAT2 inhibitors may make it easier to find a job and/or maintain a job. The ongoing prospective RE-Kinect study (designed to quantify the prevalence of TD in the outpatient psychiatry practices in the US, as well as to describe the associated disease burden in a cohort of patients) when completed, may be able to provide more data on the social impact of TD on patients.

Furthermore, some stakeholders highlighted that VMAT2 inhibitors may have a positive impact on adherence to treatment of the underlying psychiatric and other medical conditions, especially if DRBAs are needed. Although there are no data available on these potential benefits, it was noted that for patients with serious psychiatric conditions in whom DRBAs are the most effective treatments available, patient concerns about side effects, including TD, may influence their decision to take DRBAs or comply with therapy if prescribed. More effective treatment for individuals with TD in whom DRBAs are the therapy of choice may improve compliance with DRBA therapy and the control of the underlying psychiatric condition.

Among the VMAT2 inhibitors, tetrabenazine requires three times per day dosing, deutetrabenazine requires twice a day dosing, and valbenazine requires once daily dosing. Adherence with treatment may be somewhat improved by using medications that require less frequent dosing, although the degree of potential improvement is unclear. However, potential differences in side effects with long-term use are more likely to be important for adherence than dosing frequency.

For many patients, TD is a chronic condition. Since data suggests stopping VMAT2 inhibitors leads to a recurrence of TD symptoms, treatment will require long-term use. As newly approved drugs, the long-term risks of valbenazine and deutetrabenazine will only become apparent with ongoing use in a large number of treated individuals. Currently, the only comparative data for VMAT2 inhibitors is to placebo, and the duration of the randomized portion of clinical trials was only 6-12 weeks. Thus, it is unclear how valbenazine and deutetrabenazine may compare to each other and to other therapies that have been used off-label for TD in terms of effectiveness and safety with longer-term use. In addition, the magnitude and durability of ongoing use of VMAT2 inhibitors is uncertain and will require prospective study.

Although many questions remain about the benefits and harms of VMAT2 inhibitors for TD, there is considerable interest among patients and their healthcare professionals in having an FDA approved treatment for this condition. Approval of these drugs for TD represents a potentially important advancement for individuals with this frequently irreversible condition. In particular, for individuals with severe disabling TD, the use of VMAT2 inhibitors may decrease caregiver/family burden.

Potential Cost-Saving Measures in Tardive Dyskinesia

We sought to identify areas of waste and low-value care in psychiatry that could be reduced to make way in health care budgets for new innovations. We reached out to clinicians, patients and patient groups, manufacturers, and other payers for input on potential targets for waste reduction. The following areas were highlighted by stakeholders:

- *Stakeholders from Mental Health America (MHA)* suggested that early intervention programs can be cost-saving over the long term for standard mental health services by delivering better initial intervention for patients with first-time psychosis. The suggestion is strengthened by a small study conducted in Australia which found cost savings in a small group of patients who were treated for up to two years with an early psychosis intervention, and yielded better health outcomes and lower health care costs eight years later.³²
- *Stakeholders from the Depression and Bipolar Support Alliance (DBSA)* highlighted the results from a 2015 DBSA survey on agitation and emergency care, which showed that about 60% of patients presenting with agitation in the ED returned within a year (34% within 60 days). They suggested that patients should be routinely provided with information about mental health services in the community or be referred to psychiatrists upon discharge from the ED to decrease return visits and their associated costs to the health care system.

Additionally, we reviewed the American Board of Internal Medicine's Choosing Wisely® campaign, which encourages specialty societies to identify areas of low-value care that could be reduced or eliminated. Below are recommendations we identified that could potentially be cost-saving.

- *Choosing Wisely* suggests ensuring an appropriate initial evaluation and ongoing monitoring for patients before prescribing antipsychotic medications for any indication due to metabolic, neuromuscular, and cardiovascular side effects.³³ These side effects may potentially result in additional costs.
- *Choosing Wisely* also recommends against prescribing antipsychotics as first choice to treat behavioral and psychological symptoms of dementia, and as a first-line intervention for insomnia in adults, because the evidence demonstrates that the risks (e.g. cerebrovascular effects, parkinsonism, extrapyramidal signs, TD, confusion, increased body weight) outweigh the potential benefits in these populations.^{33,34}

7. Summary of the Votes and Considerations for Policy

7.1 About the New England CEPAC Process

During New England CEPAC public meetings, the New England CEPAC Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Panel members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to New England CEPAC Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the CEPAC Panel during their deliberation, and help to shape recommendations on ways the evidence can apply to policy and practice.

After the CEPAC Panel votes, a policy roundtable discussion is held with the CEPAC Panel, clinical experts, patient advocates, payers, and when feasible, manufacturers. The goal of this discussion is to bring stakeholders together to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the December 5 meeting, the New England CEPAC Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of VMAT2 Inhibitors for treating symptoms of Tardive Dyskinesia. Following the evidence presentation and public comments (public comments from the meeting can be accessed [here](#), starting at minute 1:42:23), the CEPAC Panel voted on key questions concerning the comparative clinical effectiveness, and other benefits and contextual considerations related to VMAT2 inhibitors. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making.

Given the high incremental cost effectiveness ratios – that far exceeded commonly agreed upon thresholds for cost effectiveness—the panel did not vote on any questions related to the long-term

value for money. The voting results are presented below, along with specific considerations mentioned by CEPAC Panel members during the voting process.

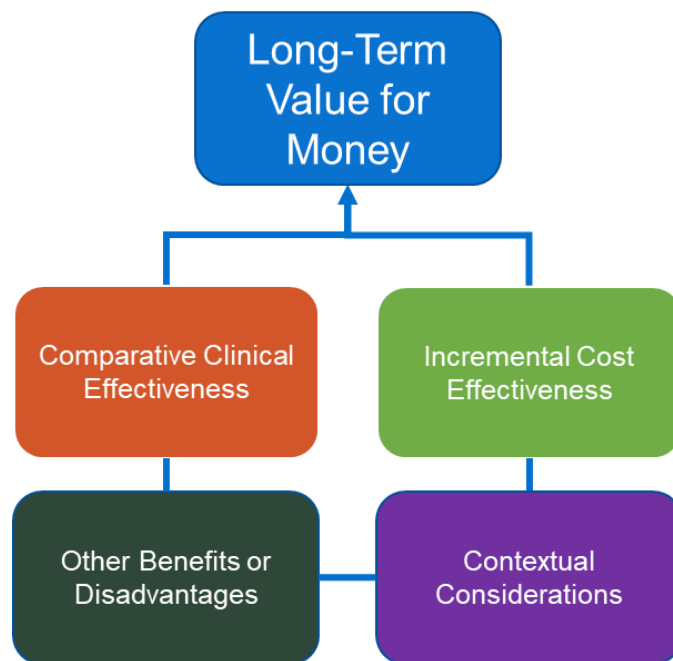
In its deliberations and votes related to value, the New England CEPAC Panel considered the individual patient benefits, and incremental costs to achieve such benefits, from a given intervention over the long term.

There are four elements to consider when deliberating on long-term value for money (see Figure X below):

1. Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. The New England CEPAC Panel uses the [ICER Evidence Rating Matrix](#) as its conceptual framework for considering comparative clinical effectiveness.
2. Estimated incremental cost-effectiveness is the average incremental cost per patient of one intervention compared to another to achieve a desired “health gain,” such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost-effectiveness, the New England CEPAC voting panel follows common academic and health technology assessment standards by using cost per quality-adjusted life year (QALY), with formal voting on “long-term value for money” when the base case incremental cost-effectiveness ratio is between \$50,000 per QALY and \$175,000 per QALY.
3. Other benefits refer to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of other benefits include better access to treatment centers, mechanisms of treatment delivery that require fewer visits to the clinician’s office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether other benefits or disadvantages such as these are important enough to factor into the overall judgment of long-term value for money. There is no quantitative measure for other benefits or disadvantages.

- Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the condition severely affects quality of life or not, and whether there is significant uncertainty about the magnitude of benefit or risk of an intervention over the long term. There is no quantitative measure for contextual considerations.

Figure 7.1. Conceptual Structure of Long-term Value for Money



7.2 Voting Results

Patient Population for all questions: Adults ages 18 and older with symptoms of tardive dyskinesia for at least three months and history of use of dopamine receptor blocking agents (DRBAs).

- Is the evidence adequate to demonstrate a positive net health benefit from treating patients with TD with valbenazine?

Yes: 11 votes	No: 4 votes
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Comments: The majority of the panel voted that valbenazine offered a net health benefit for patients being treated for TD. The conversation largely focused around the primary trial

outcome, the change in AIMS score, and whether the magnitude of the benefit in the trials demonstrated a clinically important difference for patient health and functionality. One panel member impressed on his colleagues that the percentage of patients who saw a 50% improvement on the AIMS was convincing enough for him to vote yes on the question. Other panelists were also satisfied with the directional improvement on the AIMS; however, even those who voted yes expressed concern about the short duration of the trials, and the lack of long term safety data. Those who voted no did not believe the data was sufficient and questioned the validity of the AIMS as a sensitive measure of patient benefit.

2. Is the evidence adequate to demonstrate a positive net health benefit from treating patients with TD with deutetrabenazine?

Yes: 10 votes	No: 5 votes
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Comment: The majority of the panel also voted that deutetrabenazine offered a net health benefit for treating patients with TD. Many of the panelists used a similar rationale to that for their earlier vote on valbenazine. Panelists referenced the positive direction of the AIMS. One panelist switched his vote from a yes vote for valbenazine to a no vote for deutetrabenazine because the secondary clinician- and patient-reported outcomes did not achieve statistically significant benefits. Like their rationale for valbenazine, those who voted no did not believe there was sufficient data and questioned the validity of the AIMS for measuring patient benefit.

3. Is the evidence adequate to demonstrate a positive net health benefit from treating patients with TD with tetrabenazine?

Yes: 2 votes	No: 13 votes
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Comment: The majority of the panel voted that there was not adequate evidence to demonstrate that tetrabenazine offered a positive net health benefit. Those who voted no argued primarily that there was a lack of randomized data and pointed out that the variable outcomes used were outdated and inconsistent. One panelist also had concerns about safety, pointing to the label for Huntington's disease with a warning for increased rates of suicidality, particularly with a patient population that is already susceptible to depression. Many recognized the expert testimony at the meeting that tetrabenazine was an effective agent. However, this only convinced a minority of panelists that the evidence was adequate to demonstrate the clinical effectiveness of tetrabenazine.

4. Is the evidence adequate to distinguish between the net health benefit of valbenazine and deutetrabenazine in the treatment of TD?

Yes: 1 vote	No: 14 votes
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Comment: Only one panelist voted that the evidence was adequate to distinguish the net health benefit between valbenazine and deutetrabenazine, arguing that the relative improvement for valbenazine relative to placebo was greater than that for deutetrabenazine. All other panelists voted that the evidence was not sufficient to distinguish the health benefit between valbenazine and deutetrabenazine. Given the comparable trial results and similar mechanisms of action, panelists suggested that they needed to see head-to-head comparisons of the two therapies in order to demonstrate superiority of either one.

5. Does treating patients with one of the new FDA approved drugs offer one or more of the following “other benefits”? (select all that apply)

# of Votes	Other Benefits
8	This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.
3	This intervention offers reduced complexity that will significantly improve patient outcomes.
2	This intervention will reduce important health disparities across racial, ethnic, gender, socioeconomic, or regional categories.
3	This intervention will significantly reduce caregiver or broader family burden.
12	This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.
5	This intervention will have a significant impact on improving return to work and/or overall productivity.

Comment: A majority of voting members of the CEPAC panel voted that these new therapies provided significant patient health benefits that are not adequately captured by the QALY; they also voted that these therapies offer a novel approach to treat patients with TD.

Panelists suggested that the QALY is unable to capture social isolation and stigmatization of patients with severe TD who are already vulnerable to marginalization based on their mental health condition. Panelists generally recognized the lack of data on any of these ‘other benefits;’ however, they cautiously relied on their personal judgments in evaluating the patient presentations, oral remarks, and survey presentation to make their determinations.

Regarding caregiver burden, CEPAC panelists pointed to the lack of good data, and also to the patient survey that demonstrated that caregiver burden was not a significant concern among those who were surveyed. However, experts recognized that, while there is no strong data on caregiver burden, there is an anecdotal effect for caregivers when patients

who can treat their TD are able to better adhere to their treatment for managing their underlying mental health condition.

Most panelists allowed that that these new therapies provided an important and novel approach to treating patients with TD in comparison with no treatment. In particular, expert clinicians acknowledged the discomfort that practicing psychiatrists have in treating patients with tetrabenazine, since was developed to treat a movement disorder managed by neurologists, as well as the potential for psychiatrists to build expertise in prescribing these new therapies approved for TD, instead of referring to a neurologist.

Finally, some patients discussed the potential impact that these therapies had on helping patients return to or be more productive in the workplace.

6. Are any of the following contextual considerations important in assessing the new FDA approved drugs' long-term value for money in patients with tardive dyskinesia? (select all that apply)

# of Votes	Contextual Considerations
9	This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
8	This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
3	This intervention is the first to offer any improvement for patients with this condition.
14	Compared to usual care, there is significant uncertainty about the long-term risk of serious side effects of this intervention.
12	Compared to usual care, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.

Comment: A majority of panelists voted affirmatively that these new therapies are intended for patients with a particularly high severity in terms of impact on quality of life, are intended for the care of individuals with a particularly high lifetime burden of illness, and are subject to significant uncertainty about the magnitude and/or durability of benefit as well as long-term risks and side effects.

Panelists discussed that for these patients, even a modest improvement on the AIMS can significantly improve quality of life. One panelist noted that the range in severity for TD is subjective depending on the patient: some patients with clinically 'severe' TD may not recognize that their TD is a problem; while others with a clinically 'low' severity of TD may find it substantially impacts their ability to function in the workplace or in social situations.

Panelists generally disagreed that these interventions were the first to offer improvement for patients with TD and referenced tetrabenazine as an option for some patients based on clinical expertise, as well as switching the offending agent if appropriate to minimize the risk of unremitting TD.

Almost all panelists were concerned about the uncertainty about the long-term risks and side effects of these new therapies, as well as the durability of long term benefits for these interventions, given the short duration of available trials.

7.3 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the New England CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on VMAT2 inhibitors in treating patients with tardive dyskinesia to policy and practice. The policy roundtable members included two patient representatives; two clinical experts, representing the fields of neurology and psychiatry; two payers, both public and private; and a representative from each of the drug manufacturers with the newly approved therapies of focus in this review. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below, and conflict of interest disclosures for all meeting participants can be found in (Appendix J).

Table 7.1. Policy Roundtable Members

Name	Title and Affiliation
Victor Abler, DO	Senior Global Medical Director for Neurodegenerative Diseases, Teva Pharmaceuticals
Teri Brister, PhD	Director Knowledge Integration Information, National Alliance on Mental Illness
Oliver Freudenreich, MD.	Co-Director, Mass General Hospital Schizophrenia Clinical Research Program
Patrick Hendry	Vice President of Peer Advocacy Support and Services, Mental Health America
Barbara Henry, RPh	Lead Clinical Pharmacy Specialist, Harvard Pilgrim
Paul Jeffrey, PharmD	Director of Pharmacy, MassHealth
Daniel Tarsy, MD	Professor of Neurology; Parkinson's Disease and Movement Disorders Center, Beth Israel, Harvard Medical School
Chuck Yonan, PharmD	Senior Director HEOR, Medical Affairs, Neurocrine Bioscience

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Manufacturers

- 1. In order to provide reasonable value and thereby facilitate improved access and affordability for patients, prices for the VMAT2 inhibitors should be reduced to better align with their demonstrated short-term clinical benefits.***

The history of VMAT2 inhibitor use and how this may have led to pricing decisions for the new VMAT2 inhibitors was highlighted during the round table discussion. The initial drug in this class, tetrabenazine, was initially approved for a rare condition, Huntington's disease, in 2008. Pricing for this drug was quite high, but given the small number of patients affected, the overall cost to payers was limited. With the approval of the new VMAT2 inhibitors for

patients with TD due to use of a dopamine receptor blocking agent (DRBA), the number of potential patients who may benefit from these drugs is much larger. However, the list prices for these agents are more similar to tetrabenazine than to other medications for more common symptomatic chronic conditions.

This apparent pricing approach stands in stark contrast to the value-based benchmark prices generated by the cost-effectiveness analysis performed as part of this review. Findings from ICER's modeling of benefits and costs indicated that the incremental cost effectiveness ratio (the ratio of incremental costs to that of clinical benefits as compared to no active TD treatment) far exceed common value thresholds (\$100,000-\$150,000 per QALY gained). In addition, multiple sensitivity analyses featuring changes in model parameters, structure, and assumptions regarding better control of underlying psychiatric conditions did not materially change the primary analysis' conclusions. Only significant decreases in the price of these drugs (85-90%) would result in achieving these common cost-effectiveness thresholds. Without these reductions, patient access to these potentially beneficial drugs will likely be restricted by payers as a way to manage overall drug costs. In such a context, the importance of substantial price reductions far outweighs that of any recommendation that follows in this document.

2. Manufacturers should support studies of patients with TD to generate evidence on the relative long-term benefits and harms of individual VMAT2 inhibitors and other treatment options.

