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

Public Meeting – December 5, 2017

Wireless Network: Marriott Conference Center Network
PW: ICER2017 (not case sensitive)
Welcome and Introduction

Why are we here today?
- Tardive dyskinesia can profoundly affect patients and families, and new drugs offer the potential for important benefits.

_Involuntary muscle movements in the mouth and face region, facial grimacing, lip smacking and other symptoms associated with TD carry enormous social stigma. This in turn leads to further social isolation and exacerbation of the negative symptoms associated with psychotic disorders such as schizophrenia. Likewise, in the case of mood disorders such as bipolar disorder the social isolation resulting from TD can further exacerbate symptoms of depression and lack of self-worth._
  - National Alliance on Mental Illness

There is no known cure for TD. That is precisely why treatments that improve the quality of life for patients who suffer from this complex disease are significant.
  - Movement Disorder Policy Coalition
Welcome and Introduction

Why are we here today?

• New treatment options often raise questions about appropriate use, cost
• Increasing health care costs affecting individuals’, state and federal budgets
An Affordability Index

Welcome and Introduction

Why are we here today?

• New treatment options often raise questions about appropriate use, cost
• Increasing health care costs affecting individuals’, state and federal budgets
• Patients can have difficulty accessing drugs
  • Tight prior authorization criteria
  • Step therapy protocols
  • Requirements to switch drugs with new insurance
  • High out-of-pocket costs
• Potential benefit of objective evaluation and public discussion of the evidence on effectiveness and value of emerging treatment options
Welcome and Introduction

• New England Comparative Effectiveness Public Advisory Council (CEPAC)

• The Institute for Clinical and Economic Review (ICER)
Sources of Funding, 2017

Funding Sources - %

- Non-profit foundations: 78%
- Manufacturer grants, contracts and contributions: 9%
- Contributions from health plans and provider groups: 3%
- Government grants and contracts: 10%

ICER Policy Summit only
Welcome and Introduction

How was the ICER report on treatments for Tardive Dyskinesia developed?

- Scoping with guidance from patients, patient groups, clinical experts, and manufacturers
- ICER evidence analysis and cost-effectiveness modeling
- Survey of patients with TD on the impact on quality of life
- Public comment and revision
- Clinical and patient expert report reviewers
  - Robert Rosenheck, MD, Yale Medical School
  - Daniel Tarsy, MD, Beth Israel Deaconess Medical Center
  - Cindy Specht, Depression and Bipolar Support Alliance (DBSA)

- How is the evidence report structured to support CEPAC voting and policy discussion?
Goal: Sustainable Access to High-Value Care for All Patients

Long-Term Value for Money
- Comparative Clinical Effectiveness
- Incremental Cost Effectiveness
- Other Benefits or Disadvantages
- Contextual Considerations

Short-Term Affordability
- Potential Budget Impact
Agenda

10:00am: Welcome and Opening Remarks
10:15 am: Patient Experience Survey
          Allen Doederlein, Depression and Bipolar Support Alliance
10:25 am: Presentation of the Evidence
          Evidence Review: Steven Atlas, MD, MPH
          Cost Effectiveness: Surrey Walton PhD; Dan Touchette PharmD, MA
11:25 pm: Manufacturer Comments and Discussion
11:45 pm: Public Comments and Discussion
12:15 pm: Lunch
1:00 pm: New England CEPAC Deliberation and Votes
2:00 pm: Policy Roundtable
3:30 pm: Reflections and Wrap Up
4:00 pm: Meeting Adjourned
Results from DBSA Survey

ALLEN DOEDERLEIN
DEPRESSION AND BIPOLAR SUPPORT ALLIANCE
TUESDAY, DECEMBER 5, 2017
DBSA receives grants and sponsorships from

ALKERMES
ALLERGAN
JANSSEN PHARMACEUTICALS, INC.,
LUNDBECK
NEUROCRINE
OTSUKA
SUNOVION
TAKE DA
TEVA
Today we will cover

• About DBSA
• DBSA Survey Center *Experiences with Tardive Dyskinesia* Survey
• What’s it Like? Words from People Who’ve Experienced Tardive Dyskinesia
The Depression and Bipolar Support Alliance, DBSA, is the leading peer-directed national organization focusing on the two most prevalent mental health conditions, depression and bipolar disorder.

DBSA envisions wellness for people living with depression and bipolar disorder. Our mission is to provided hope, help, support, and education to improve the lives of people living with mood disorders.