Though the CEPAC panel felt that there was adequate evidence to demonstrate a positive net health benefit from treating TD patients with valbenazine and deutetrabenazine, they did not find that there was evidence to adequately distinguish between the benefits of these two drugs and how they may compare with other treatment options (e.g., off-label medications, switching of DRBA therapy). Given that TD symptoms have been shown to recur after stopping VMAT2 inhibitors, long-term treatment is expected for those patients whose symptoms improve and do not have intolerable side effects. Without long-term studies comparing valbenazine, deutetrabenazine, and other treatment strategies, it will remain unclear whether these new therapies represent a safe and effective long-term option for patients with TD.

3. Manufacturers and researchers should support studies to directly compare VMAT2 inhibitors by standardizing research protocols and outcome assessments to permit real-world, long-term outcome assessment.

The CEPAC panel voted that there was inadequate evidence to distinguish between the two VMAT2 inhibitors in part because the design of the key trials, patient entry criteria, timing of outcome evaluation, and other differences precluded any formal indirect comparisons of the benefits and potential harms of valbenazine and deutetrabenazine. This is a common challenge with new agents but one that is completely avoidable. Manufacturers and the research community should collaboratively develop standard approaches for trial recruitment, entry criteria, study duration, and measurement of key outcomes to better facilitate such comparisons.

Payers

- 4. *Given that the new VMAT2 inhibitors are priced far beyond their relative benefits for patients, payers should use available evidence, along with patient and clinical expert input, to develop prior authorization criteria, periods of authorized treatment, and methods for feedback to clinicians regarding the potential for alternative management of TD (e.g., switching from an offending DRBA to another agent).***

Patient eligibility

The FDA labels for the VMAT2 inhibitors include all adult patients with tardive dyskinesia. Potential specific eligibility criteria that may be considered based on the patient populations involved in the pivotal trials for both drugs include:

- a. Prior use of a DRBA for at least three months.**

- b. Diagnosis of TD by a neurologist or psychiatrist.**

Discussion during the policy roundtable highlighted that rural populations may have poor access to neurologists or psychiatrists with expertise in managing TD, but clinical experts are aware of many cases in which TD has been misdiagnosed and therefore consideration of specialty diagnosis is not unreasonable.

- c. Presence of an underlying condition requiring treatment with a DRBA.**

For patients using DRBAs for indications with a broad array of treatment options (e.g., affective disorders), payers may consider ascertaining whether stopping the offending DRBA and switching to another class of drugs or a different DRBA has been tried or considered. For patients using antipsychotic drugs for an indication where they are first line therapy without good alternatives, consideration could be given for use of other antipsychotic drugs less likely to cause TD, such as clozapine.

- d. Moderate-severe symptoms.**

Although the AIMS score was used to assess whether patients had moderate-to-severe TD in some of the trials, clinical experts at the policy roundtable did not

believe that the AIMS could serve as a useful tool in routine clinical settings, given that for many patients the severity of TD is more closely related to the location of the symptoms (e.g. face) than whether their presence is widespread. Clinician attestation of “moderate to severe” symptoms appears to be the most reasonable potential patient eligibility criterion.

e. Trial of reduction or switching of the causative DRBA

Clinical experts did not believe that this would be a reasonable prior authorization criterion given that many patients struggle to achieve mental health symptom management with various medications and dose reduction can actually increase TD symptoms in some cases. Nevertheless, experts did believe that payers could consider some kind of peer-to-peer discussion or communication encouraging some consideration of discontinuation or switching to a different antipsychotic drug, including clozapine, which, despite its own downsides, does not pose a risk of TD.

Provider criteria

a. Specialist training in neurology and/or psychiatry.

Although clinical experts currently believe that the drug treatment of TD has been managed primarily by neurologists, the availability of on-label VMAT2 inhibitors is likely to expand clinical demand. More psychiatrists are likely to gain experience in managing TD, and, especially in some rural areas, primary care clinicians may request permission to prescribe these agents. The goal of achieving expert use of these drugs in the management of TD (along with patient comorbidities) must therefore be balanced with realistic efforts to assure adequate access to treatment to patients in various locales. One option that may strike this balance is to require some form of consultation/discussion with a specialist if the prescriber is a primary care clinician.

Step therapy

AAN specialty guidelines consider multiple off-label treatments for TD to be clinically reasonable, offering payers the option of considering step therapy with one or more less expensive options before approving coverage for the new VMAT2 inhibitors. Payers on the policy roundtable who had evaluated payer policies around the country suggested that perhaps 50% of payers may require step therapy for VMAT2 inhibitors. The evidence base for these off-label options is not strong, however, as shown by the NE CEPAC vote that the evidence is insufficient to demonstrate the clinical effectiveness of tetrabenazine, which also has a black box warning, the need for titration, and

multiple daily dosing. Requiring off-label treatment when on-label options are available is not generally viewed as clinically appropriate by clinical experts and patients.

Time of authorization

Given that not all patients will benefit from treatment with the VMAT2 inhibitors and that side effects may emerge, payers may consider a time-limited authorization for coverage (e.g. 6-12 months), with some form of reassessment of symptom management prior to continued coverage. Study data suggests that many patients stop taking the medication in the first months or year due to lack of effectiveness and/or side effects.

Stopping rules

Time-limited trials of therapy as described above may be challenged, as no current tangible method of assessing clinical success/failure was mentioned by clinical experts, who reaffirmed that the AIMS measure would not prove useful in clinical practice as an element in a formal stopping rule.

- 5. Payers can leverage competitive market forces by negotiating for the best possible price in exchange for exclusive formulary placement of only one VMAT2 inhibitor. Other drugs in the class should remain available through an individual appeal process.***

The CEPAC panel did not find evidence to adequately distinguish the net health benefit of valbenazine and deutetrabenazine in the treatment of patients with TD. Until comparative data becomes available, it would be reasonable for payers to aggressively negotiate with manufacturers based upon price for exclusive formulary placement of a single VMAT2 inhibitor. A lower price will permit payers to treat more of their eligible patients with less restrictive access criteria.

However, price alone should not be the only determinant. There may be reasons beyond efficacy and side effects to favor one drug over another, including the complexity of dose titration, drug-drug interactions, or frequency of dosing. For those individuals who do not tolerate the preferred VMAT2 inhibitor or demonstrate a benefit from a different VMAT inhibitor, the non-preferred drug should be able to be accessed on an appeals basis.

Patient Advocacy Organizations and Researchers

6. Patients and their representatives should work with researchers to develop outcome measures that better document the impact of TD on functional domains related to work, family, and social interactions.

Patients and patient advocates have highlighted that the primary outcomes used to assess the impact of VMAT2 inhibitors are performed by clinicians, not patients, and that they do not adequately capture the impact of TD on social stigmatization, work, and family life, and caregiver burden.

The primary outcome used in all trials submitted for FDA approval of VMAT2 inhibitors for patients with TD was the Abnormal Involuntary Movement Scale (AIMS). A higher AIMS score is meant to reflect increased severity of TD symptoms. However, the AIMS has not been well validated and is based upon physician assessment, and not what is most important to patients. Higher scores are meant to reflect increased severity. However, they do not capture the difference between focused symptoms, which may have more of an impact on patient quality of life, and more diffuse symptoms, which may make less of an impact. For example, severe facial symptoms alone could lead to the same AIMS as very mild symptoms in four different body regions.

Patients and advocacy groups need to work closely with researchers who are expert in outcome measure development to lead efforts to modify the AIMS so that it includes the impact on patient quality of life, social function and work productivity in order to improve its usefulness as an outcome measure in clinical trials; and perhaps even more importantly, as a clinical tool to measure severity for patients. Only by putting pressure on regulators to require manufacturers to develop, validate and include such outcomes, will there be concerted effort to improve the assessment of potentially important new therapies.

Specialty Societies

7. Professional societies should accept the responsibility to update their clinical practice guidelines rapidly following the advent of paradigm-changing treatment options like the VMAT2 inhibitors.

The two VMAT2 inhibitors of focus in our review are the first FDA-approved medications for the treatment of TD, signaling a potentially major change in clinical practice. Though psychiatrists are primarily responsible for prescribing antipsychotic drugs, the most frequent class of DRBAs, few may feel well-prepared to assess and treat movement disorders such as TD, and to manage the new treatment options. Similarly, many neurologists and movement

disorder specialists may have seen few patients with TD, since historical treatment alternatives have been lacking. For these reasons, it is incumbent on professional societies to develop and update clinical practice guidelines, especially when potentially paradigm changing therapies are made available. Placing these new agents into practice and helping clinicians identify their role in a rapidly changing landscape is critical to ensuring clinicians have the knowledge to wisely use these new therapies. A key aspect of these efforts is to ensure that guidelines are developed using rigorous methods that include input from a range of experts, including patients with the condition, as well as explicit disclosure and monitoring of potential conflicts of interest. Psychiatric and neurologic professional societies should work together in such efforts, and include recommendations on interdisciplinary management.

- 8. Given that VMAT2 inhibitors may be prescribed by a larger group of specialist and primary care clinicians, professional societies should develop educational materials to educate clinicians about TD management and to encourage close coordination among all clinicians caring for these patients.***

Though TD has been known since the introduction of antipsychotic drugs in the 1950s, few proven treatment options have been available to clinicians and patients. Even psychiatrists and neurologists familiar with TD note that familiarity with the management of TD is limited, and considerable effort will be needed to educate clinicians who are likely to prescribe DRBAs for long-term use and evaluate patients with suspected TD symptoms. With the approval of valbenazine and deutetrabenazine, there is renewed interest in the identification, evaluation and treatment of TD. Professional societies should seek to develop coordinated efforts as part of ongoing continuing medical education and maintenance of certification activities. Ensuring that such efforts are developed in ways to ensure avoiding conflict of interest will require societies and its members to rigorously develop, disseminate and monitor such policies.

Regulators

- 9. Regulators should require post-approval, long-term comparative outcomes studies for treatments initially evaluated and approved in very short-term randomized trials, but for which long-term therapy would be expected.***

The FDA approval of valbenazine and deutetrabenazine for use in patients with TD was based upon short-term outcomes of randomized controlled trials (6 and 12-week RCTs for valbenazine and deutetrabenazine respectively). Subsequent open-label extension studies with drug washout and follow-up at the end of treatment (after 48 and 54 weeks) showed a

return of symptoms with cessation of the VMAT2 inhibitor. Therefore, if initial benefit is found, it is expected that these drugs will require long-term use. Though manufacturers have performed and reported single-arm, long-term follow-up studies without active comparators, it is uncertain what the long-term relative benefits of these VMAT2 inhibitors will be, compared to each other or to other treatments. Therefore, regulators should require manufacturers to perform long-term comparative outcome studies within a well-defined period of time to provide patients, clinicians and payers with evidence to support ongoing use and coverage for these new drugs.

7.4 Affordability and Access Alert

ICER is issuing an *Affordability and Access Alert* as part of its final report on VMAT2 inhibitors for treating TD. During the public meeting of the New England CEPAC, we asked clinical experts and patient advocates on our policy roundtable what the appropriate target should be for the percentage of eligible patients who should receive treatment with either of the new drugs for TD. Their view was that insurance coverage should facilitate a trial of treatment with the new therapies for *all* patients with moderate-to-severe TD. We used this target for optimal clinical application of the new drugs, and assumed treatment initiation would be spread over 5 years. Our estimates of the potential net budget impact of VMAT2 inhibitors indicated that at an estimated national average discount price of 27% off the WAC price for each drug, only 21% and 20% of all eligible patients could be treated with valbenazine and deutetrabenazine, respectively, before costs would exceed ICER's potential budget impact threshold of \$915 million per year. At the prices that would meet ICER's value-based price benchmark, all eligible patients could be treated without exceeding the potential budget impact threshold.

Given that optimal clinical uptake at current estimated discount prices would lead to 5-year costs far in excess of this threshold, ICER's *Affordability and Access Alert* is intended to provide a signal to manufacturers, insurers, patient groups, and other stakeholders when the amount of added health care costs associated with these new treatments may be difficult for the health care system to absorb over the short term without displacing other needed services or contributing to rapid growth in health care insurance costs that threaten sustainable access to high-value care for all patients. ICER encourages all stakeholders to consider whether action should be taken to achieve additional price discounts, prioritize treatment access, find ways to reduce waste to provide additional resources, or take other policy steps to manage these budget implications.

This is ICER's first review of VMAT2 inhibitors for treating patients with Tardive Dyskinesia.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
Abstract		
Structured Summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
Introduction		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
Methods		
Protocol and Registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility Criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information Sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study Selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data Collection Process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data Items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of Bias in Individual Studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary Measures	13	State the principal summary measures (e.g., risk ratio, difference in means).

Synthesis of Results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of Bias Across Studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional Analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
Results		
Study Selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study Characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of Bias Within Studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of Individual Studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of Results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of Bias Across Studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional Analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
Discussion		
Summary of Evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
Funding		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

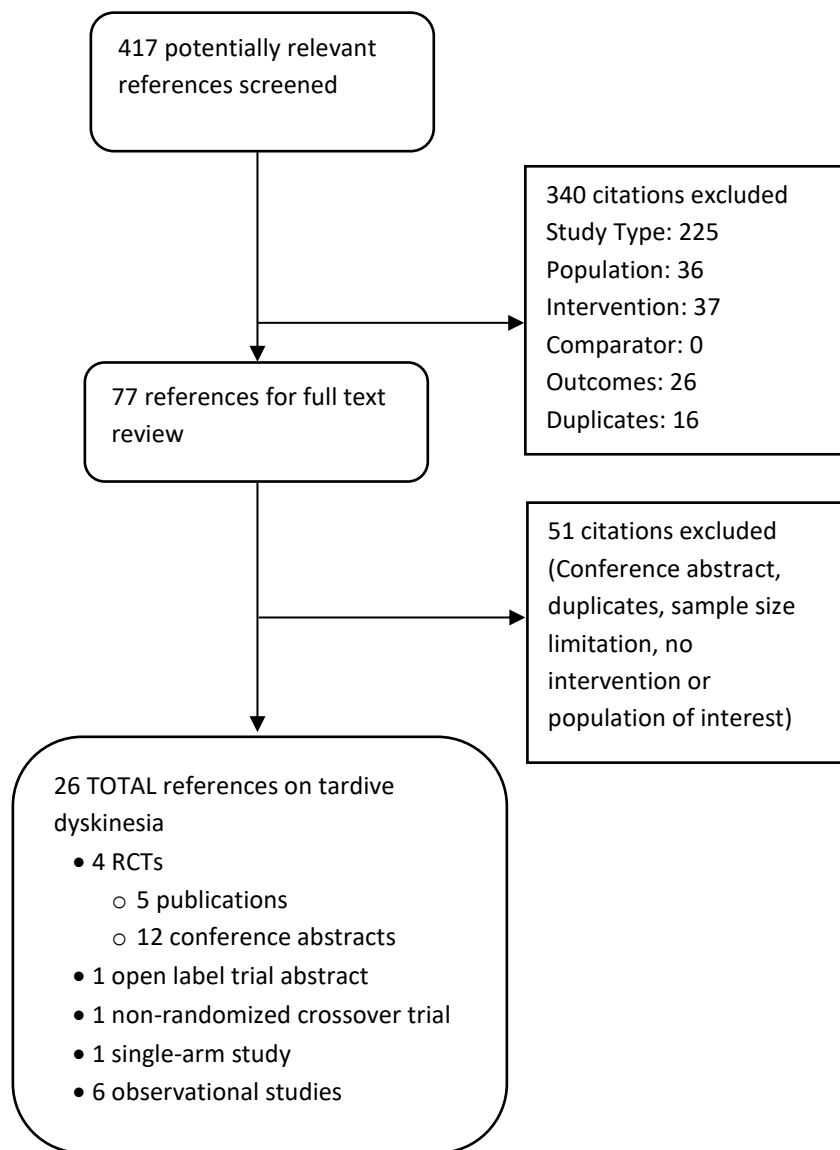
Table A2. Search Strategies of Medline 1996 to Present with Daily Update, Psych INFO and Cochrane Central Register of Controlled Trials, May 26, 2017

1	exp tardive dyskinesia/
2	(tardive adj3 (dyskine\$ or diskine\$ or syndrome\$ or dystonia\$)).ti,ab.
3	1 or 2
4	(movement* adj disorder*).mp.
5	((involuntary* or abnormal* or hyperkinetic) adj3 movement*).mp.
6	3 or 4 or 5
7	exp tetrabenazine/
8	(Tetrabenazine or Xenazine).mp.
9	(Deutetrabenazine or Austedo).mp.
10	(Valbenazine or ingrezza).mp.
11	7 or 8 or 9 or 10
12	vesicular monoamine transporter adj3 inhibitor.mp
13	11 or 12
14	6 and 13
15	(animals not (humans and animals)).sh.
16	14 not 15
17	limit 16 to english language
18	(abstract or addresses or autobiography or bibliography or biography or clinical trial, phase I or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or videoaudio media).pt.
19	17 not 18
20	remove duplicates from 19

Table A3. Embase Search Strategy, May 26, 2017

#1	'tardive dyskinesia'/exp
#2	(tardive NEAR/3 (dyskine* OR diskine* OR dystonia* OR syndrome*)):ab,ti
#3	#1 OR #2
#4	'movement disorder':ab,ti
#5	((involuntary* OR abnormal*) NEAR/3 movement*):ab,ti
#6	#3 OR #4 OR #5
#7	'tetrabenazine'/exp OR tetrabenazine:ab,ti OR xenazine:ab,ti
#8	'deutetrabenazine'/exp OR deutetrabenazine:ab,ti OR austedo:ab,ti
#9	'valbenazine'/exp OR valbenazine:ab,ti OR ingrezza:ab,ti
#10	#7 OR #8 OR #9
#11	'vesicular monoamine transporter' NEAR/3 inhibitor*
#12	#10 OR #11
#13	#6 AND #12
#14	'animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp
#15	'human'/exp
#16	#14 AND #15
#17	#14 NOT #16
#18	#13 NOT #17
#19	#18 AND ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#20	#18 NOT #19
#21	#20 AND [english]/lim
#22	#21 AND [medline]/lim
#23	#21 NOT #22