DBSA reaches millions of people each year with

• in-person and online peer support
• current, readily understandable information about mood disorders
• empowering tools focused on an integrated approach to wellness
Experiences with Tardive Dyskinesia

Background

• DBSA Survey Center on DBSAlliance.org
• Conducted August 14-September 4, 2017
• Prospective participants from
  ➢ DBSA newsletters
  ➢ Individual constituent and local chapter outreach
  ➢ Social media
  ➢ Colleague organizations
• 211 responded
Experiences with Tardive Dyskinesia

Diagnosis

Has a doctor, nurse or other health professional EVER told you that you had tardive dyskinesia caused by a medicine you were using? (n=211)

- Yes: 41.23%
- No: 45.97%
- Unsure: 12.80%
Experiences with Tardive Dyskinesia

Diagnosis

What health conditions do you/did you have that required you to take a medicine that caused tardive dyskinesia? Please check all that apply.
(n=87)

- Schizophrenia: 2.30%
- Schizoaffective disorder: 12.64%
- Bipolar disorder: 83.91%
- Depression: 33.33%
- Insomnia (trouble sleeping): 14.94%
- Stomach problems: 3.45%
- Other (please specify): 10.34%
Experiences with Tardive Dyskinesia

Diagnosis

How long have you had symptoms of tardive dyskinesia? (n=87)

- I no longer have symptoms: 22.99%
- More than 10 years: 11.49%
- Between 6-10 years: 13.79%
- Between 1-5 years: 28.74%
- 1 year or less: 6.90%
- 6 months or less: 16.09%
Experiences with Tardive Dyskinesia

Impact

For each of the following tardive dyskinesia symptoms, select the option that best fits your experience (n=86)

- Rocking, jerking, thrusting of mid-section or hips
- Writhing, twisting, dancing of fingers/toes
- Uncontrollable movements of the tongue, jaw or lips (such as lip smacking, grimacing, tongue darting, etc)
- Uncontrollable blinking or eye closing
How has your doctor attempted to address your tardive dyskinesia?
Please check all that apply. (n=85)

- Switched the medication that caused the tardive dyskinesia to a different one: 47.06%
- Reduced the dose or stopped the medication that caused the tardive dyskinesia: 35.29%
- Added a new medication to improve the symptoms: 35.29%
- Added a new non-prescription medication, vitamin or herbal treatment to improve the symptoms: 4.71%
- No attempts have been made: 15.29%
- Added an other form of treatment (please specify): 3.53%
Experiences with Tardive Dyskinesia

Treatment

How has your doctor’s treatment of your tardive dyskinesia impacted your symptoms? (n=72)

- **Switched the medication that caused the tardive dyskinesia to a different one**
  - Made it a lot better: 65.00%
  - Made it a little better: 15.00%
  - Stayed the same: 20.00%

- **Reduced the dose or stopped the medication that caused the tardive dyskinesia**
  - Made it a lot better: 53.33%
  - Made it a little better: 33.33%
  - Stayed the same: 13.33%

- **Added a new non-prescription medication, vitamin or herbal treatment to improve the symptoms**
  - Made it a lot better: 75.00%
  - Made it a little better: 25.00%

- **Added a new medication to improve the symptoms**
  - Made it a lot better: 40.00%
  - Made it a little better: 33.33%
  - Stayed the same: 26.67%
Experiences with Tardive Dyskinesia

Treatment

Please rate from most important (1) to least important (5) the following reasons for treating your tardive dyskinesia? (n=80)

- It could help me feel more self-confident. 2.13
- It could allow me to stay on a medication for my mental health condition that is working well for me except for the tardive dyskinesia. 2.38
- It could improve my interactions in social settings. 2.47
- It could improve my quality of life, and my ability to perform daily tasks, such as cooking and driving. 2.77
- It could reduce the burden on my family and caregivers. 3.53
- It could improve my performance at work. 3.38
Summary and Discussion

• Impact on social and leisure time, family time, and work is significant
• Over 15% of people had not yet tried anything to improve TD symptoms
• For many, treatments that have been tried have been successful in improving the symptoms
• DBSA hopes to utilize survey results to increase awareness of TD and show the negative impact this condition can have
What’s it Like?

Open-ended Survey Responses

• “It has ruined my life due to police ignorance.”
• “One of very few medications that helped, but had to stop taking for fear of symptoms becoming permanent.”
• “At the time it was completely disabling. Removing the medication that caused it was a must. But now greatly limited by what medications can assist the bipolar. Very frustrating and concerning.”
• “I experienced the onset of symptoms in the 1970s...I remember the pharmacists always asking me, ‘Are you sure your doc wants you to take these meds at the same time?’ By the time I heard about TD, mine was permanent. I am fortunate to have mild symptoms that only affect my self-confidence, outward appearance, my face.”
Open-ended Survey Responses

• “Very emotionally damaging...It still affects my anxiety when trying to leave the house to this day.”
• “I actually stopped eating in front of people because I spit and drooled. It was AWFUL!”
• “My tardive dyskinesia is humiliating, degrading, and I feel like I can't show myself in public because of it. It jeopardizes my mental health treatment, burdens the ones I love the most, and I feel keeps me from finding a romantic partner.”
Jeff’s Story: Living with TD
Kim’s Story: Living with TD
Thank you

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DEPRESSION AND BIPOLAR SUPPORT ALLIANCE
TUESDAY, DECEMBER 5, 2017
Evidence Review

Steven Atlas, MD, MPH
Director, Primary Care Research and Quality Improvement Network, Massachusetts General Hospital
Key Review Team Members

Foluso Agboola, MBBS, MPH
Ifeoma Otuonye, MPH
Aqsa Mugal, BA

Disclosures:
We have no conflicts of interest relevant to this report.
**Topic in Context**

- Tardive dyskinesia (TD) is a repetitive, involuntary movement disorder with a delayed onset caused by prolonged use of dopamine receptor blocking agents (DRBAs), most commonly antipsychotic drugs.
- 20-50% of individuals taking antipsychotic drugs develop TD, with slightly lower rates for second generation drugs.
- Estimated population in the US: 500,000.
- No FDA-approved therapies for TD before recent approval of two vesicular monoamine transporter 2 (VMAT2) inhibitors.
VMAT2 Inhibitors:

<table>
<thead>
<tr>
<th>VMAT2 Inhibitors</th>
<th>Brand name</th>
<th>Recommended Dose</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valbenazine</td>
<td>Ingrezza</td>
<td>80 mg daily dose</td>
<td>April 2017 (TD)</td>
</tr>
<tr>
<td>Deutetrabenazine</td>
<td>Austedo</td>
<td>12mg – 48mg/day in two divided dose</td>
<td>April 2017 (HD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>August 2017 (TD)</td>
</tr>
<tr>
<td>Tetrabenazine*</td>
<td>Xenazine</td>
<td>12.5mg – 100mg/day in two to three divided doses</td>
<td>May 2008 (HD)</td>
</tr>
</tbody>
</table>

*Not approved for TD, but used off label
TD from a Patient Perspective

• Symptoms can vary in terms of severity
• Because it often involves the face, TD can be socially stigmatizing
• Can make it difficult to find and keep a job
• When severe, TD can be disabling and require help from family and other caregivers
• Despite this impact on quality of life, there are no validated patient reported outcome measures
Scope of Review

• To compare clinical effectiveness of VMAT2 inhibitors for treatment of TD due to DRBAs

• Included evidence from all relevant clinical studies, irrespective of use of a comparative study design:
  ▪ Adults 18 or older with symptoms for at least 3 months and history of use of DRBAs
  ▪ Excluded studies that did not meet a minimum sample size of 10 patients

• For safety outcomes included randomized trials of VMAT2 inhibitors for conditions other than TD
Body of Evidence

- 25 TOTAL references on TD in publications and conference abstracts

**Valbenazine (3 publications, 5 abstracts)**
- 2 RCTs
- 3 open-label extensions (Duration: one 6 weeks & two 48 weeks)

**Deutetradbenazine (2 publications, 7 abstracts)**
- 2 RCTS
- 1 open-label extension (Duration: 54 weeks)

**Tetrabenazine (8 publications)**
- 8 nonrandomized studies
# Overview of Randomized Trials

<table>
<thead>
<tr>
<th></th>
<th>Valbenazine</th>
<th></th>
<th>Deutetrabenazine</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KINECT 3</td>
<td>KINECT 2</td>
<td>AIM-TD</td>
<td>ARM-TD</td>
</tr>
<tr>
<td><strong>Study Type</strong></td>
<td>Phase III RCT</td>
<td>Phase II RCT</td>
<td>Phase III RCT</td>
<td>Phase II/ III RCT</td>
</tr>
<tr>
<td><strong>Total # of Patients</strong></td>
<td>234</td>
<td>102</td>
<td>293</td>
<td>117</td>
</tr>
<tr>
<td><strong>Mean Age (Years)</strong></td>
<td>56.1</td>
<td>56.2</td>
<td>56.4</td>
<td>54.6</td>
</tr>
<tr>
<td><strong>Comorbid Psychiatric Condition (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia/ Schizoaffective</td>
<td>66.1</td>
<td>58</td>
<td>60</td>
<td>68.4</td>
</tr>
<tr>
<td>Bipolar Disorder/ Depression</td>
<td>33.9</td>
<td>38</td>
<td>36</td>
<td>48.7</td>
</tr>
<tr>
<td>Gastrointestinal Disorder</td>
<td>--</td>
<td>4</td>
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</tr>
</tbody>
</table>
Key clinical outcomes