Figure A1. PRISMA Flow Chart Showing Results of Literature Search for Tardive Dyskinesia



Appendix B. Clinical Guidelines

Table B1. American Academy of Neurology Guidelines: Level of Evidence for TD Interventions¹

Insufficient	Weak	Moderate
Altering DRBA Therapy		
Withdrawing DRBA		
Switching from older (first-generation) to newer (second-generation or atypical) anti-psychotic DRBA		
Pharmacologic Therapies		
First-generation anti-psychotics Although haloperidol and thioropazate possibly reduce TDS, they are not recommended because of the competing risk of akinetic-rigid syndrome.		
Second-generation anti-psychotics Because neuroleptic agents may themselves cause TDS and may mask its symptoms rather than treat it, these drugs cannot be recommended for TDS treatment		
Dopamine Depleting Agents		
Reserpine or α -methyldopa	Tetrabenazine Possibly reduces symptoms and may be considered. No evidence that long-term TBZ administration induces TDS, but it can cause parkinsonism	
Cholinergic and Anticholinergic Drugs		
All other cholinergic and anticholinergic drugs	Galantamine is possibly ineffective and should not be considered	
Antioxidants		
Vitamin E, melatonin, vitamin B6, selegiline, and yi-gan san	Eicosapentaenoic acid possibly ineffective and should not be considered	Ginkgo biloba is likely helpful for patients, but data is limited to those with schizophrenia
Gaba Agents		
Baclofen		Clonazepam should be considered for short term treatment
Calcium Channel Blockers		

Nifedipine		Diltiazem should not be considered a treatment
Other Pharmacologic Agents or Health System Interventions		
Acetazolamide	Amantadine may be used with neuroleptics for short term use	
Buspirone		
Biperiden (Akineton) Discontinuation		
Chemodenervation with botulinum toxin		
Dopamine agonists: bromocriptine		
Electroconvulsive therapy		
Levetiracetam		
Pallidal deep brain stimulation		

Appendix C. Public and Representative Private Insurer Coverage Policies

Table C1. Coverage Policies for New England Commercial Payers

	Connecticut		Maine		Massachusetts			New Hampshire		Rhode Island		Vermont	
	Anthem (Wellpoint Inc Group) ¹⁰³	Connectica re ¹⁰⁴	Anthem (Wellpoint Inc Group) ¹⁰⁵	HPHC Maine ¹⁰⁶	BCBS of MA ¹⁰⁷	Neighbor- hood Health Plan ¹⁰⁸	Tufts Health Plan ¹⁰⁹	Anthem (Wellpoint Inc Group) ¹¹⁰	HPHC New Hampshi re ¹⁰⁶	BCBS of RI ¹¹¹	Neighbor- hood Health Plan of RI ¹¹²	BCBS of VT ¹¹³	MVP Grp ¹¹⁴
Tetrabenazine													
Covered	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tier	No	4	2	2	1	No	1	2	1	5	4	1	2
PA	No	Yes	Yes	No	No	No	Yes	Yes	No	Yes	No	No	No
Notes:		SP*		SP	SP		SP		SP		Branded preferred		SP
Valbenazine													
Covered	No	Yes	No	Yes	Yes	No	No	No	No	No	No	No	No
Tier	No	4	No	4	3	No	No	No	No	No	No	No	No
PA	No	Yes	No	Yes	Yes	No	No	No	No	No	No	No	No
Deutetrabenazine													
Covered	No	Yes	No	Yes	Yes	No	No	No	No	No	No	No	No
Tier	No	4	No	4	3	No	No	No	No	No	No	No	No
PA	No	Yes	No	Yes	Yes	No	No	No	No	No	No	No	No
Other Tardive Dyskinesia Off-Indication Coverage													
Amantadine	Tier 1		Tier 2	Tier 2	Tier 1			Tier 2	Tier 1				
Clonazepam	Tier 1		Tier 1	Tier 2	Tier 1			Tier 1	Tier 1				
*SP=Specialty pharmacy													

Appendix D. Previous Systematic Reviews and Technology Assessments

Previous Systematic Reviews

We reviewed five systematic reviews of TD: 1) tetrabenazine for use in a variety of hyperkinetic movement disorders including tardive dyskinesia; 2) valbenazine for tardive dyskinesia; 3) deutetrabenazine for tardive dyskinesia; 4) comparing the efficacy between valbenazine and tetrabenazine in treating tardive dyskinesia; and 5) assessing the impact of neuroleptic reduction/cessation and neuroleptic medication use as specific treatments for TD was also identified. These reviews are summarized below.

Chen JJ, Ondo WG, Dashtipour K, Swope DM. Tetrabenazine for the Treatment of Hyperkinetic Movement Disorders: A Review of the Literature. *Clinical Therapeutics*. 2012; (34):1487-1504

In this review, Chen and colleagues describe the clinical efficacy and tolerability of tetrabenazine in the management of various hyperkinetic movement disorders including dystonia, Huntington's disease, tardive dyskinesia, and tic disorders. The researchers identified nine retrospective studies and two prospective studies of tetrabenazine in patients with tardive dyskinesia between 1974 and 2008. Only two studies reported statistical values, however in nine of the 11 studies, tetrabenazine demonstrated a clinical benefit for tardive dyskinesia symptoms. The researchers noted that additional randomized, placebo-controlled studies are necessary to demonstrate the efficacy of tetrabenazine for TD. Adverse events from tetrabenazine were found to be dose dependent and age related. Some common adverse events identified in the trials include somnolence, insomnia, akathisia, depression, parkinsonism, and fatigue. Tetrabenazine also includes a black box warning regarding depression and suicidality in its FDA approved indication for Huntington's disease.

Citrome L. Valbenazine for tardive dyskinesia: A systematic review of the efficacy and safety profile for this newly approved novel medication—What is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *International Journal of Clinical Practice*. 2017; 1-14

In this review, Citrome describes the efficacy, safety, and tolerability of valbenazine in the treatment of tardive dyskinesia. A total of 13 trials for valbenazine were identified, of which seven trials were conducted in patients with TD and included in this review. An in-depth review of two of the trials (KINECT 2 & 3 trials), including additional analyses of the number needed to treat (NNT) and number needed to harm (NNH) was conducted. Valbenazine was shown to result in a statistically significant greater AIMS response, as defined by $\geq 50\%$ reduction in AIMS score from baseline, compared to placebo in both trials. The resulting pooled NNT was five. Additionally, a

pooled NNT of five was estimated based on responders from the clinical global impression of change (CGIC) of tardive dyskinesia scale. Discontinuation rates because of an AE from the pooled study was 2.9% for patients treated with valbenazine versus 1.6% for placebo-treated patients, resulting in a non-significant NNH of 76. Although, the efficacy and tolerability of VBZ were established in these randomized, placebo-controlled clinical trials, the author noted that head-to-head comparisons with other VMAT2 inhibitors would be needed to fully evaluate the role of valbenazine in the treatment of TD.

Citrome L. Deutetrabenazine for tardive dyskinesia: A systematic review of the efficacy and safety profile for this newly approved novel medication—What is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *International Journal of Clinical Practice*. 2017; 1-17

Citrome reviewed the efficacy, tolerability, and safety profile of deutetrabenazine, indicated for the treatment of tardive dyskinesia. At 12 weeks, deutetrabenazine was shown to be more efficacious than placebo in the two identified trials, showing statistically significant improvements in the percentage of responders with $\geq 50\%$ reduction in AIMS score and CGIC response. The NNT of the pooled short-term data of all doses was seven. Discontinuation due to adverse events occurred in 3.6% of patients receiving deutetrabenazine as opposed to 3.1% of patients given placebo with a non-significant NNH of 189. The author noted the need for head-to-head trials to compare the effectiveness with other VMAT2 inhibitors in patients with TD.

Caroff S, Aggarwal S, Yonan C. Treatment of tardive dyskinesia with tetrabenazine or valbenazine: a systematic review. *Journal of Comparative Effectiveness Research*. 2017.

In this review, Caroff and colleagues compared tetrabenazine and valbenazine as effective treatments for TD. The researchers identified 11 studies that met their inclusion criteria for both tetrabenazine and valbenazine. The tetrabenazine studies consisted of one double-blinded, crossover trial and seven open-label studies. Tetrabenazine was generally found to be well tolerated and effective in treating TD with mostly dose related and reversible side effects, such as parkinsonism, drowsiness/fatigue and depression. Three studies (two 6-week randomized controlled trials and one 48-week open-label, long-term extension study) were identified for valbenazine. Treatment with valbenazine was shown to be statistically significantly better than placebo alone in RCTs. A meta-analysis comparing tetrabenazine and valbenazine was not feasible due to the differences in the study design and a lack of standardization and control in the tetrabenazine trials.

Soares-Weiser K, Rathbone J. Neuroleptic reduction and/or cessation and neuroleptics as specific treatments for tardive dyskinesia (Review). *Cochrane Database of Systematic Reviews*. 2006; (1):1-39

In this review, Soares-Weiser and colleagues sought to assess the impact of neuroleptic reduction or cessation in reducing TD symptoms. Two randomized, double-blind, controlled trials comparing neuroleptic reduction to continuing neuroleptic medications were identified. Both studies found no association between neuroleptic reduction and improvement in TD symptoms. No randomized controlled trials relevant to neuroleptic cessation as a treatment for TD were identified.

Appendix E. Ongoing Studies

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Deutetrabenazine					
<p>Reducing Involuntary Movements in Tardive Dyskinesia (RIM-TD)</p> <p>Auspex Pharmaceuticals, Inc.</p> <p>NCT02198794</p>	<p>Phase III</p> <p>Long-Term Safety Study</p> <p>Open-Label</p> <p>Estimated Enrollment: 343</p>	<p>1. Deutetrabenazine tablets dose titrated for 6 weeks until optimal dose is reached</p>	<p><u>Inclusion Criteria</u></p> <ul style="list-style-type: none"> • History of using a dopamine receptor blocking agent for at least 3 months. • History of being compliant with prescribed medications. • Subjects with underlying psychiatric diagnosis are stable and have no change in psychoactive medications. • Be in good general health and is expected to attend all study visits and complete study assessments. <p><u>Exclusion Criteria</u></p> <ul style="list-style-type: none"> • Serious untreated or undertreated psychiatric illness. • Evidence of hepatic or renal impairment. • History of alcohol or substance abuse in the previous 12 months. • Unstable or serious medical illness. • Neurological condition other than tardive dyskinesia. 	<p><u>Primary Outcome Measures</u></p> <ul style="list-style-type: none"> • Safety [Time Frame: 159 weeks] : Incidence of AEs, serious AEs, severe AEs, drug related AEs, AEs leading to withdrawal. <p><u>Secondary Outcome Measures</u> [Time Frame: 158 weeks]</p> <ul style="list-style-type: none"> • Change in AIMS score from Baseline • Quality of Life Exploratory Efficacy Assessment • PGIC Exploratory Efficacy – treatment success based on PGIC • AIMS Exploratory Efficacy Assessment - % change in AIMS score • AIMS responders Exploratory Efficacy Assessment - Proportion of responders based on AIMS change from baseline 	<p>September 2019</p>

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Tetrabenazine					
<p>Xenazine in Late Dyskinetic Syndrome With Neuroleptics (Xeladys)</p> <p>Centre Hospitalier Universitaire, Amiens</p> <p>NCT01543321</p>	<p>Phase III</p> <p>RCT</p> <p>Parallel Group</p> <p>Double-blind</p> <p>Estimated Enrollment:54</p>	<p>1.Tetrabenazine</p> <ul style="list-style-type: none"> • 5-week titration to a maximum dose of 200 mg / day • 5 weeks at stable dose • 2 weeks in wash-out <p>2. Placebo</p> <ul style="list-style-type: none"> • 5-week titration to a maximum dose of 200 mg / day • 5 weeks at stable dose • 2 weeks in wash-out 	<p><u>Inclusion Criteria</u></p> <ul style="list-style-type: none"> • QTc < 450 ms for men and <470 for women • MADRS < 18 • Adult (age over 18) or adult under judicial protection (tutor or curator). • Patient with late dyskinetic syndrome with neuroleptics yielding functional disability and/or impact in every day life, according to the investigator, and/or the patient and/or the patient's family. <p><u>Exclusion Criteria</u></p> <ul style="list-style-type: none"> • Insanity according to the DSM IV and MMS < 24 • Predominant akathisia • Renal failure • Congenital galactosemia, glucose malabsorption or lactase deficiency • Drugs: Non-selective MAOIs, dopaminergic (or other antiparkinsonian) 	<p><u>Primary Outcome Measures</u></p> <ul style="list-style-type: none"> • Changes in Extrapyramidal Symptoms Rating Scale (ESRS) [Time Frame: 10 weeks after randomization] <p><u>Secondary Outcome Measures</u></p> <ul style="list-style-type: none"> • AIMS improvement • Changes in Quality of life • Changes in intermediate ESRS and post-treatment ESRS • Tolerance • CGI amelioration • Changes in Sub-score ESRS-II 	<p>June 2017</p>

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Valbenazine					
Rollover Study for Continuing Valbenazine (NBI-98854) Administration for the Treatment of Tardive Dyskinesia Neurocrine Biosciences NCT02736955	Phase III Interventional Open label Estimated Enrollment: 150	1. Fixed dose of valbenazine administered once daily for up to 72 weeks	<u>Inclusion Criteria</u> <ul style="list-style-type: none"> • Have participated in and completed the Kinect 3 or Kinect 4 Phase 3 study. • Have a negative urine drug screen for amphetamines, barbiturates, benzodiazepine, phencyclidine, cocaine, opiates, or cannabinoids. • If using maintenance medication(s) for schizophrenia or schizoaffective disorder, mood disorder, or other conditions, be on stable doses. <u>Exclusion Criteria</u> <ul style="list-style-type: none"> • Have a known history of long QT syndrome or cardiac arrhythmia. • Have a known history of substance dependence, substance (drug) or alcohol abuse. • Have a known history of neuroleptic malignant syndrome. • Have a blood loss ≥550 mL or donated blood within 30 days prior to Baseline. 	<u>Primary Outcome Measures</u> <ul style="list-style-type: none"> • Safety and tolerability measurements (incidence and types of adverse events, physical examination, laboratory tests) [Time Frame: Up to 72 weeks] <u>Secondary Outcome Measures</u> <ul style="list-style-type: none"> • CGI-TD-Severity • Patient Satisfaction Questionnaire • Social Functioning Scale (SFS) 	June 2017

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix F. Comparative Clinical Effectiveness

Supplemental Information

We performed screening at both the abstract and full-text level. Three investigators screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described in the published protocol (<https://osf.io/q6hxt/>). We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. Three investigators reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to the agents of interest. These included manufacturer submissions to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions. All literature that did not undergo a formal peer review process is described separately.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories “good,” “fair,” or “poor” (see Appendix Table F2)¹¹⁵ Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intent-to-treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all-important outcomes are considered; and some but not all potential confounders are addressed. Intent-to-treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intent-to-treat analysis is lacking.*

Data Extraction

Three reviewers extracted key information from the full set of accepted studies. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance. Summary tables of extracted data are available in Appendix G.