• **Primary Outcome:**
  • Abnormal Involuntary Movement Scale (AIMS)
    • 7 items measured on a five-point (0-4) scale of severity
    • Total score ranges from 0-28, with higher scores reflecting increased severity

• **Secondary Outcomes:**
  • Clinical Global Impression of Change (CGIC)
  • Patients’ Global Impression of Change (PGIC)
  • Single item with score ranging from 1 (“very much improved”) to 7 (“very much worse”).
  • Reports of “1” or “2” classified as “responders”
## Comparability of VMAT2 Trials

- ICER did not attempt to conduct a formal comparison of these VMAT2 inhibitors to each other

<table>
<thead>
<tr>
<th></th>
<th>Valbenazine</th>
<th>Deutetrabenazine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eligibility Criteria</strong></td>
<td>• Moderate - severe TD based on qualitative assessment</td>
<td>• Moderate - severe TD based on AIMS score ≥6</td>
</tr>
<tr>
<td></td>
<td>• Severity based on review of screening videos by multiple external raters</td>
<td>• Severity criterion required at both screening and baseline assessment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• AIMS score assessed by investigator and confirmed by an independent expert via central video rating</td>
</tr>
<tr>
<td><strong>Duration of Trials</strong></td>
<td>6 weeks</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>
Results
## Valbenazine – Primary AIMS Outcomes

<table>
<thead>
<tr>
<th>Trials</th>
<th>Baseline AIMS Score (Mean)</th>
<th>AIMS Reduction from Baseline (LS Mean)</th>
<th>≥50% AIMS Improvement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kinect 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valbenazine 80mg/D</td>
<td>10.4</td>
<td>-3.2†</td>
<td>40.0*</td>
</tr>
<tr>
<td>Valbenazine 40mg/D</td>
<td>9.7</td>
<td>-1.9†</td>
<td>23.8*</td>
</tr>
<tr>
<td>Placebo</td>
<td>9.9</td>
<td>-0.1</td>
<td>8.7</td>
</tr>
<tr>
<td><strong>Kinect 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valbenazine (Max 75mg/D)</td>
<td>8.0</td>
<td>-2.6†</td>
<td>48.9*</td>
</tr>
<tr>
<td>Placebo</td>
<td>7.0</td>
<td>-0.2</td>
<td>18.2</td>
</tr>
</tbody>
</table>

†statistically significant change; *statistically significant compared to placebo
# Valbenazine – Secondary Outcomes

<table>
<thead>
<tr>
<th>Trials/ Arms</th>
<th>CGIC Responders (%)</th>
<th>PGIC Responders (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kinect 3</strong></td>
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<td>31.4</td>
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</tr>
<tr>
<td>Valbenazine 40mg/D</td>
<td>31.7</td>
<td>31.7</td>
</tr>
<tr>
<td>Placebo</td>
<td>20.3</td>
<td>42.0</td>
</tr>
<tr>
<td><strong>Kinect 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valbenazine (Max 75mg/D)</td>
<td>66.7*</td>
<td>57.8*</td>
</tr>
<tr>
<td>Placebo</td>
<td>15.9</td>
<td>31.8</td>
</tr>
</tbody>
</table>

* statistically significant compared to placebo
Valbenazine - Harms

• Most common side effects: drowsiness, fatigue, headache, decreased appetite, akathisia, nausea, vomiting, and dry mouth

• No evidence of increased rates of depression and suicidal ideation compared to placebo at six weeks
## Deutetrabenazine – Primary AIMS Outcomes

<table>
<thead>
<tr>
<th>Trials</th>
<th>Baseline AIMS Score (Mean)</th>
<th>AIMS Reduction from Baseline (LS Mean)</th>
<th>≥50% AIMS Improvement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIM-TD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTBZ 36mg/D</td>
<td>10.1</td>
<td>-3.3†</td>
<td>33*</td>
</tr>
<tr>
<td>DTBZ 24mg/D</td>
<td>9.4</td>
<td>-3.2†</td>
<td>35*</td>
</tr>
<tr>
<td>Placebo</td>
<td>9.5</td>
<td>-1.4</td>
<td>12</td>
</tr>
<tr>
<td>ARM-TD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTBZ</td>
<td>9.6</td>
<td>-3.0†</td>
<td>--</td>
</tr>
<tr>
<td>Placebo</td>
<td>9.6</td>
<td>-1.6</td>
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</tr>
</tbody>
</table>

†statistically significant change; *statistically significant compared to placebo
## Deutetrabenazine: Secondary Outcomes

<table>
<thead>
<tr>
<th>Trials</th>
<th>CGIC Responders (%)</th>
<th>PGIC Responders (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIM-TD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTBZ 36mg/Day</td>
<td>44</td>
<td>40</td>
</tr>
<tr>
<td>DTBZ 24mg/Day</td>
<td>49*</td>
<td>45</td>
</tr>
<tr>
<td>Placebo</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>ARM-TD</td>
<td></td>
<td></td>
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<td>Placebo</td>
<td>40.4</td>
<td>29.8</td>
</tr>
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</table>

*statistically significant compared to placebo
Deutetrabenazine - Harms

• Similar side effects to valbenazine: drowsiness, headache, and fatigue
• Other common side effects: diarrhea, insomnia, anxiety, and nasopharyngitis
• No evidence of increased rates of depression and suicidal ideation compared to placebo at 12 weeks (despite boxed warning from earlier indication)
Tetrabenazine

- May reduce symptoms of TD
- Lack of randomized controlled trials
- Variety of non-standardized outcome measures
- Difficult to make qualitative or quantitative comparisons to other VMAT2 inhibitors
- Harms: drowsiness, fatigue, insomnia, fall, agitation, parkinsonism, akathisia, and anxiety
- Boxed warning for HD: increased depression and suicidality
Controversies and Uncertainties

• Trials of valbenazine and deutetrabenazine only compared to placebo
  • No direct comparisons to each other or non-FDA approved TD treatments

• No randomized controlled trials of tetrabenazine in TD patients

• Variation in patient- and clinician-reported outcomes of VMAT2 inhibitors in TD patients

• Lack of comparative efficacy and safety data to support long-term use of VMAT2 inhibitors
## Summary

<table>
<thead>
<tr>
<th></th>
<th>AIMS</th>
<th>CGIC</th>
<th>PGIC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Valbenazine</strong></td>
<td>Greater reduction in AIMS scores and more patients with ≥50% AIMS improvement compared to placebo</td>
<td>Conflicting study findings with no consistent benefit over placebo on the CGIC scale</td>
<td>Conflicting study findings with no consistent benefit over placebo on the PGIC scale</td>
</tr>
<tr>
<td><strong>Deutetrabenazine</strong></td>
<td>Greater reduction in AIMS scores and more patients with ≥50% AIMS improvement compared to placebo</td>
<td>Did not demonstrate a statistically significant benefit over placebo on the CGIC scale</td>
<td>Did not demonstrate a statistically significant benefit over placebo on the PGIC scale</td>
</tr>
</tbody>
</table>
### Ratings

<table>
<thead>
<tr>
<th>VMAT2 Inhibitors</th>
<th>ICER Evidence Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valbenazine</td>
<td>Promising but Inconclusive (P/I)</td>
</tr>
<tr>
<td>Deutetrabenazine</td>
<td>Promising but Inconclusive (P/I)</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>Insufficient (I)</td>
</tr>
</tbody>
</table>
Other Benefits/Considerations

• VMAT2 inhibitors are the first FDA-approved therapies for TD
  • Patients and clinicians optimistically view VMAT2 inhibitors as important advancement in a frequently irreversible condition

• VMAT2 inhibitors could potentially improve control of underlying psychiatric condition with better adherence to antipsychotics

• VMAT2 inhibitors could facilitate TD patients’ ability to find a job and/or maintenance of job

• Their use may decrease caregiver or family burden
Comments Received

• Tetrabenazine should not be included in this review because it is not FDA approved for TD
• ICER should withhold judgment on these therapies until more data is available
• By effectively treating TD, VMAT2 inhibitors may help patients and their caregivers return to work and not need government health insurance
• TD can worsen social isolation and exacerbate the negative symptoms associated with schizophrenia and serious mood disorders
Cost Effectiveness

Surrey Walton, PhD,
University of Illinois at Chicago College of Pharmacy

Daniel Touchette, PharmD, MA, FCCP,
University of Illinois at Chicago College of Pharmacy
Key Review Team Members

Want to acknowledge important input and assistance from Varun Kumar and Rick Chapman from ICER and Kate Harrigan from UIC