Table F1. Abnormal Involuntary Movement Scale (AIMS)

MOVEMENT RATINGS: Rate highest severity observed. Rate movements that occur upon activation one less than those observed spontaneously. Circle movement as well as code number that applies.		RATER	RATER	RATER	RATER
	Date	Date	Date	Date	
Facial and Oral Movements	1. Muscles of Facial Expression e.g. movements of forehead, eyebrows, periorbital area, cheeks, including frowning, blinking, smiling, grimacing	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	2. Lips and Perioral Area e.g., puckering, pouting, smacking	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	3. Jaw e.g. biting, clenching, chewing, mouth opening, lateral movement	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	4. Tongue Rate only increases in movement both in and out of mouth. NOT inability to sustain movement. Darting in and out of mouth.	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Extremity Movements	5. Upper (arms, wrists, hands, fingers) Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous) athetoid movements (i.e., slow, irregular, complex, serpentine). DO NOT INCLUDE TREMOR (i.e., repetitive, regular, rhythmic)	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	6. Lower (legs, knees, ankles, toes) e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot.	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Trunk Movements	7. Neck, shoulders, hips e.g., rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
0 = None, normal; 1 = Minimal, may be extreme normal; 2 = Mild; 3 = Moderate; 4 = Severe					
<i>Note: Although a typical AIMS contains up to 14 items, the valbenazine and deutetrabenazine trials only used items 1-7 to rate AIMS scores, but includes all potentially affected body parts</i>					

Table F2: Valbenazine: Subgroup Analysis of AIMS Change by Psychiatric Diagnosis

Trials	AIMS Reduction from Baseline	
	Schizophrenia/Schizoaffective Subgroup	Mood Disorder Subgroup
KINECT 3 Trial^{13,71}		
Valbenazine 80mg/D	-2.9 [†]	-3.6 [†]
Valbenazine 40mg/D	-1.6 [†]	-2.4
Placebo	+0.3	-0.7
KINECT 2 Trial⁷²		
Valbenazine (Max 75mg/D)	-3 [†]	-4.5 [†]
Placebo	-1	-1.4

Table F3. Changes in MADRS and YMRS from Baseline at Weeks Six and 48 (Mood Disorder Subgroup)

Mood Disorder			
Psychiatric Scale	80mg VBZ	40mg VBZ	PBO
6 Week Data			
MADRS, Mean change	-1.5	0.0	1.2
YMRS, Mean change	-1.4	-0.4	0.5
48 Week Data			
MADRS, Mean change (SEM)	0.6 (-0.6, 1.9)	-0.2 (-1.1, 0.7)	NA
YMRS, Mean change (SEM)	-1.4 (-1.9, -0.7)	-1.2 (-1.8, -0.6)	NA

**Table F4. Changes in PANSS and CDSS from Baseline at Weeks Six and 48
(Schizophrenia/Schizoaffective Disorder Subgroup)**

Schizophrenia/Schizoaffective Disorder			
Psychiatric Scale	80mg VBZ	40mg VBZ	PBO
6 Week Data			
PanSS Positive, Mean Change	-0.3	-0.5	-0.0
PanSS Negative, Mean Change	0.5	-0.0	-0.0
PanSS General Psychopathology, Mean Change	-0.8	-1.3	-0.2
Cdss, Mean Change	-0.4	-0.5	-0.1
48 Week Data			
PanSS Positive, Mean Change (Sem)	-1.7 (-2.2, -1.2)	-0.6 (-1.3, 0.1)	Na
PanSS Negative, Mean Change (Sem)	-1.2 (-1.7, -0.7)	0.7 (-0.1, 1.4)	Na
PanSS General Psychopathology, Mean Change (Sem)	-3.7 (-4.5, -2.9)	-0.5 (-1.7, 0.6)	Na
Cdss, Mean Change (Sem)	-0.3 (-0.9, -0.1)	-0.5 (-0.7, 0.0)	Na

Table F5: Deutetrabenazine: Subgroup Analysis of AIMS Change by Baseline DRBA Use

Trials	AIMS Reduction from Baseline	
	Not receiving DRBA	Receiving DRBA
AIM-TD ⁷		
DTBZ 12mg/day	-2.4*	-2
DTBZ 24mg/day	-3.1*	-3.2*
DTBZ 36mg/day	-3.1*	-3.4*
Placebo	0	-1.7

Table F6: Deutetrabenazine: Subgroup Analysis of CGIC Treatment Success by Baseline DRBA

Trials	CGIC Treatment Success	
	Not Receiving DRBA	Receiving DRBA
AIM-TD ⁷		
DTBZ 12mg/day	27	29
DTBZ 24mg/day	58 [†]	46
DTBZ 36mg/day	60 [†]	34
Placebo	8	31

Table F7. Deutetrabenazine: mCDQ-24 Across Trials at 12 Weeks

Trials	LS Mean Change in Mcdq-24 Score	LS Mean Difference Vs Placebo
AIM-TD⁷		
DTBZ 12mg/day	-5.9	1.2
DTBZ 24mg/day	-10.6	-3.5
DTBZ 36mg/day	-11.6	-4.4
Placebo	-7.1	--
ARM-TD¹¹⁶		
DTBZ	-11.1	-2.8
Placebo	-8.3	--

Table F8: Tetrabenazine: Summary of Evidence

Study	Design/Treatment	Primary Outcome Measure	Findings	Study Procedures
Kazamatsuri 1972	Non-randomized cross over study PBO for 4 weeks, TBZ for 6 weeks, and PBO for another 2 weeks (N=24)	Mean oral dyskinesia frequency/minute	Vs. placebo Mean difference TBZ (after 6 weeks): 19.2 (p<0.0005 vs. PBO)	All neuroleptics were withdrawn 4 weeks prior to TBZ initiation
Ondo 1999	Open label single blind TBZ starting dose of 25mg/d to maximum of 100mg/d (N=20)	Blinded AIMS change from baseline	TBZ: Mean change after 20 weeks: -9.7 (p<0.001)	Patients stopped taking offending medications for at least 30 days before study initiation
Jankovic 1988	Retrospective (18 months [†]) TBZ starting dose of 25mg/d to maximum of 100mg/d (N=44)	Global Response Scale: composite score by patients, caretakers & investigators. Ranges from 1 (marked improvement) to 5 (worsening)	TBZ: Average score: 2.3; 93% had marked or moderate improvement	Many patients were also being treated concurrently with other medications
Watson 1988	Open label, case series TBZ starting dose of 37.5mg/d (3 divided doses) to maximum of 200mg/d 94 divided doses) (N=23)	0 (No movement) to 4 (severe movement) involuntary movement scale	TBZ: involuntary movement stopped completely in 40% of patient	Antipsychotic medication was continued where indicated
Jankovic 1997	Retrospective (28.9 months [†]) TBZ starting dose of 25mg/d to maximum of 100mg/d (N=93)	Global Response scale (see Jankovic 1988 above)	TBZ: 93% had marked or moderate improvement	Many patients were also being treated concurrently with other medications
Paleacu 2004	Retrospective TBZ starting dose of 25mg/d to maximum of 150mg/d (N=17)	Clinical Global Impression of Change (1 to 7): composite score developed with patients	TBZ: 41% had marked or moderate improvement	Chart review
Kenney 2007	Retrospective (28 months [†]) TBZ (dose range 12.5mg/d-300mg/d) (N=149)	Global Response scale (see Jankovic 1988 above)	TBZ: 84% had marked or moderate improvement	Chart review
Miguel 2017	Retrospective (49 months [†]) TBZ starting dose of 12.5mg/d to maximum of 225mg/d (N=35)	Subjective Clinical improvement	TBZ: 77% were classified as responders	Chart review

Table F9. Tetrabenazine: Adverse Events at 12 weeks and 80 weeks

	Any AE≥1 (%)	Saes≥1 (%)	Discontinuation Due to AE (%)	Somnolence (%)	Insomnia (%)	Depression (%)	Suicidal Ideation (%)
12-Week Placebo Controlled Studies Of HC¹⁴							
TBZ (25mg-100mg/D)	91	7.4	9.3	31.5	25.9	14.8	NR (1 Suicide)
Placebo	70	0	3.3	3.3	0	0	NR
80-Week Long Term Extension Study¹⁵							
TBZ (Max 200mg/D)	74.6	16	4	24	13	22.6	NR (1 Suicide Attempt)

Table F10. Tetrabenazine: Adverse Events from Retrospective Studies

Side Effects	Jankovic 1988	Jankovic 1997	Kenney 2007	Shen 2013	Miguel 2017
Number of Patients	217	400	448	145	108
Dose/Day	25mg-100mg	25mg-100mg	12.5mg-300mg	12.5mg-300mg	12.5mg-225mg
Mean Follow Up	18 Months	29 Months	28 Months	37 Months	49 Months
Somnolence/Fatigue	13%	37%	25%	45%	5%
Parkinsonism	24%	29%	15%	14%	52%
Depression	11%	15%	8%	27%	5%
Insomnia	5%	11%	5%	28%	NR
Nervousness/Anxiety	7%	10%	5%	21%	4%
Akathisia	5%	10%	8%	12%	2%
Nausea/Vomiting	2.3%	5%	6%	NR	1%

Appendix G. Evidence Tables

Author & Year of Publication (Trial Name) Quality rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Valbenazine (VBZ)						
O'Brien Mov. Disord. 2015 ⁵ KINECT 2 Fair	Phase II, RCT, double-blind, parallel-group, placebo-controlled dose-titration study 22 sites across USA 6 weeks	<i>mITT population</i> 1) Placebo, n=44 2) VBZ, n=45 once daily starting dose of 25mg increased in increments of 25mg/2weeks to a maximum of 75mg	Inclusions: Medically and psychiatrically stable male & female subjects 18-85 years old with moderate to severe TD and a clinical diagnosis of schizophrenia, schizoaffective disorder, mood disorder or gastrointestinal disorder	Mean age (SD) 1) 55.6 (9.8) 2) 56.7 (10.8) Mean age at TD diagnosis, (SD) 1) 49.5 (12.1) 2) 48.9 (13.0) Male/Female, n (%) 1) 27 (55.1)/ 22 (44.9) 2) 30 (58.8)/ 21 (41.2) AIMS at baseline, mean(SD) 1) 7.9 (4.5) 2) 8.0 (3.5) Schizophrenia or schizoaffective disorder/mood disorder/gastrointestinal disorder, % 1) 61.2/36.7/2.0 2) 54.9/39.2/5.9	Week 6 Mean change in AIMS (SD) 1) -1.1 (3.7) 2) -3.6 (3.5) Least Squares Mean Change in AIMS from baseline (SEM) 1) -0.2 (1.1) 2) -2.6 (1.2) CGI-TD response, n (%) 1) 7 (15.9) 2) 30 (66.7) PGIC response, n (%) 1) 14 (31.8) 2) 26 (57.8)	Week 6 Overall treatment-emergent adverse events (TEAEs), % 1) 32.7% 2) 49.0% Fatigue, n (%) 1) 2 (4.1) 2) 5 (9.8) Headache, n (%) 1) 2 (4.1) 2) 5 (9.8) Somnolence, n (%) 1) 1 (2.0) 2) 3 (5.9)

Hauser, Am J Psychiatry, 2017 ⁴ KINECT 3 Good	Phase III, RCT, double-blind, placebo-controlled trial 59 centers in United States 2 centers in Canada 2 centers in Puerto Rico 6 weeks	<i>ITT population</i> = received ≥1 dose of study drug & had ≥1 post-baseline AIMS assessment 1) Placebo, n=76 2) VBZ 40 mg/day, n=70 3) VBZ 80mg/day, n=79	Inclusion: Participants 18-85 years old with medically stable diagnosis of schizophrenia, schizoaffective disorder, or mood disorder for ≥ 3 months prior to screening; had moderate or severe DRA-induced TD for ≥ 3 months prior to screening	Mean age (SD) 1) 57.0 (10.5) 2) 55.3 (8.5) 3) 56.0 (10.1) Baseline AIMS, mean (SD) 1) 9.9 (4.3) 2) 9.7 (4.1) 3) 10.4 (3.6) Male, n (%) 1) 42 (55.3) 2) 42 (58.3) 3) 39 (49.4) White/Black, n (%) 1) 43 (56.6) /29 (38.2) 2) 41 (56.9) /26 (36.1) 3) 44 (55.7) /32 (40.5) Schizophrenia & schizoaffective disorder/mood disorder, n (%) 1) 50 (65.8)/26 (34.2) 2) 48 (66.7)/24 (33.3) 3) 52 (65.8)/27 (34.2) Concomitant medications Any Antipsychotic, n (%) 1) 62 (82.9) 2) 66 (91.7) 3) 65 (82.3)	Week 6 Least Squares Mean Change in AIMS from baseline 1) -0.1 (NS) 2) -1.9, p=0.0021 3) -3.2, p<0.001 ≥50% AIMS response reduction, % 1) 8.7 (NS) 2) 23.8, p=0.02 3) 40.0, p<0.001 CGI-TD Score 1) 3.2 (NS) 2) 2.9, p=0.074 3) 2.9, p=0.056	Week 6 Any AE, n (%) 1) 33 (43.4) 2) 29 (40.3) 3) 40 (50.6) Discontinuation due to AEs, n (%) 1) 4 (5.3) 2) 4 (5.6) 3) 5 (6.3) Death, n (%) 1) 0 (0) 2) 0 (0) 3) 1 (1.3) Somnolence, n (%) 1) 3 (3.9) 2) 4 (5.6) 3) 4 (5.1) Akathisia, n (%) 1) 1 (1.3) 2) 3 (4.2) 3) 2 (2.5) Suicidal Ideation, n (%) 1) 4 (5.3) 2) 3 (4.2) 3) 1 (1.3)
Factor, J Clin Psych, 2017 ⁷³	Phase III, RCT, double-blind, placebo-controlled	<i>DBPC Period</i> 1) PBO, n=76 2) VBZ 40 mg/day, n=70	<i>See Hauser, Am J Psychiatry, 2017</i> ¹⁸	Mean age (SD) 2) 55.8 (9.5) 3) 56.0 (9.9)	Week 48 AIMS score mean change 2) -3.0 3) -4.8	<i>LTE period, Overall Safety Population (≥1 dose of assigned drug)</i>

<p>(KINECT 3 Extension)</p> <p>Good</p>	<p>(DBPC) followed by a long-term extension (LTE), and Drug-free washout periods</p> <p>DBPC: 6 weeks LTE: 42 weeks followed by 4 weeks washout period</p>	<p>3) VBZ 80mg/day, n=79</p> <p><i>LTE and Washout periods</i></p> <p>2) VBZ 40 mg/day, n=97 (combined w/ prior placebo group)</p> <p>3) VBZ 80mg/day n=101 (combined w/ prior placebo group)</p>		<p>Male, n (%)</p> <p>2) 55 (58.5)</p> <p>3) 48 (49.5)</p> <p>White, n (%)</p> <p>2) 51 (54.3)</p> <p>3) 59 (60.8)</p> <p>Schizophrenia & schizoaffective disorder/mood disorder, n (%)</p> <p>2) 61 (64.9)/33 (35.1)</p> <p>3) 62 (63.9)/35 (36.1)</p> <p>Baseline AIMS, mean (SD)</p> <p>2) 9.6 (4.0)</p> <p>3) 10.4 (4.0)</p> <p>Concomitant medications</p> <p>Any Antipsychotic, n (%)</p> <p>2) 81 (86.2)</p> <p>3) 80 (82.5)</p>	<p>CGI-TD mean score</p> <p>2) 2.4</p> <p>3) 2.1</p> <p>≥50% AIMS response reduction, %</p> <p>2) 28.3</p> <p>3) 52.4</p> <p>CGI-TD response, (%)</p> <p>2) 59.0</p> <p>3) 76.2</p> <p>Week 52</p> <p>≥50% AIMS response reduction, %</p> <p>2) 15.0</p> <p>3) 19.7</p> <p>CGI-TD response, (%)</p> <p>2) 36.7</p> <p>3) 27.9</p>	<p>Any treatment emergent AE, n (%)</p> <p>2) 60 (61.9)</p> <p>3) 77 (76.2)</p> <p>Discontinuation due to AE, n (%)</p> <p>2) 13 (13.4)</p> <p>3) 18 (17.8)</p> <p>Somnolence, n (%)</p> <p>2) 3 (3.1)</p> <p>3) 4 (4.0)</p> <p>Deaths, n (%)</p> <p>2) 0</p> <p>3) 1 (1.0)</p>
<p>Remington, ACNP, 2016 ¹¹⁷</p> <p>POSTER ABSTRACT</p>	<p>Pooled LTE population included VBZ-treated subjects from 3 studies</p> <p>KINECT: 50mg/day, 6-week double blind, placebo-controlled</p>	<p>1) LTE VBZ 40mg/day, n=197</p> <p>2) LTE VBZ 80mg/day, n=230</p>	<p>Inclusions: DSM-IV diagnosis of moderate to severe DRA-induced TD for ≥3 months prior to screening; DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or mood disorder and Brief Psychiatric Rating</p>	<p><i>Safety Population</i></p> <p>Mean Age (%<65years)</p> <p>1) 56.2 (81.7)</p> <p>2) 56.9 (81.3)</p> <p>Male, %</p> <p>1) 59.4</p> <p>2) 52.2</p> <p>White/Black, %</p>	<p>NR</p>	<p><i>Safety Population</i></p> <p>Any treatment emergent AE, %</p> <p>1) 61.0</p> <p>2) 71.3</p> <p>All subject</p> <p>Any serious AE, %</p> <p>1) 11.5</p> <p>2) 16.5</p>

	(DBPC) period, 6 week open-label treatment period; KINECT 3: 80 or 40mg/day, 6-week DBPC, 42-week double-blind extension period; KINECT 4: 80 or 40mg/day, 48-week open-label treatment Mean duration of exposure: 6 months		Scale < 50 at screening with stable psychiatric status and stable doses of concomitant medications	1) 56.3/37.6 2) 65.7/31.3 Mean Age at TD diagnosis 1) 48.6 2) 48.2 Current schizophrenia & schizoaffective disorder/ mood disorder, % 1) 76.6/23.4 2) 67.4/32.6 Any Concomitant antipsychotic, % 1) 88.3 2) 83.0		Discontinuation due to AE, % 1) 16.0 2) 13.5 AE leading to dose reduction, % 1) 5.0 2) 8.3 Somnolence, % 1) 7.5 2) 5.2
Correll, CPNP, 2017 118 KINECT 3 Extension POSTER ABSTRACT <i>See Grigoriadis, ACNP, 2016⁶⁸</i>	<i>See Grigoriadis, ACNP, 2016⁶⁸</i>	<i>DBPC Period: Mood Disorder Subgroup</i> 1) PBO, n=26 2) VBZ 40 mg/day, n=24 3) VBZ 80mg/day, n=27 <i>LTE and Washout periods: Overall population</i> 2) VBZ 40 mg/day, n=97 (combined w/ prior placebo group)	<i>See Grigoriadis, ACNP, 2016⁶⁸</i>	<i>Mood Disorder Subgroup</i> Mean Age (SD) 1) 57.4 (11.6) 2) 54.7 (9.1) 3) 54.5 (11.1) Mean Age at TD diagnosis, mean (SD) 1) 51.6 (11.8) 2) 48.7 (9.3) 3) 47.6 (10.4) Male, n (%) 1) 8 (30.8) 2) 11 (45.8)	<i>Week 48</i> AIMS score mean change 2) -4.2 3) -5.8 CGI-TD mean score 2) 2.2 3) 2.0 ≥50% AIMS response reduction, % 2) 33.3 3) 56.0 CGI-TD response, n (%) 2) 61.0	<i>LTE period, Overall Safety Population (≥1 dose of assigned drug)</i> Any treatment emergent AE, n (%) 2) 60 (61.9) 3) 77 (76.2) Discontinuation due to AE, n (%) 2) 13 (13.4) 3) 18 (17.8) Somnolence, n (%) 2) 3 (3.1) 3) 4 (4.0)