Disclosures:
We have no conflicts of interest to disclose.
Objective

To model the health system costs and patient outcomes associated with treating symptoms of tardive dyskinesia (TD) using valbenazine and deutetrabenazine compared with placebo in a representative population of U.S. adults aged 18 and older with the underlying conditions of schizophrenia, schizoaffective disorders, and affective disorders.
Methods in Brief
Methods Overview

- Model: Semi-Markov model with time-dependent mortality rates
- Setting: United States
- Perspective: Payer (direct medical care and drug costs)
- Time Horizon: Lifetime
- Discount Rate: 3% per year (costs and outcomes)
- Cycle Length: 1 year
- Outcomes by Intervention: Costs, Quality-Adjusted Life Year (QALY)
- Primary Outcome: Cost per QALY Gained
Details on the Patient Population

• Adult U.S. population
• Age: 18-64
• Underlying conditions:
  • Schizophrenia or schizoaffective disorder
  • Affective disorder
• Patients with schizophrenia/schizoaffective disorder
  • Mean age of 38 years
  • 52.5% female
  • Represents 70.2% of modeled population
• Patients with affective disorder
  • Mean age of 40 years
  • 64.8% female
  • Represents 29.8% of modeled population
### Parameters: Drug Regimens

<table>
<thead>
<tr>
<th></th>
<th>Dosage</th>
<th>Schedule</th>
<th>Route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Valbenazine</strong></td>
<td>80 mg</td>
<td>1x80 mg capsule daily</td>
<td>Oral</td>
<td>Until Discontinuation or Death</td>
</tr>
<tr>
<td><strong>Deutetrabenazine</strong></td>
<td>36 mg*</td>
<td>2x9 mg tablets twice daily</td>
<td>Oral</td>
<td>Until Discontinuation or Death</td>
</tr>
</tbody>
</table>

The rationale for using the maximal dose is that in clinical practice patients will be titrated to maximum medication effectiveness without intolerable side effects.

*Data on the efficacy of 48 mg deutetrabenazine on 50% reduction in AIMS score was not available from clinical trials. Therefore the 36 mg dose and cost were used to estimate cost-effectiveness.
Model Overview

Treatment Model

Placebo Model
Key Assumptions

- Patient response to treatment is reflected in their *initial* health states and all treated patients incurred one month of treatment costs.
- Patients not responding to treatment with valbenazine or deutetrabenazine discontinue their treatment in that first month and enter the model with moderate to severe TD.
- Response to treatment remains constant for all responders thereafter unless they subsequently discontinue treatment.
- Patients not responding to treatment were assumed to have two additional primary care and two additional neurologist visits per year.
Key Assumptions

• Long-term discontinuation rates were modeled from open-labeled studies with less than one year of observation. Following the first cycle, discontinuation rates were modeled as being 50% of that observed in the first cycle.

• Following discontinuation a percentage of patients, based on the placebo results, remain in the Improved TD state.

• All patients who discontinue treatment stop incurring costs associated with the treatment.

• TD treatments do not have a direct effect on mortality.

• For the base-case, treatment of TD has no effect on the outcomes or costs of treating the underlying conditions.
  • A scenario analysis was developed incorporating an effect of treatment on improving treatment of underlying conditions
# Key Model Inputs: Treatment Response and Long Term Discontinuation

<table>
<thead>
<tr>
<th>Model Inputs</th>
<th>Valbenazine</th>
<th>Reference</th>
<th>Deutetrabenazine</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of PLACEBO Responders with ≥50% Reduction in AIMS</td>
<td>8.7%</td>
<td>Hauser 2017</td>
<td>12.0%</td>
<td>Anderson 2017</td>
</tr>
<tr>
<td>Proportion of TREATMENT Responders with ≥50% Reduction in AIMS</td>
<td>40.0%</td>
<td>Hauser 2017</td>
<td>33.1%</td>
<td>Anderson 2017</td>
</tr>
<tr>
<td>Annual Discontinuation Rate (First Year)*</td>
<td>17.6%</td>
<td>Remington 2016 Hauser 2017</td>
<td>13.0%</td>
<td>Anderson [2] 2017</td>
</tr>
</tbody>
</table>

*Assumed 50% decrease after 1st year
# Key Model Inputs: Drug Costs

<table>
<thead>
<tr>
<th>Drug and Daily Dose</th>
<th>Annual WAC</th>
<th>Annual Net Price (at 27% discount)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valbenazine 80 mg</td>
<td>$75,789</td>
<td>$55,326</td>
<td>Redbook 2017</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aitkin et al. 2016</td>
</tr>
<tr>
<td>Deutetrabenazine 36 mg</td>
<td>$90,071</td>
<td>$65,751</td>
<td>Redbook 2017</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aitkin et al. 2016</td>
</tr>
</tbody>
</table>
## Key Model Inputs: Utilities

<table>
<thead>
<tr>
<th>Model Inputs</th>
<th>Base Case Value</th>
<th>Reference</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Utility for Modeled Population</td>
<td>0.82</td>
<td>Wang 2004</td>
<td>Weighted average of patients with schizophrenia disorders (0.83) and bipolar disorders (0.80).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calvert 2006</td>
<td></td>
</tr>
<tr>
<td>Utility Decrement from Moderate to Severe TD</td>
<td>0.095</td>
<td>Lenert 2004</td>
<td>Assumed constant across age and underlying condition.</td>
</tr>
</tbody>
</table>
Results
## Model Results: Base Case

<table>
<thead>
<tr>
<th>Model Inputs</th>
<th>Valbenazine</th>
<th>Deutetrabenazine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Valbenazine</td>
<td>Placebo</td>
</tr>
<tr>
<td>Total Costs</td>
<td>$185,167</td>
<td>$6,876</td>
</tr>
<tr>
<td>Total QALYs</td>
<td>15.35</td>
<td>15.12</td>
</tr>
</tbody>
</table>
## Model Results: Base Case Cost per QALY

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Incremental Costs</th>
<th>Incremental QALYs</th>
<th>Incremental Cost-Effectiveness Ratios versus Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valbenazine</td>
<td>$178,291</td>
<td>0.24</td>
<td>$752,080</td>
</tr>
<tr>
<td>Deutetrabenazine</td>
<td>$213,795</td>
<td>0.19</td>
<td>$1,100,773</td>
</tr>
</tbody>
</table>
One Way Sensitivity Analysis: Tornado Diagram for Valbenazine

Disutility with TD (0.19-0.0475)
Annual cost of valbenazine ($27,663-$82,989)
Proportion of responders: placebo group in valbenazine comparison (.236-.150)
Proportion of responders: valbenazine (.292-.508)
Annual proportion discontinuing valbenazine CYCLE 1 (.139-.241)
Annual cost with TD ($131-$392)

Note for comparison 0.159 disutility associated with new-onset depression.[Roberts, 2014]
## Model Results: Scenario Analyses for Improvement in Underlying Conditions

<table>
<thead>
<tr>
<th>Base Case Vs. Placebo</th>
<th>Underlying Condition</th>
<th>Incremental Cost Per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valbenazine</td>
<td>Schizophrenia/ Schizoaffective Disorders</td>
<td>$552,589</td>
</tr>
<tr>
<td>Deutetrabenazine</td>
<td>Schizophrenia/ Schizoaffective Disorders</td>
<td>$779,342</td>
</tr>
<tr>
<td>Valbenazine</td>
<td>Bipolar Disorder</td>
<td>$604,568</td>
</tr>
<tr>
<td>Deutetrabenazine</td>
<td>Bipolar Disorder</td>
<td>$874,934</td>
</tr>
</tbody>
</table>
Sensitivity and Scenario Analyses

- Including potential productivity gains based on available literature related to employment levels for patients with and without TD and median US salaries resulted in small improvements in the incremental ratios
  - Valbenazine: $728,000 per QALY gained
  - Deutetrabenazine: $1,077,000 per QALY gained

- None of the sensitivity or scenario analyses resulted in incremental cost-effectiveness ratios of below $150,000 per QALY gained.
# Model Results: Threshold Analysis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Annual WAC</th>
<th>Annual Net Price (at 27% discount)</th>
<th>Annual Price to Achieve $50,000 per QALY</th>
<th>Annual Price to Achieve $100,000 per QALY</th>
<th>Annual Price to Achieve $150,000 per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valbenazine 80 mg per day</td>
<td>$75,789</td>
<td>$55,326</td>
<td>$3,941</td>
<td>$7,600</td>
<td>$11,260</td>
</tr>
<tr>
<td>Deutetrabenazine 36 mg per day</td>
<td>$90,071</td>
<td>$65,751</td>
<td>$3,205</td>
<td>$6,181</td>
<td>$9,158</td>
</tr>
</tbody>
</table>
Limitations

• The effectiveness of the treatment is based on limited intermediate measures from the clinical trials.

• We used a utility value for complete removal of moderate to severe TD for a 50% improvement in the AIMS score.

• In general, there are relatively few and relatively limited studies available from which to build models for TD patients particularly in terms of the scenario analyses mentioned here.

• As with all models the results reflect averages for the patient population as described above.
Summary

• Valbenazine and Deutetrabenazine are projected to improve patient health.