		3) VBZ 80mg/day n=101 (combined w/ prior placebo group)		3) 10 (37.0) White, n (%) 1) 23 (88.5) 2) 18 (75.0) 3) 17 (63.0) AIMS score, mean (SD) 1) 11.2 (3.6) 2) 11.4 (3.5) 3) 10.9 (3.8)	3) 80.0	
Kane, CPNP, 2017 ¹³ KINECT 3 Extension POSTER ABSTRACT <i>See Grigoriadis, ACNP, 2016</i> ⁶⁸	<i>See Grigoriadis, ACNP, 2016</i> ⁶⁸	<i>Schizophrenia/Schizoaffective Disorder subgroup</i> <i>DBPC Period</i> 1) PBO, n=50 2) VBZ 40 mg/day, n=48 3) VBZ 80mg/day, n=52 <i>VE and Washout periods</i> 2) VBZ 40 mg/day, n=97 (combined w/ prior placebo group) 3) VBZ 80mg/day n=101 (combined w/ prior placebo group)	<i>See Grigoriadis, ACNP, 2016</i> ⁶⁸	<i>Schizophrenia/Schizoaffective Disorder subgroup</i> Mean age (SD) 1) 56.8 (10.0) 2) 55.6 (8.3) 3) 56.8 (9.5) Mean Age at TD diagnosis (SD) 1) 47.7 (9.6) 2) 47.2 (11.2) 3) 47.6 (13.6) Male, n (%) 1) 34 (68.0) 2) 31 (64.6) 3) 29 (55.8) White/Black, n (%) 1) 20 (40.0)/ 27 (54.0) 2) 23 (47.9)/ 21 (43.8)	<i>Week 48: Schizophrenia/Schizoaffective Disorder subgroup</i> AIMS score mean change 2) -2.5 3) -4.2 CGI-TD mean score 2) 2.4 3) 2.2	<i>Overall safety population</i> <i>See Correll, CPNP, 2017</i> ⁷¹

				3) 27 (51.9)/ 24 (46.2) AIMS score, mean (SD) 1) 9.3 (4.5) 2) 8.8 (4.2) 3) 10.1 (3.5)		
Josiassen, APA, 2016 ⁷² KINECT 2 POSTER ABSTRACT <i>See O'Brien Mov. Disord. 2015</i> ⁵	<i>See O'Brien Mov. Disord. 2015</i> ⁵	<i>Schizophrenia & schizoaffective subgroup</i> 1) PBO, n=27 2) VBZ, n=26 once daily starting dose of 25mg increased in increments of 25mg/2weeks to a maximum of 75mg <i>Mood disorder subgroup</i> 1) Placebo, n=16 2) VBZ, n=19 once daily starting dose of 25mg increased in increments of 25mg/2weeks to a maximum of 75mg	<i>See O'Brien Mov. Disord. 2015</i> ⁵	<i>See O'Brien Mov. Disord. 2015</i> ⁵	Week 6 <i>Schizophrenia & schizoaffective subgroup</i> AIMS mean score change 1) -1.0 2) -3.0, p<0.05 CGI-TD mean score 1) 3.1 2) 2.4 CGI-TD responders, % 1) 14.8 2) 61.5 <i>Mood disorder subgroup</i> AIMS mean score change 1) -1.4 (NS) 2) -4.5, p<0.05 CGI-TD mean score 1) 3.1 2) 2.1 CGI-TD responders, % 1) 18.8	NR

					2) 73.7	
Bari, <i>Neurology</i>, 2016 ⁶⁹ KINECT extension POSTER ABSTRACT	Open label extension (OLE) followed a phase II, double-blind, placebo-controlled period (DBPC) DBPC: 6 weeks OLE: 6 weeks	DBPC 1) Placebo (n=54) 2) VBZ (n=53) OLE 1) VBZ (n=89) Open label extension subjects received once-daily VBZ 50 mg for 6 weeks	NR	Mean age (SD) 55.1 (10.5) Male, n (%) 71 (66.4) Mean age at TD diagnosis (SD) 47.6 (11.8) Mean video AIMS score (SD) 12.3 (5.1)	<i>Week 12</i> AIMS change from baseline -5.9 ≥50% AIMS improvement, % 54 CGI-TD mean score (SD) 2.5 (0.9) CGI-TD responders, % 61 <i>Week 16 (after washout)</i> CGI-TD responders, % 29	<i>Week 12</i> Any treatment emergent AE, n (%) 42 (41.2) Serious AEs, n (%) 0 Suicidal ideation, n 3

Marder, ACNP, 2017⁷⁰ KINECT 4 POSTER ABSTRACT	Phase III, open label trial	1) 40 mg/day Week 8, n= 33 Week 48, n= 20	Inclusions: Psychiatrically stable adults (18-85) with moderate or severe TD and diagnosis of schizophrenia/ schizoaffective disorder or mood disorder with stable regimens of concomitant psychiatric medications	N=163 Mean Age 57.4 Male, % 52.8 White, % 67.5 Schizophrenia/schizoaffective disorder, % 73.0 <i>2 blinded central raters</i> AIMS at baseline, mean 1) 10.2 2) 10.0 3) 9.3	Week 8, n=149 <i>2 blinded central raters</i> Mean change in AIMS 1) -4.5 2) -3.5 3) -4.9 <i>1 investigator/site rater</i> Mean change in AIMS 1) -7.1 2) -5.4 3) -7.4 CGIC/ PGIC score, mean 1) 2.5/ 2.2 2) 2.6/ 2.5 3) 2.0/ 2.4 Week 48, n=103 <i>1 investigator/ site rater</i>	Safety Population, N=163 Any treatment emergent AE ≥1, % 67.5 Discontinuation due to ≥1 AE, % 14.7 Any serious AE ≥1, % 12.9 Urinary tract infection, % 8.5 Headache, % 5.2 <i>1 death unrelated to VBZ treatment.</i>
	Open label treatment period: 48 weeks Washout period: 4 weeks	2) 80 mg/day (Initial dose of 40 mg/day VBZ increased to 80 mg/day after 4 weeks if: CGIC score of ≥3 and safety/tolerability with 40mg/day dose) Week 8, n=105 Week 48, n=74 3) 80/40 mg/day (Participants decreased down to 40 mg/day dose if low tolerability with 80 mg/day dose) Week 8, n=11 Week 48, n=9				

				1 investigator/site rater AIMS at baseline, mean 1) 14.2 2) 15.0 3) 12.8	Mean change in AIMS 1) -10.2 2) -11.0 3) -7.2 CGIC/ PGIC score, mean 1) 1.7/ 1.6 2) 1.6/ 1.7 3) 2.3/ 2.0 CGIC/ PGIC responders, % 1) 90.0/ 90.0 2) 95.9/ 89.2 3) 66.7/ 77.8	
Deutetrabenazine (DTBZ)						
Anderson Lancet Psychiatry 2017 ⁷ AIM-TD Fair	Phase III, RCT, double-blind, placebo-controlled, parallel-group study 75 sites across USA and Europe 12 Weeks	<i>Safety population</i> 1) PBO (n=72) 2) DTBZ, 12mg/d (n=74) 3) DTBZ, 24mg/d (n=73) 4) DTBZ, 36mg/d (n=74) Treatments were administered in 2 divided doses, approximately 10 hrs apart; dose escalation through wk 4 for 24mg and 36 mg, weekly increments of	Inclusion: 18-80 years old with TD diagnosis ≥3 months prior to screening (≥1 month in patients >60); AIMS score ≥6 at screening and baseline; history of DRA use for ≥3 months; stable psychiatric illness on stable medication for ≥30 days; stable antidepressant dose for ≥45 days	<i>Safety population</i> Mean age (SD) 1) 54.2 (12.1) 2) 57 (10) 3) 55.6 (11.3) 4) 58.3 (11.6) Mean duration of TD, yrs (SD) 1) 5.8 (0.7) 2) 5.8 (0.7) 3) 4.4 (0.9) 4) 6.2 (0.7)	<i>Week 12: mITT population</i> LS Mean Change in AIMS score 1) -1.4 2) -2.1 (NS) 3) -3.2 (p=0.003 vs PBO) 4) -3.3 (p=0.001 vs PBO) ≥50% improvement in AIMS score, % 1) 12 2) 13 (NS)	<i>Week 12: safety population</i> Serious AEs, n (%) 1) 4 (6) 2) 2 (3) 3) 6 (8) 4) 4 (5) Withdrawal due to AEs, n (%) 1) 2 (3) 2) 4 (5)

		6 mg/d starting from 12 mg/d; maintenance period for 8 wks; dose could be decreased by 6 mg/d d/t AEs	Exclusion: Neurological condition other than TD; history of suicidal ideation ≤6 months of screening; score ≥11 on the depression subscale of HADS at screening; use of TBZ, reserpine or strong anticholinergic within 30 days	DRA at baseline, n (%) 1) 45 (77.6) 2) 45 (75.0) 3) 37 (75.6) 4) 35 (63.6) Schizophrenia /mood disorders (%) 1) 58/42 2) 53/47 3) 68/32 4) 59/41	3) 35 (p=0.005 vs. PBO) 4) 33 (p=0.007 vs. PBO) CGIC treatment success, % 1) 26 2) 28 (NS) 3) 49 (p=0.014 vs PBO) 4) 44 (p=0.059 vs PBO) PGIC treatment success, % 1) 31 2) 23 3) 45 4) 40 All NS vs. PBO	3) 2 (3) 4) 3 (4) Nervous system disorders, n (%) 1) 10 (14) 2) 6 (8) 3) 6 (8) 4) 16 (22) Psychiatric disorders, n (%) 1) 7 (10) 2) 10 (14) 3) 7 (10) 4) 9 (12)
Jimenez-Shahed AAN 2017a ¹¹⁶ AIM-TD POSTER ABSTRACT <i>See Anderson Lancet Psychiatry 2017</i> ⁷	<i>See Anderson Lancet Psychiatry 2017</i> ⁷	<i>mITT population</i> 1) PBO (n=58) 2) DTBZ, 12mg/d (n=60) 3) DTBZ, 24mg/d (n=49) 4) DTBZ, 36mg/d (n=55) For DTBZ 24 mg/d or 36 mg/d, DTBZ was started at 12 mg/d and titrated up during a 4-week dose escalation phase	<i>See Anderson Lancet Psychiatry 2017</i> ⁷	<i>mITT population</i> Mean age (SE) 1) 54.3 (1.6) 2) 57.9 (1.2) 3) 56.3 (1.5) 4) 59.7 (1.4) Duration of TD, yrs (SE) 1) 5.8 (0.7) 2) 5.8 (0.7) 3) 4.4 (0.9) 4) 6.2 (0.7) Receiving DRA at baseline, n (%) 1) 45 (77.6) 2) 45 (75.0) 3) 37 (75.6) 4) 35 (63.6)	<i>Week 12: by baseline DRA use</i> LS Mean Change in AIMS score <i>Not receiving DRA</i> 1) 0 2) -2.4 (p=0.048) 3) -3.1 (p=0.013) 4) -3.1 (p=0.006) <i>Receiving DRA</i> 1) -1.7 2) -2.0 3) -3.2 (p=0.036) 4) -3.4 (p=0.017) CGIC treatment success, % <i>Not receiving DRA</i> 1) 8 2) 27	<i>See Anderson Lancet Psychiatry 2017</i> ⁷

				Psychotic disorders, n (%) 1) 34 (58.6) 2) 33 (55.) 3) 31 (63.3) 4) 30 (54.5) <i>See Anderson Lancet Psychiatry 2017 ⁷</i>	3) 58; OR: 16.8 (p=0.011) 4) 60; OR: 18.0 (p=0.004) <i>Receiving DRA</i> 1) 31 2) 29 3) 46 4) 34	
Jimenez-Shahed AAN 2017b ⁷⁷ AIM-TD POSTER ABSTRACT <i>See Anderson Lancet Psychiatry 2017 ⁷</i>	<i>See Anderson Lancet Psychiatry 2017 ⁷</i>	1) PBO (n=58) 2) DTBZ, 12mg/d (n=60) 3) DTBZ, 24mg/d (n=49) 4) DTBZ, 36mg/d (n=55) For DTBZ 24 mg/d or 36 mg/d, DTBZ was started at 12 mg/d and titrated up during a 4-week dose escalation phase	<i>See Anderson Lancet Psychiatry 2017 ⁷</i>	<i>See Anderson Lancet Psychiatry 2017 ⁷ & Jimenez-Shahed AAN 2017a ⁷⁷</i>	Week 12 Odds ratio of AIMS Responder Rates vs. PBO <i>DTBZ 24mg/d</i> 50%: 3.96 (p<0.01) 70%: 7.92 (p<0.05) 80%: 1.22 (NS) 90%: Odds was not higher <i>DTBZ 36 mg/d</i> 50%: 3.80 (p<0.01) 70%: 10.76 (p<0.05) 80%: 8.06 (p<0.05) 90%: 3.15 (NS)	<i>See Anderson Lancet Psychiatry 2017 ⁷</i>

<p>Anderson APA 2017a ⁷</p> <p>AIM-TD</p> <p><i>See Anderson Lancet Psychiatry 2017</i> ⁷</p>	<p><i>See Anderson Lancet Psychiatry 2017</i> ⁷</p>	<p>1) PBO (n=58) 2) DTBZ, 12mg/d (n=60) 3) DTBZ, 24mg/d (n=49) 4) DTBZ, 36mg/d (n=55)</p> <p>Treatments were administered in 2 divided doses, approximately 10 hrs apart; dose escalation through wk 4 for 24mg and 36 mg, weekly increments of 6 mg/d starting from 12 mg/d; maintenance period for 8 wks; dose could be decreased by 6 mg/d d/t AEs</p>	<p><i>See Anderson Lancet Psychiatry 2017</i> ⁷</p>	<p><i>See Anderson Lancet Psychiatry 2017</i> ⁷ & Jimenez-Shahed AAN 2017a ⁷⁷</p>	<p>Week 12 Mean mCDQ-24 change (LS) vs placebo 3) -3.5* 4) -4.4*</p> <p>Improvement in QoL by Baseline DRA use <i>Not receiving DRA Vs placebo</i> 3) -10.1* 4) -6.4* <i>Receiving DRA Vs placebo</i> 3) No reduction 4) -2.6</p> <p>Improvement in QoL by underlying psychiatric conditions <i>Bipolar:</i> 3) -5.7* 4) -4.3* <i>Schizophrenia:</i> 3) -1 (approx.) 4) -3.2*</p> <p>*clinically meaningful</p>	<p><i>See Anderson Lancet Psychiatry 2017</i> ⁷</p>

Fernandez Neurology 2017 ⁸ ARM-TD Fair	RCT, double-blind, placebo-controlled, multicenter trial 46 sites in the United States and Europe 12 weeks	1) DTBZ (n=58) 2) PBO (n=59) Tablets are taken orally twice daily for 12 weeks; DTBZ intervention includes a dose titration period and maintenance period DTBZ was started at 12mg/d (6 mg twice daily) and titrated weekly by 6 mg/d for up to 6 weeks until adequate dyskinesia control; the dose would increase until a significant AE occurred or the max dose (48 mg/d) was reached; this was followed by a 6-week maintenance and 1-week washout period	Inclusion: DRA use for ≥3 months; clinical diagnosis of TD for ≥3 months prior to screening; patients with psychiatric diagnosis must be stable and have no change in psychoactive medications; have a mental health provider and doesn't anticipate any changes to treatment in next 3 months; AIMS score ≥6 Exclusion: Receiving TD treatment medication; have another neurological condition besides TD; history of substance/alcohol abuse in last 12 months; have a serious untreated/undertreated psychiatric illness; have unstable or serious medical illness; known allergy to any component of SD-809	Mean age (SD) 1) 55.9 (9.8) 2) 53.3 (10.6) White, n (%) 1) 37 (63.8) 2) 44 (74.6) Duration of TD, mo 1) 72.6 (81.7) 2) 76.8 (82.1) DRA use at baseline, n (%) 1) 45 (77.6) 2) 49 (83.1) Baseline AIMS score, items 1—7 (SD) 1) 9.6 (4.1) 2) 9.6 (3.8) Psychiatric disorders <i>Schizophrenia/ Schizoaffective disorder</i> 1) 29 (50)/ 11 (19) 2) 29 (49.2)/ 11 (18.6) <i>Bipolar disorder</i> 1) 12 (20.7) 2) 15 (25.4)	Week 12 LS Mean AIMS change (SE) 1) -3.0 (0.45) 2) -1.6 (0.46) P=0.019 95% CI: -2.6 to -0.2 CGIC treatment success, % 1) 48.2 2) 40.4 PGIC treatment success, % 1) 42.9 2) 29.8	Week 12 Serious AE, n (%) 1) 3 (5.2) 2) 5 (8.5) Treatment-related AEs, n (%) 1) 28 (48.3) 2) 21 (35.6) AEs leading to dose reduction, n (%) 1) 6 (10.3) 2) 3 (5.1) AEs leading to dose suspension, n (%) 1) 3 (5.2) 2) 5 (8.5) AEs leading to discontinuation, n (%) 1) 1 (1.7) 2) 2 (3.4) Somnolence, n (%) 1) 8(13.8) 2) 6 (10.2)
Anderson APA 2017b ⁷⁵ AIM-TD and ARM-TD	Open-label, single-arm, long-term safety study after washout of	1) Prior PBO (n=102) 2) Prior DTBZ (n=202) Total N=304 N at week 54=78	Inclusion: Successful completion of either ARM-TD or AIM-TD study; adults with clinical diagnosis of TD for ≥3	Mean age (SE) 1) 54.3 (1.1) 2) 57.1 (0.7) Female, n (%)	Week 54 Mean AIMS score improvement (SE) 1) -4.6 (0.77) 2) -5.4 (0.69)	See Anderson APA 2017d ⁷⁶

POSTER ABSTRACT <i>See Anderson Lancet Psychiatry 2017</i> ⁷ <i>See Fernandez Neurology 2017</i> ⁷⁸	treatment in the parent study Data cutoff: June 30, 2016	Patients were rolled over from parent study after completing 1-week washout and week 13 evaluation Started at 12mg/d and titrated once a week until adequate dyskinesia control was achieved, a clinically significant AE occurred (investigator determined if dose reduction or suspension was necessary), or the max dose of 48 mg/d was reached Study was ongoing through week 158	months prior to screening; history of DRA use for ≥ 3 months (≥ 1 months if ≥ 60 yrs); if psychiatric illness must be stable with no psychoactive medication change for ≥ 30 days (antidepressants ≥ 45 days) before screening Exclusion: Neurological condition other than TD; history of suicidal ideation/behavior w/i 6 months of screening; score ≥ 11 on the depression subscale of the Hospital Anxiety and Depression Scale at screening or baseline	1) 55 (53.9) 2) 114 (5.4) White, n (%) 1) 80 (78.4) 2) 156 (77.2) Mean TD duration, yrs (SE) 1) 5.9 (0.6) 2) 5.6 (0.4) Receiving DRA at baseline, n (%) 1) 80 (78.4) 2) 147 (72.8) Psychotic Disorders, n (%) 1) 62 (60.8) 2) 122 (60.4) Mood disorders, n (%) 1) 39 (38.2) 2) 80 (39.6)	Patients who were “Much Improved” or “Very Much Improved” by the CGIC (receiving DTBZ) -At week 6: 58% -AT week 54: 72% By the PGIC scale (receiving DTBZ) -at week 6: 53% -at week 54: 59%	
Anderson APA 2017c ⁷⁶ ARM-TD and AIM-TD	Open-label, single-arm, long-term safety study after washout of treatment in the parent study Data cutoff: June 30, 2016	1) Prior PBO (n=102) 2) Prior DTBZ (n=202) Total N=304 Patients were rolled over from parent study after completing 1-week washout and week 13 evaluation	See Anderson APA 2017c ⁷⁵	See Anderson APA 2017c ⁷⁵	See Anderson APA 2017 ⁷⁵	Week 54 Exposure-Adjusted Incidence Rate of Patients with AEs (Number of Patients/Patient-year) Serious AEs: 0.14 (29/202.6)

<p><i>See Anderson Lancet Psychiatry 2017</i>⁷</p> <p><i>See Fernandez Neurology 2017</i>⁷⁸</p>		<p>Started at 12mg/d and titrated once a week until adequate dyskinesia control was achieved, a clinically significant AE occurred (investigator determined if dose reduction or suspension was necessary), or the max dose of 48 mg/d was reached</p> <p>Study was ongoing through week 158</p>				<p>Treatment-related AEs: 0.67 (101/150.1)</p> <p>AEs leading to discontinuation: 0.08 (18/212.4)</p> <p>Nervous system: <i>Somnolence</i>: 0.11 (22/201.5) <i>Headache</i>: 0.10 (21/200.3)</p> <p>Psychiatric disorders: <i>Depression</i>: 0.11 (22/206.1) <i>Anxiety</i>: 0.12 (24/201.5)</p>
<p>Fernandez APA 2017a⁷⁸</p> <p>AIM-TD and ARM-TD</p> <p>POSTER ABSTRACT</p> <p><i>See Anderson Lancet Psychiatry 2017</i>⁷</p>	<p>ARM-TD: Phase II/III, RCT, double-blind, placebo-controlled study</p> <p>12 weeks</p> <p>AIM-TD: Phase III, RCT, double-blind, placebo-controlled, parallel-group study</p>	<p><i>In Pooled Efficacy Population</i></p> <p>1) PBO (n=107) 2) DTBZ (n=152)</p> <p>152 patients received DTBZ in ARM-TD or 24 or 36mg/d DTBZ in AIM-TD</p>	<p><i>See Anderson Lancet Psychiatry 2017</i>⁷ & <i>Fernandez Neurology 2017</i>⁷⁸</p>	<p><i>In Pooled Efficacy Population</i></p> <p>Mean age (SD) 1) 54.5 (10.9) 2) 57.9 (9.9)</p> <p>Female, n (%) 1) 55 (51.4) 2) 84 (55.3)</p> <p>Caucasian, n (%) 1) 84 (78.5) 2) 115 (75.7)</p> <p>Duration of TD, yrs (SD) 1) 6.0 (6.1)</p>	<p><i>In Pooled Efficacy Population Week 12</i></p> <p>Patients “Much Improved” or “Very Much Improved” on the CGIC 1) 30 2) 48 OR: 2.12, p=0.005</p>	<p><i>Pooled Safety Population Week 12</i></p> <p>Serious AE, n (%) 1) 9 (6.9) 2) 13 (6.3)</p> <p>Treatment-related AEs, n (%) 1) 40 (30.5) 2) 57 (27.8)</p> <p>AE leading to discontinuation, n (%) 1) 4 (3.1) 2) 6 (2.9)</p>

<p><i>See Fernandez Neurology 2017</i> ⁷⁸</p>	12 Weeks			<p>2) 5.6 (6.1)</p> <p>Psychotic disorders, n (%)</p> <p>1) 68 (63.6)</p> <p>2) 93 (61.2)</p> <p>Mood disorders, n (%)</p> <p>1) 38 (35.5)</p> <p>2) 59 (38.8)</p>		<p>AE leading to dose reduction, n (%)</p> <p>1) 3 (2.3)</p> <p>2) 10 (4.9)</p> <p>Deaths, n (%)</p> <p>1) 0</p> <p>2) 2 (1.0)</p> <p>Common AE>3% Somnolence, n (%)</p> <p>1) 9 (6.9)</p> <p>2) 12 (5.9)</p> <p>Headache, n (%)</p> <p>1) 10 (7.6) 2) 10 (4.9)</p>
<p>Fernandez APA 2017b ⁷⁹</p> <p>AIM-TD and ARM-TD</p> <p><i>See Anderson Lancet Psychiatry 2017</i> ⁷</p> <p><i>See Fernandez Neurology 2017</i> ⁷⁸</p>	<p>ARM-TD: Phase II/III, RCT, double-blind, placebo-controlled study</p> <p>12 weeks</p> <p>AIM-TD: Phase III, RCT, double-blind, placebo-controlled, parallel-group study</p> <p>12 Weeks</p>	<p><i>In Pooled Efficacy Population</i></p> <p>1) PBO (n=107)</p> <p>2) DTBZ (n=152)</p> <p>152 patients received DTBZ in ARM-TD or 24 or 36mg/d DTBZ in AIM-TD</p>	<p><i>See Anderson Lancet Psychiatry 2017</i> ⁷ & <i>Fernandez Neurology 2017</i> ⁷⁸</p>	<p>Fernandez APA 2017a ⁷⁸</p>	<p>Week 12</p> <p>Patients “Much Improved” or “Very Much Improved” on PGIC</p> <p><i>Overall</i></p> <p>1) 30</p> <p>2) 43</p> <p>OR: 1.81; p=0.026</p> <p><i>With Underlying Mood Disorder</i></p> <p>1) 26/38</p> <p>2) 47/59</p> <p>OR: 2.76; p=0.028</p> <p><i>With Underlying Psychotic Disorder</i></p> <p>1) 32/68</p> <p>2) 41/93</p>	<p>Fernandez APA 2017a ⁷⁸</p>

					OR: 1.38; p=0.342	
Tetrabenazine (TBZ)						
Miguel R, Ther Adv Neurol Disord. 2017 84	Retrospective observational study	TBZ Initial TBZ dose was 12.5mg and maximum daily dose was 37.5mg.	Inclusions: All consecutive patients with hyperkinetic movement disorders who were under TBZ treatment, observed between 1 January 2006 and 31 December 2015, in Egas Moniz Hospital Outpatient Clinic were included.	Tardive OM dysk patients Males, n (%) 35 (45.7)	<i>Tardive OM dysk patients</i> Total responder, (n) 27	Tardive OM dys / TS patients AE, n (%)
	Duration of TBZ treatment, months Median: 40 Range: 1 – 239	<i>Tardive Oromandibular Dyskinesia</i> (n=35) <i>Other Tardive Syndrome*</i> (n=22) Other TS population is defined as patients with dystonia, chorea, akathisia and tic manifestations.	Exclusion: Insufficient follow up or insufficient compliance information.	Age at TBZ onset, yrs 75 Concomitant medication, n (%) 4 (11.4) Duration of motor symptoms before TBZ onset, m 12	Asymptomatic responders, n (%) 3 (11.1) Improvement but symptomatic, n (%) 24 (88.9) Nonresponder, (n) 8 Responder rate, (%) 77.1	21 (60)/ 9 (40.9) Parkinsonism, n (%) 14 (40)/ 7 (31.8) Psychiatric disorders, n (%) 3 (8.6)/ 1 (4.5) *Other side effects, n (%) 3 (8.6)/ 2 (9.1)
	Study population: Patients with hyperkinetic movement (e.g. Tardive OM dyskinesia, TS, HD, chorea)	*Total population on TBZ (n=111), subpopulations of focus mentioned above		Other TS patients Males, n (%) 22 (13.4) Age at TBZ onset, yrs 64.5 Concomitant medication, n (%) 10 (47.6) Duration of motor symptoms before TBZ onset, m	<i>Other TS patients</i> Total responder, (n) 21 Asymptomatic, n (%) 3 (14.3) Improvement but symptomatic, n (%) 18 (85.7) Nonresponder, (n) 1	All patients AE, n (%) 52 (48.1) Parkinsonism, n (%) 29 (26.9) Psychiatric disorders, n (%) 14 (13) *Other side effects, n (%) 11 (10.2)

				12	Responder rate, (%) 95.5	*Somnolence, rash, mental confusion
Kazamatsuri H Arch Gen Psychiat 1972⁹ Poor	Non- randomized cross over study Duration of follow-up: 6 weeks At four weeks, all patients were placed on placebo, and all the neuroleptic drugs were completely withdrawn for four weeks.	PBO (4 weeks) TBZ (6 weeks) 50mg daily for first 2 weeks, 100mg daily for next 2 weeks, 100 or 150mg daily for last 2 weeks. PBO (2 weeks) Total N (n = 24)	Inclusions: All patients on the chronic wards of Boston State Hospital with oral dyskinesia. Exclusion: Patients with borderline cases not showing clear oral dyskinesia were eliminated.	Males, (n) 13 Mean age, yrs (range) 55 (30-81) Mean length of psychiatric hospitalization, yrs (range) 28.8 (10-52) Psychiatric diagnoses, n Chronic schizophrenia: 17 Chronic brain syndrome: 4 Mental deficiency: 3 Baseline oral dyskinesia mean frequency/minute: 29.6	Oral dyskinesia Mean frequency/ minute: 1) 30 (after 4 weeks of PBO) 2) 10.8 (after 6 weeks of PBO) p value 2 vs.1 <0.0005 Efficacy of TBZ compared with PBO, n (%) At 2 weeks: 100% symptoms disappearance: 3 (12.5) 50% or more reduction: 9 (37.5) At 4 weeks 100% symptoms disappearance: 4 (16.7) 50% or more reduction: 13 (54) At 6 weeks 100% symptoms disappearance: 8 (33.3) 50% or more reduction: 9 (58.3)	TBZ related AE, n (%) Severe malaise, 2 (8.3) Psychotic exacerbation 1 (4.2)

Jankovic J Neurology 1988 ⁸²	Single-Arm, Open Label, Long term Study Mean follow-up, m (range): 18 (1 to 80) Study population: Patients with hyperkinetic movement (e.g. TD, Huntington's disease, Tourette's syndrome)	1) TBZ Tardive dyskinesia (n=44) patients started on 25mg/d, dose increase of 25mg/d until 100 mg was reached/patient noted adverse side effects. Tardive dystonia (n=15) patients started on 25mg/d and dose increase of 25mg/d until 100 mg was reached/pt noted adverse side effects *Total population on TBZ (n=217), subpopulations of focus mentioned above	Inclusions: Patients with movement disorder interfering with activities of daily living or with their job; and must have failed all other conventionally used medication (e.g. patients with TD must have been first treated with reserpine).	Tardive dyskinesia Mean age at onset of movement disorder, yrs (range) 60.4 (34-83) Mean duration of symptoms before TBZ, yrs (range) 2.5 (0.5-11) Mean duration of TBZ therapy, m 21.1 (0.12-79) Tardive dystonia Age at onset of movement disorder, yrs 36.1 (2-67) Mean duration of symptoms before TBZ, yrs (range) 3.9 (0.2-21) Mean duration of TBZ therapy, m 15.7 (0.75-57)	*Global response scale (1 = marked improvement, 2 = moderate improvement, 3 = fair improvement, 4 = no response, 5 = worsening) <u>Tardive dyskinesia</u> Average response to TBZ Scale* of 1-5: 2.3 Response to TBZ on a scale of 1-5, n (%) Marked improvement, 6 (14) Moderate improvement, 25 (57) Fair improvement, 11 (25) No response, 1 (2) Worsening, 1 (2) <u>Tardive dystonia</u> Average response to TBZ Scale* of 1-5: 2.6 Response to TBZ Scale of 1-5, n Marked improvement, 0 Moderate improvement, 8 Fair improvement, 6 No response, 1 Worsening, 0	*TBZ related AE, n Parkinsonism, 53 Drowsiness/ fatigue, 28 Depression, 23 Anxiety, 16 Insomnia, 11 Akathisia, 10 *(n=217) – Total population on TBZ
Jankovic J Neurology 1997 ¹²	Single-Arm, Open Label, Long term Study	1) TBZ Treatment regimen was modified during the study: Patients seen before 1991 were started at 25 mg/d,	Inclusions: Patients with various hyperkinetic movement disorders	Tardive dyskinesia (n=93) Males; Females, n 22; 71 Mean age at onset of movement disorder, yrs	*Global response scale (1 = marked improvement, 2 = moderate improvement, 3 = fair improvement, 4 = no response, 5 = worsening)	TBZ related AE, n (%) Drowsiness/ fatigue 146 (36.5)

	Mean follow-up, m (range): 28.9 (0.25 to 180)	with a dose increase of 25 mg/d until a total dose of 150-200 mg/d was reached or observed side effect. Patients seen since 1991 were maintained at a dose of 25 to 75 mg/d. <i>Tardive dyskinesia (n=93)</i> <i>Tardive dystonia (n=82)</i> *Total population on TBZ (n=400), subpopulations of focus mentioned above	Exclusions: A single evaluation without a follow-up visit, insufficient information about response, discontinued TBZ within the first 2 weeks, already on TBZ when first seen in the clinic, or noncompliant (n=126/526)	63 (7-86) Maximum daily dose, mg 96 (25-400) Duration of TBZ therapy, m 35 (0.3-171) <i>Tardive dystonia (n=82)</i> Males; Females, n 22; 60 Mean age at onset of movement disorder, yrs 45 (2-72) Maximum daily dose, mg 125 (38-400) Duration of TBZ therapy, m 32 (0.75-180) <i>All patients</i> Mean duration of symptoms before TBZ, yrs 6.6 (3 weeks to 48 years)	<i>Tardive dyskinesia</i> Response to TBZ Scale* of 1-5, n (%) <table><tr><th></th><th>1) IR[†]</th><th>2) LR[†]</th></tr><tr><td>1</td><td>83 (89.2 4)</td><td>79 (84.9)</td></tr><tr><td>2</td><td>4 (4.3)</td><td>7 (7.4)</td></tr><tr><td>3</td><td>2 (2.1)</td><td>1 (1.1)</td></tr><tr><td>4</td><td>4 (4.3)</td><td>5 (5.3)</td></tr><tr><td>5</td><td>0</td><td>1 (1.18)</td></tr></table> <i>Tardive dystonia</i> Response to TBZ Scale* of 1-5, n (%) <table><tr><th></th><th>1) IR[†]</th><th>2) LR[†]</th></tr><tr><td>1</td><td>66 (80.5)</td><td>60 (73.2)</td></tr><tr><td>2</td><td>6 (7.3)</td><td>8 (9.8)</td></tr><tr><td>3</td><td>7 (8.5)</td><td>7 (8.5)</td></tr><tr><td>4</td><td>3 (3.7)</td><td>3 (3.7)</td></tr><tr><td>5</td><td>0</td><td>0</td></tr></table> †IR – Initial Response (3 to 6 months after starting TBZ) †LR- Response at last visit		1) IR [†]	2) LR [†]	1	83 (89.2 4)	79 (84.9)	2	4 (4.3)	7 (7.4)	3	2 (2.1)	1 (1.1)	4	4 (4.3)	5 (5.3)	5	0	1 (1.18)		1) IR [†]	2) LR [†]	1	66 (80.5)	60 (73.2)	2	6 (7.3)	8 (9.8)	3	7 (8.5)	7 (8.5)	4	3 (3.7)	3 (3.7)	5	0	0	Parkinsonism 114 (28.5) Depression, 60 (15.0) Insomnia, 44 (11.0) Anxiety, 41 (10.3) Akathisia, 38 (9.5) *Total population on TBZ (n=400)
	1) IR [†]	2) LR [†]																																								
1	83 (89.2 4)	79 (84.9)																																								
2	4 (4.3)	7 (7.4)																																								
3	2 (2.1)	1 (1.1)																																								
4	4 (4.3)	5 (5.3)																																								
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3	7 (8.5)	7 (8.5)																																								
4	3 (3.7)	3 (3.7)																																								
5	0	0																																								
Paleacu D Clin Neuropharmacol 2004 ¹¹	Retrospective observational study	1) TBZ <i>Tardive dyskinesia</i>	Inclusions: Patients with a hyperkinetic movement	Total Population on TBZ Mean Age, yrs 48.8	<i>Tardive dyskinesia</i> CGIC Scale* of 1-5, n	Total Population on TBZ TBZ related AE, n																																				

	Mean follow-up time, m 22	(n=17) starting dose of 12.5 mg BID, dose increase of 25 mg once a week to a target dose of 150 mg/d in 2 or 3 divided doses daily. *Total population on TBZ (n=118), subpopulation of focus mentioned above	disorder including dystonia, Huntington disease (HD) or other choreas, tardive dyskinesia (TD) or akathisia, and Tourette syndrome.	Males, n 48 Mean disease duration, m 93 Mean TBZ dose, mg/d (range) 76.2 (25-175) Mean CGIC score +1 (mild improvement)	<table><tr><th colspan="2">No Response or Worsening</th></tr><tr><td>0</td><td>4</td></tr><tr><td>-1</td><td>1</td></tr><tr><td>-2</td><td>N o n e</td></tr><tr><td>-3</td><td>N o n e</td></tr><tr><th colspan="2">Improved</th></tr><tr><td>1</td><td>3</td></tr><tr><td>2</td><td>6</td></tr><tr><td>3</td><td>1</td></tr></table> <p>Impression of Change (CGIC) –3 was marked worsening, –2 moderate worsening, –1 mild worsening, 0 no change, +1 was mild improvement, +2 moderate improvement, and +3 marked improvement</p>	No Response or Worsening		0	4	-1	1	-2	N o n e	-3	N o n e	Improved		1	3	2	6	3	1	No data: 2 *Clinical Global	*Somnolence/ Weakness/Apathy, 5 Depression, 2 Parkinsonism, 6 Acute akathisia, 1 Tardive dyskinesia TBZ related AE, n *Somnolence/ Weakness/Apathy, 2 Worsening of underlying condition, 2 *4/7 patients among this group discontinued treatment.
No Response or Worsening																									
0	4																								
-1	1																								
-2	N o n e																								
-3	N o n e																								
Improved																									
1	3																								
2	6																								
3	1																								
Kenney C Mov Disorders 2007 ⁸³	Retrospective observational study Time frame – 1997-2004	1) TBZ January 1997- 2004 (n=448) Patients treated with TBZ 50-75 mg/d; 18.2% of patients required doses greater than 75 mg/d (range: 12.5–300 mg/d).	Inclusions: Patients with involuntary movements that were troublesome or disabling despite optimal conventional therapy.	Tardive dyskinesia (n=149) Mean age at onset of movement disorder, yrs 59.8 TBZ treatment duration, yrs 2.5 Baseline severity (prior to TBZ), %	Tardive Dyskinesia Efficacy response to TBZ Scale* of 1-5, % <table><tr><th></th><th>Initial Resp onse</th><th>Last respo nse</th></tr><tr><td>1</td><td>65%</td><td>71%</td></tr></table>		Initial Resp onse	Last respo nse	1	65%	71%		*TBZ related AE, n (%) Drowsiness, 112 (25) Parkinsonism, 69 (15.4) Depression, 34 (7.6)												
	Initial Resp onse	Last respo nse																							
1	65%	71%																							

	Mean follow-up time: 2.3 -3.4 years			Mild, 1.3; Moderate, 40.3; Severe, 50.3; Disabling, 8.1 Tardive dystonia (n=132) Mean age at onset of movement disorder, yrs 44.6 TBZ treatment duration, yrs 3.0 Baseline severity (prior to TBZ), % Mild, 0; Moderate, 37.4; Severe, 45.8; Disabling, 16.8 All patients (n=448) Mean daily dose of TBZ: 60.4 mg/d	<table><tr><td>2</td><td>18%</td><td>13%</td></tr><tr><td>3</td><td>6%</td><td>4%</td></tr><tr><td>4</td><td>5%</td><td>5%</td></tr><tr><td>5</td><td>3%</td><td>3%</td></tr></table> <i>Tardive Dystonia</i> Efficacy response to TBZ Scale* of 1-5, % <table><tr><th></th><th>Initial Resp onse</th><th>Last respo nse</th></tr><tr><td>1</td><td>45%</td><td>45%</td></tr><tr><td>2</td><td>21%</td><td>23%</td></tr><tr><td>3</td><td>12%</td><td>10%</td></tr><tr><td>4</td><td>18%</td><td>16%</td></tr><tr><td>5</td><td>2%</td><td>3%</td></tr></table> *Modified AIMS score (1 = marked improvement, 2 = moderate improvement, 3 = fair improvement, 4 = no response, 5 = worsening) (% values in both tables are represented as approximate values from the text).	2	18%	13%	3	6%	4%	4	5%	5%	5	3%	3%		Initial Resp onse	Last respo nse	1	45%	45%	2	21%	23%	3	12%	10%	4	18%	16%	5	2%	3%	Akathisia, 34 (7.6) Nausea/Vomiting 25 (5.6) *Total population on TBZ (n=448)
2	18%	13%																																		
3	6%	4%																																		
4	5%	5%																																		
5	3%	3%																																		
	Initial Resp onse	Last respo nse																																		
1	45%	45%																																		
2	21%	23%																																		
3	12%	10%																																		
4	18%	16%																																		
5	2%	3%																																		
Ondo W AM J psych 1999 ¹⁰	Randomized single-blind Mean duration of follow-up – 20.3 weeks Patients stopped taking offending	1) TBZ (n=20) starting dose of 12.5/mg BID and then increased to a maximum of 50/mg TID in weekly increments until satisfactory benefit was experienced or if adverse events became troublesome.	Inclusions: Patients diagnosed with TD who didn't respond to conventional anti-tardive-dyskinesia treatment Patients were required to stop taking offending medications at least 30 days before start of study	Females:75% Mean age, yrs: 65.2 Drugs causing TD, n Metoclopramide:7 Haloperidol: 7 Chlorpromazine:2 Perphenazine: 1 Thiethylperazine: 1 Amoxapine: 1	Improvement in AIMS score, Mean change from baseline By blinded raters 9.7 (p<0.001) Subjective 5.5 (p<0.001)	TBZ related AE, n Sedation, 5 Mild Parkinsonism, 5																														

<p>Watson MW Can J Psych 1988 ⁸⁵</p>	<p>medications and any other treatments for tardive dyskinesia at least 30 days before they entered the study.</p> <p>Open-label, case series</p> <p>Treatment duration: NR; Case series follow-up duration: up to 4 years</p>	<p>1) TBZ (n=23) QD or TID: 37.5–150 mg/day (mean dose: 91.3 mg/day)</p> <p>Dosage had been adjusted to achieve satisfactory control of abnormal movements; always starting with a small dose and increasing only if adequate control was not achieved.</p>	<p>Patients with tardive dyskinesia.</p>	<p>Fluphenazine:1</p> <p>Mean duration of TD, m 43.7 (2-420)</p> <p>Mean TBZ dose, mg/d (SD) 57.9 (22.8)</p> <p>Mean baseline AIMS score (SD) By blinded raters 17.9 (4.4) Subjective score 9.1 (1.5)</p> <p>Females, n 18</p> <p>Males, n 5</p> <p>Age range 29-88</p> <p>Drugs causing TD, n Antipsychotic, 21 Metoclopramide, 2</p>	<p>Involuntary movement scale:</p> <p>0- None 1 -Minimal (may be extreme normal) 2-Mild 3 - Moderate 4 – Severe</p> <p>N=23 Baseline overall appearance: 0; 0/23 1; 0/23 2; 4/23 3; 12/23 4; 7/23</p>	<p>TBZ-related AE, n</p> <p>Drooling, 2</p> <p>Parkinsonism with Tremor, 1</p>
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					After TBZ overall appearance: 0; 9/23 1; 11/23 2; 3/23 3; 0/23 4; 0/23	
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Appendix H. Comparative Value Supplemental Information

Table H1: Impact Inventory ¹¹⁹

Sector	Type of Impact	Included in This Analysis from... Perspective?		Notes on Sources
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
	Health-related quality of life effects	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
	Adverse events	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
Medical Costs	Paid by third-party payers	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
	Paid by patients out-of-pocket	<input type="checkbox"/>	<input type="checkbox"/>	
	Future related medical costs	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
	Future unrelated medical costs	<input type="checkbox"/>	<input type="checkbox"/>	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	<input type="checkbox"/>	
	Unpaid caregiver-time costs	NA	<input type="checkbox"/>	
	Transportation costs	NA	<input type="checkbox"/>	

Non-Health Care Sectors				
Productivity	Labor market earnings lost	NA	<input checked="" type="checkbox"/>	
	Cost of unpaid lost productivity due to illness	NA	<input type="checkbox"/>	
	Cost of uncompensated household production	NA	<input type="checkbox"/>	
Consumption	Future consumption unrelated to health	NA	<input type="checkbox"/>	
Social Services	Cost of social services as part of intervention	NA	<input type="checkbox"/>	
Legal/Criminal Justice	Number of crimes related to intervention	NA	<input type="checkbox"/>	
	Cost of crimes related to intervention	NA	<input type="checkbox"/>	
Education	Impact of intervention on educational achievement of population	NA	<input type="checkbox"/>	
Housing	Cost of home improvements, remediation	NA	<input type="checkbox"/>	
Environment	Production of toxic waste pollution by intervention	NA	<input type="checkbox"/>	
Other	Other impacts (if relevant)	NA	<input type="checkbox"/>	

Table H2. Drug Cost Inputs

Drug Name, Labeled Dose, Administration Route	Package Size	WAC per Package	Annual WAC	Annual Net Price*	Source
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Valbenazine 80mg Oral	80mg 30s ea	\$6,225	\$75,789	\$55,326	Redbook, 2017 ³⁰ , Aitkin et al., 2016 ²⁹
Deutetrabenazine 36mg Oral	9mg 60s ea	\$3,699	\$90,071	\$65,751	Redbook, 2017 ³⁰ Aitkin et al., 2016 ²⁹
*Assumed discount of 27%					

Table H3. Non- Drug Cost Inputs

	Base Case Estimate	Source
General Practitioner Visit (CPT Code 99213, Non-Institutional Charge)	\$73.93	2017 Physician Fee Schedule ⁹⁶
Specialist (Neurologist) Visit (CPT Code 99213, Non-Institutional Charge)	\$108.74	2017 Physician Fee Schedule ⁹⁶

Table H4. Utility Inputs

Parameters	Base Case Value	Reference	Notes
Baseline Utility for Modeled Population	0.82	Wang 2004 ²⁴ Calvert 2006 ²³	Weighted average of patients with schizophrenia disorders (0.83) and bipolar disorders (0.80).
Utility Decrement from TD	0.095	Lenert 2004 ¹²⁰	Assumed constant across age and underlying condition.

Table H5. Probabilistic Sensitivity Analysis Inputs

Input Varied	Distribution
Proportion of Placebo Responders (Valbenazine Comparison) ¹⁸	Beta ($\alpha = 6.61$, $\beta = 69.39$, $\mu = 8.7$)
Proportion of Valbenazine Responders ¹⁸	Beta ($\alpha = 31.60$, $\beta = 47.40$, $\mu = 40.0$)
Proportion of Placebo Responders (Deutetrabenazine Comparison) ¹⁹	Beta ($\alpha = 7.00$, $\beta = 51.00$, $\mu = 12.0$)
Proportion of Deutetrabenazine Responders ¹⁹	Beta ($\alpha = 24.50$, $\beta = 49.50$, $\mu = 33.1$)
Valbenazine Discontinuation Rate ^{18,94}	Beta ($\alpha = 43.70$, $\beta = 186.30$, $\mu = 19.0$)
Deutetrabenazine Discontinuation Rate ²²	Beta ($\alpha = 2$, $\beta = 13.4$, $\mu = 13.0$)
Disutility with TD	Beta ($\alpha = 95$, $\beta = 905$, $\mu = 9.5$)
Annual Cost of TD	Uniform (min = 183, max = 548, $\mu = 365.34$)

Annual Cost of Valbenazine	Uniform (min = 27,726, max = 83,177, μ = 55,451)
Annual Cost of Deutetrabenazine	Uniform (min = 32,854, max = 98,561, μ = 65,707)

Figure H1. Incremental Cost-Effectiveness Scatterplot of Valbenazine – Placebo

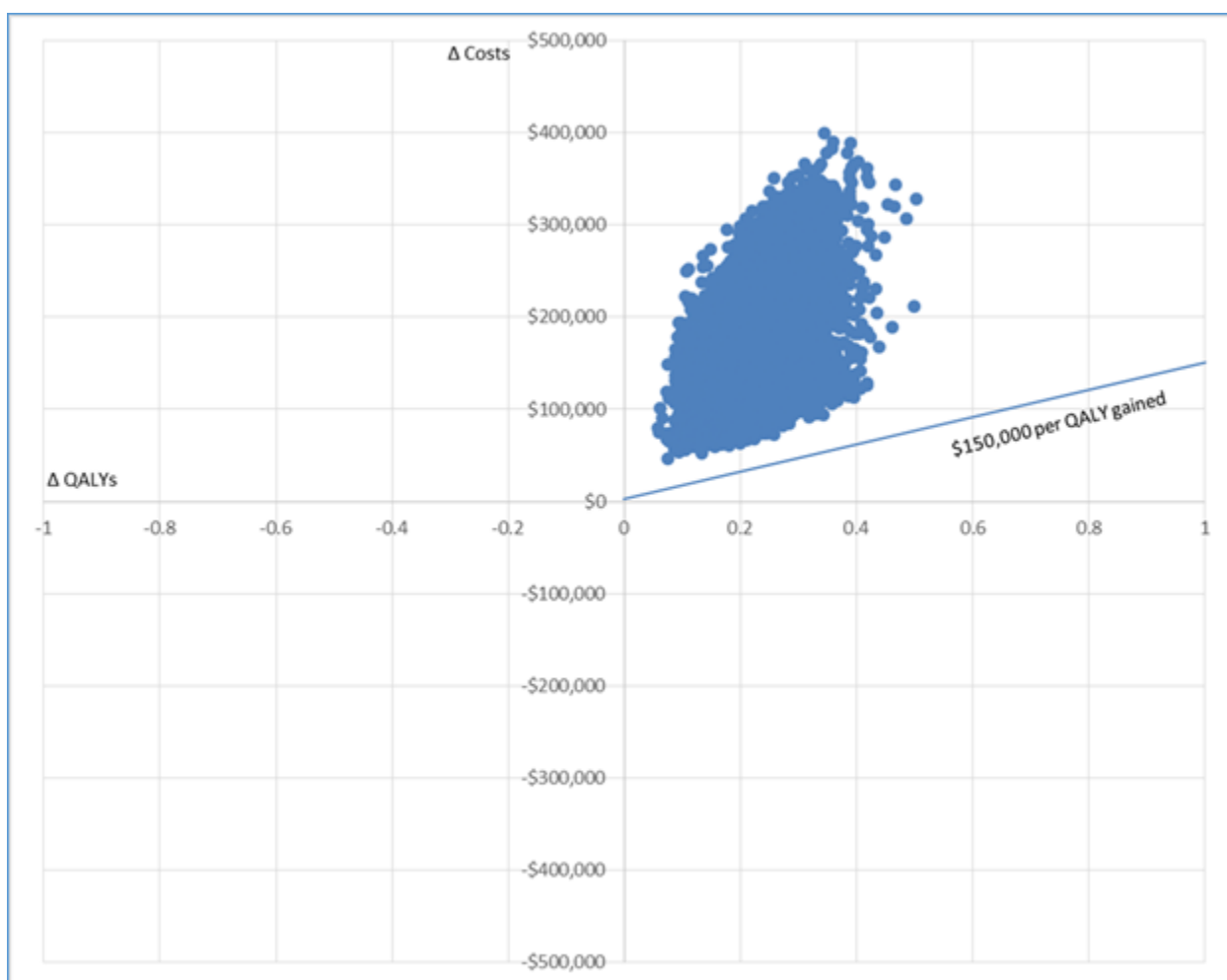
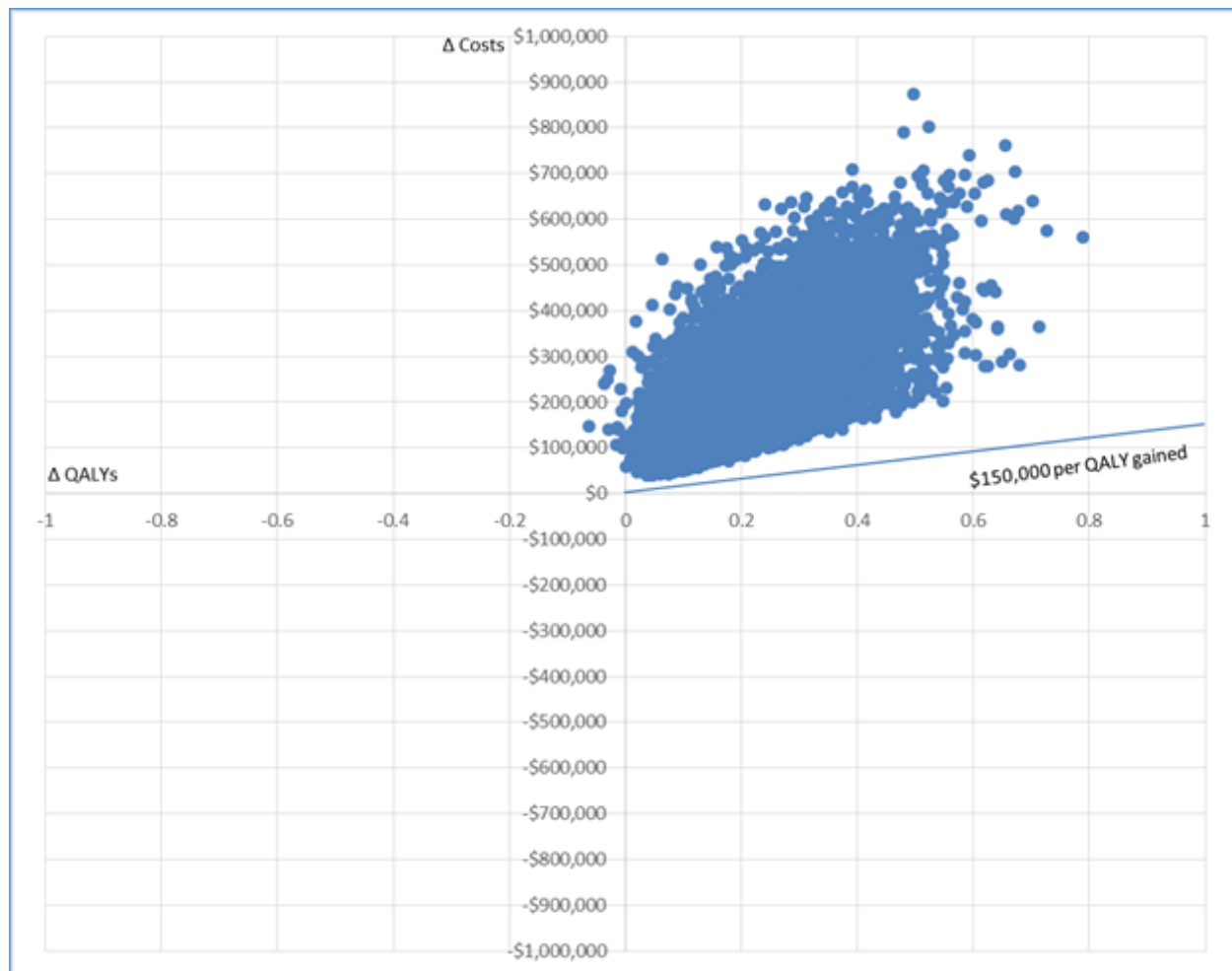


Figure H2. Incremental Cost-Effectiveness Scatterplot of Deutetrabenazine – Placebo



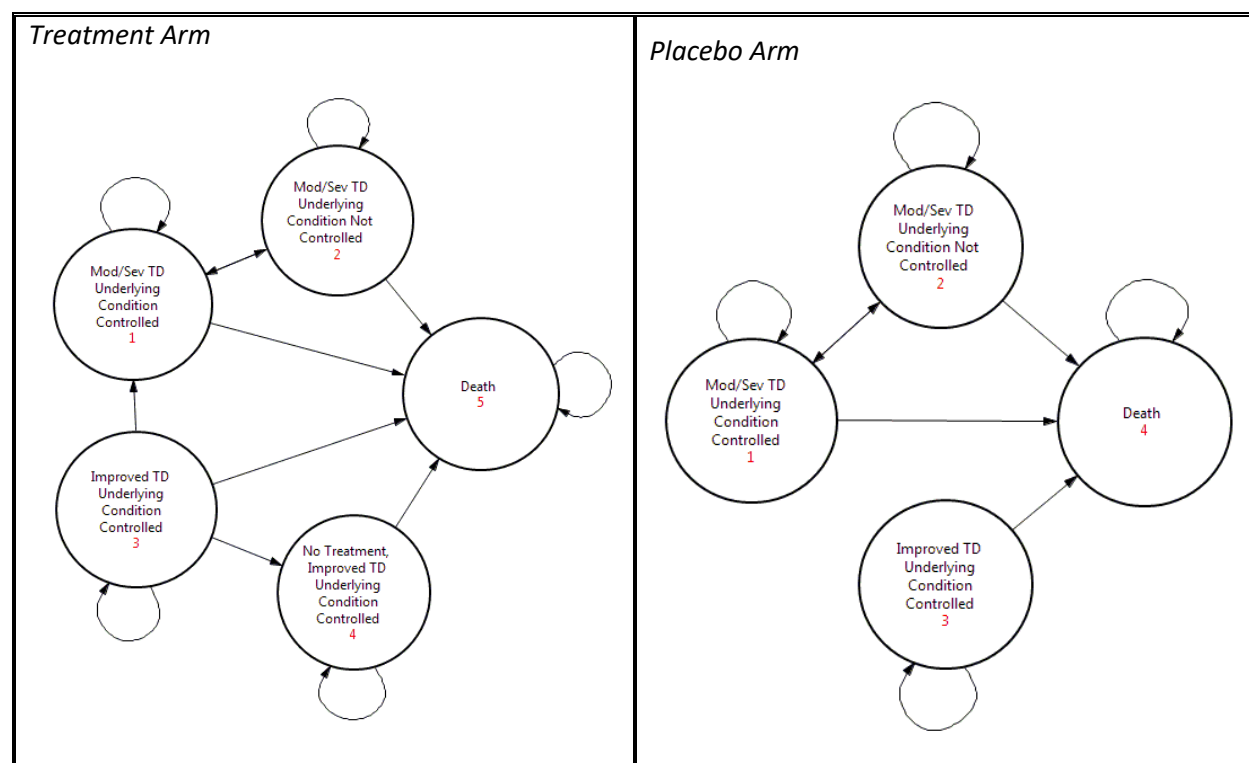
Scenario Analyses

Effect of TD medication on underlying affective disorders

The five main health states for the scenario analyses are as follows: 1) moderate to severe TD with the underlying condition well controlled, 2) moderate to severe TD with the underlying condition poorly controlled, 3) improved TD (on TD treatment) with the underlying condition well controlled, 4) improved TD (without TD treatment) with the underlying condition controlled, and 5) death (Figure H3). It has been hypothesized that improved tardive dyskinesia control results in better management of the underlying conditions. In these scenario analyses, treatment with valbenazine and deutetrabenazine were modeled to improve management of schizophrenia/schizoaffective disorders and bipolar disorders, resulting in additional utility gains and reduced total costs. To model this possibility, patients with moderate to severe TD were given a 10% probability each year of having their underlying condition become poorly controlled. Control of the underlying condition

was assumed to be re-established each subsequent cycle. The probability of developing poorly controlled schizophrenia/schizoaffective disorder or bipolar disorder was varied in a threshold analysis from 0-100%.

Figure H3. Scenario Analysis Model Structure



Additional model inputs were utilized in the scenario analyses (Table H6). These additional inputs were obtained from published literature where possible. In particular, the proportion of patients with TD becoming non-adherent to their antipsychotic medication had no associated data in the literature so a potential effect was used. The annual costs of well-controlled and poorly-controlled schizophrenia/schizoaffective and bipolar disorders were taken from the literature and then inflation adjusted to 2016.

Table H6. Additional Model Inputs for the Scenario Analysis on Effect of TD Medication on Underlying Affective Disorders

Parameters	Value	Reference	Notes
Proportion of Patients with TD Becoming Non-adherent to Antipsychotics	10.0%	Unknown; assumed	Applied each cycle
Annual Cost of Well Controlled Schizophrenia/Schizoaffective Disorders	\$22,175	Peng 2011 ¹²¹	Inflation-adjusted to Dec. 2016
Annual Cost of Poorly Controlled Schizophrenia/Schizoaffective Disorders	\$31,253	Peng 2011 ¹²¹	Inflation-adjusted to Dec. 2016
Annual Cost of Well Controlled Bipolar Disorder	\$6,568	Calvert 2006 ²³	Inflation-adjusted to Dec. 2016
Annual Cost of Poorly Controlled Bipolar Disorder	\$10,722	Calvert 2006 ²³	Inflation-adjusted to Dec. 2016
Productivity Losses Due to TD	\$2,252	Ascher-Svarnum 2008 ¹⁰¹	Based on study of employment differences with TD and median salary in the US in 2016
Disutility Resulting from Poorly Controlled Schizophrenia/Schizoaffective Disorders	-0.27	Wang 2004 ²⁴	
Disutility Resulting from Poorly Controlled Bipolar Disorder	-0.24	Calvert 2006 ²³	

Alternative Time Horizons

Table H7. Incremental Cost-Utility, Alternative Time Horizons

Base Case Versus Placebo	Valbenazine	Deutetrabenazine
	Incremental Cost per QALY	Incremental Cost per QALY
1-year	\$826,288	\$1,250,704
2-year	\$787,701	\$1,173,819
5-year	\$764,081	\$1,126,119

Appendix I. Summaries of Oral Comment

Chuck Yonan, PharmD.

**Senior Director of Health Economics Outcomes Research, Medical Affairs
Neurocrine Biosciences**

Neurocrine Biosciences would like to thank ICER for the opportunity to comment on the report.

Neurocrine takes great pride in the discovery and development of valbenazine and the value the treatment provides for patients suffering with tardive dyskinesia. We agree that there had been a significant unmet need for a safe and effective therapy. We also agree that off label products should not be included in the report due to the lack of safety and efficacy evidence.

Valbenazine and its development program provided high quality data showing the greatest treatment effect size of the reviewed agents and that our 3 long-term 1-year extension trials add to the efficacy and safety knowledge base. These data should lead to a better evidence grade than Promising/Inconclusive.

We applaud your collaboration with DBSA and other patient advocacy groups to help inform an understanding of the burden of TD symptoms and the value of treatment.

We assert any assessment of treatment value should consider individual patient information such as the underlying psychiatric condition and its severity, the TD symptom location and severity and the impact of TD on daily function and socialization for both patients and caregivers. Most importantly, such an assessment should include how the treatment affects each of these aspects, not just the symptoms.

We have seen the impact of life altering responses to valbenazine treatment and we agree this is very difficult to model.

Finally, we agree that, of the two products evaluated, valbenazine is the best and lowest cost agent.

Victor Abler, DO,
Senior Global Medical Director, Neurodegenerative Disorders
Teva Pharmaceuticals

ICER TD Evaluation Public Meeting – Teva Statement

Thank you for this opportunity to provide remarks on this evaluation of VMAT-2 class inhibitors for treating tardive dyskinesia (TD).

There are limited treatment options for TD, and people living with this condition face enormous stigma. TD has a serious impact on physical, functional and emotional well-being.

I'd like to emphasize a few key considerations, particularly the limitations of the ICER evaluation's design.

- Given lack of scientific evidence for this indication, using a cost-utility model to assess the value for TD treatments is premature. ICER's cost utility approach does not capture the full patient experience or the significant burden experienced by patients.
- ICER's calculations of direct healthcare utilization costs fails to account for the full scope of costs due to TD. For example, antipsychotic dose reduction, which is a common treatment, may potentially increase healthcare utilization costs. Treating TD allows for consistent APD dosing by the clinician.
- Teva questions the appropriateness of including tetrabenazine in the evaluation. Tetrabenazine is not FDA-approved for treating TD and data using tetrabenazine in TD is scarce. The American Academy of Neurology's guidelines suggest weak evidence that tetrabenazine reduces TD symptoms.
- The draft report states that ICER modeled the effects and costs of the highest doses reported in clinical trial (36 milligrams/day) because those doses were, and I quote, "generally associated with the highest effects;" however, the lowest effective dose was determined to be 24 milligrams in the Phase III AIM-TD trial. The label states that the dose of AUSTEDO is determined individually for each patient based on reduction of TD and to titrate up to a maximum dose of 48 milligrams based on tolerability and efficacy.
- Lastly, as the majority of patients with TD have underlying psychiatric conditions, adherence to medications in this patient population may be a challenge. This should also be considered in the economic models of any medication use in this patient population.

Our hope is that the final ICER evaluation takes these important points into consideration and does not ultimately limit access for appropriate patients.

Daniel Tarsy MD**Professor in Neurology; Harvard Medical School****Parkinson Disease & Movement Disorders Center; Beth Israel Deaconess Medical Center**

The point is currently made by pharmaceutical companies who manufacture the two new tetrabenazine congeners, valbenazine and deutetrabenazine, to psychiatrists and neurologists in publications and at professional meetings is that the advantage of the new tetrabenazine formulations is they can be safely administered to patients still taking an antipsychotic drug (APD), including even the one responsible for their tardive dyskinesia (TD). Although this has been true in short-term studies it goes against the usual more prudent recommendation that, if psychiatrically safe, an APD the patient is taking should be tapered and discontinued before treating with a tetrabenazine congener in order to see if the TD remits. The rationale for this recommendation is that TD may remit if the APD drug is stopped. In a significant although uncertain proportion of patients' TD is not necessarily a permanent condition. A recent often cited published report that TD is permanent in a very large proportion of patients was based on possibly skewed data coming from a major movement disorders center likely to be seeing patients with more persistent examples of TD. In addition, the safety of long-term treatment (greater than 2 years) with these two new tetrabenazine congeners, when given together with an APD, has not yet been established by publication in a peer-reviewed journal. The possibility should be considered that long-term use of a dopamine receptor blocker (APD) together with a presynaptic dopamine depletor (tetrabenazine congener) could possibly reduce the likelihood of eventual remission of TD.

Appendix J. Conflict of Interest Disclosures for External Meeting Participants

Victor Abler, DO. Senior Global Medical Director for Neurodegenerative Diseases; Teva Pharmaceuticals

Do you have a relationship with any health care company (life sciences manufacturer, health plan, health plan association, life sciences manufacturer association, etc.) that falls under any of the following categories? A relationship extends to anyone in your household and/or any entity in which you have an interest. Please mark all that apply within the last 12 months.

- Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of \$5,000
- Equity interests such as individual stocks, stock options or other ownership interests in excess of \$10,000. Ownership of stock in a mutual fund over which an individual has no trading

Disclosure: I am a full-time employee of Teva and receive a salary and stock options from Teva Pharmaceuticals

Teri Brister, PhD. Director Knowledge Integration Information; National Alliance on Mental Illness

Do you have a relationship with any health care company (life sciences manufacturer, health plan, health plan association, life sciences manufacturer association, etc.) that falls under any of the following categories? A relationship extends to anyone in your household and/or any entity in which you have an interest. Please mark all that apply within the last 12 months.

- Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of \$5,000

Disclosure: NAMI is the recipient of grant funds through a variety of entities including industry partners and foundations.

Arthur Allen Doederlein, President, Depression and Bipolar Support Alliance

Do you have a relationship with any health care company (life sciences manufacturer, health plan, health plan association, life sciences manufacturer association, etc.) that falls under any of the following categories? A relationship extends to anyone in your household and/or any entity in which you have an interest. Please mark all that apply within the last 12 months.

- Status or position as an officer, board member, trustee, owner or employee of a health care company, or an organization which receives more than 25% of its funding from health care

Disclosure: DBSA's mean level of support from healthcare companies across 2014-2016 was 42%, which is roughly on par with DBSA's funding since c. 2005.

Healthcare company contributions are accepted only for DBSA-initiated programming for which DBSA has sole creative, approval, and dissemination authority.

Oliver Freudenreich, MD; Co-Director, MGH Schizophrenia Clinical and Research Program

Do you have a relationship with any health care company (life sciences manufacturer, health plan, health plan association, life sciences manufacturer association, etc.) that falls under any of the following categories? A relationship extends to anyone in your household and/or any entity in which you have an interest. Please mark all that apply within the last 12 months.

- Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of \$5,000
- Manufacturer support of research in the clinical area of this meeting in which you are participating

Disclosure:

- Avanir (PI - research grant)
- Neurocrine (CME talk – Honoraria)
- Janssen (PI - research grant; Advisory Board)
- Otsuka (Site-PI - research grant)
- Global Medical Education (CME speaker and content developer - Honoraria)
- Wolters-Kluwer (content developer - royalties)
- UpToDate (content developer and editor - royalties, honoraria)

Patrick Hendry; Vice President of Peer Advocacy Support and Services; Mental Health America

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Disclosure: Provided first person patient perspective to Neurocrine Life Sciences and Teva about experience of living with TD. None of these activities pertained to their medications. My organization was paid for my participation.

Barbara Henry RPh; Lead Clinical Pharmacy Specialist; Harvard Pilgrim

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- Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of \$5,000

Disclosure: I am an employee at Harvard Pilgrim Health Care.

Paul L. Jeffrey, PharmD; Director of Pharmacy; MassHealth

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- Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of \$5,000

Disclosure: I am an employee of MassHealth.

Daniel Tarsy, MD. Professor of Neurology; Parkinson's Disease and Movement Disorders Center; Beth Israel Hospital; Harvard Medical School

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Disclosure: I have no conflicts of interest as defined in the above categories

Chuck Yonan, PharmD. Senior Director HEOR, Medical Affairs; Neurocrine Bioscience

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- Equity interests such as individual stocks, stock options or other ownership interests in excess of \$10,000. Ownership of stock in a mutual fund over which an individual has no trading

Disclosure: I am employed by Neurocrine Biosciences