• At the current prices the projected base case incremental cost effectiveness ratios for both drugs are well above usual thresholds.

• While the model results did vary across the rate of symptom relief with no treatment, the disutility of TD, and the price of the drugs, all of the sensitivity analyses and scenario analyses resulted in incremental cost effectiveness ratios above usual thresholds.
Public Comments

• The impact of TD is not adequately measured by QALYs and/or the utility decrement from moderate to severe TD is too small.

• Reduction of TD symptoms will result in better adherence to medications for underlying conditions and therefore better outcomes in those underlying conditions along with lower costs.

• Reduction of TD symptoms will have a substantial impact on productivity.

• Reduction of TD symptoms will have positive spillover effects on family and caregivers.
Manufacturer Public Comments and Discussion
Manufacturer Public Comments and Discussion

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chuck Yonan, PharmD</td>
<td>Senior Director of Health Economics Outcomes Research, Medical Affairs</td>
<td>Neurocrine Biosciences</td>
</tr>
<tr>
<td>Victor Abler, DO</td>
<td>Senior Global Medical Director, Neurodegenerative Disorders</td>
<td>Teva Pharmaceuticals</td>
</tr>
</tbody>
</table>
Public Comment and Discussion
Conflicts of interest:

- 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 companies
- Any other relationship that could reasonably be considered a financial conflict of interest, please note below

If yes, please describe the relationship(s) below.

I am a non-officer employee of an organization which receives more than 25% of its funding from health care companies, including multiple life sciences manufacturers, health plans or managed care organizations, life sciences manufacturer associations, and hospital systems. A public list of funds received by funder by program is available on our website.

I am on the Board of Directors of an organization that receives more than 25% of its funding from health care companies, including life sciences manufacturers.
Allen Doederlein, President, Depression and Bipolar Support Alliance

Conflicts of interest:  
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 companies.

If yes, please describe the relationship(s) below.  
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.
Dr. Daniel Tarsy, MD, Professor of Neurology, Harvard Medical School Parkinson’s Disease and Movement Control Disorder Center

Conflicts of interest: If yes, please describe the relationship(s) below.

I have no conflicts of interest.
Lunch Meeting will resume at 1:00 pm
Voting Questions
What famous historic event in American History occurred on December 5?

A. Pearl Harbor was bombed, launching American involvement in World War II
B. The first day of the Montgomery Bus Boycott
C. Thomas Edison created the light bulb
D. Abraham Lincoln issued the emancipation proclamation
E. Ronald Reagan gave his famous ‘Tear Down this Wall’ speech in 1987
1. Is the evidence adequate to demonstrate a positive net health benefit from treating patients with TD with valbenazine?

A. Yes
B. No
2. Is the evidence adequate to demonstrate a positive net health benefit from treating patients with TD with deutetrabenazine?

A. Yes
B. No
3. Is the evidence adequate to demonstrate a positive net health benefit from treating patients with TD with tetrabenazine?

A. Yes
B. No
4. Is the evidence adequate to distinguish between the net health benefit of valbenazine and deutetrabenazine in the treatment of TD?

A. Yes
B. No
Does treating patients with one of the new FDA approved drugs offer one or more of the following “other benefits”? (select all that apply)

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

A. 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.

B. This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.

C. This intervention is the first to offer any improvement for patients with this condition.

D. Compared to usual care, there is significant uncertainty about the long-term risk of serious side effects of this intervention.

E. Compared to usual care, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
Policy Roundtable
# Policy Roundtable

<table>
<thead>
<tr>
<th>Victor Abler, DO.</th>
<th>Barbara Henry, RPh.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Senior Global Medical Director for Neurodegenerative Diseases Teva Pharmaceuticals</td>
<td>Lead Clinical Pharmacy Specialist Harvard Pilgrim</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Teri Brister, PhD.</th>
<th>Paul Jeffrey, PharmD.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Director Knowledge Integration Information National Alliance on Mental Illness</td>
<td>Director of Pharmacy MassHealth</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oliver Freudenreich, MD.</th>
<th>Daniel Tarsy, MD.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-Director, Schizophrenia Clinical Research Program Mass General Hospital</td>
<td>Professor of Neurology; Parkinson’s Disease and Movement Disorders Center Beth Israel Hospital; Harvard Medical School</td>
</tr>
</tbody>
</table>

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<tr>
<th>Patrick Hendry</th>
<th>Chuck Yonan, PharmD.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vice President of Peer Advocacy Support and Services Mental Health America</td>
<td>Senior Director HEOR, Medical Affairs Neurocrine Bioscience</td>
</tr>
</tbody>
</table>
New England CEPAC Panel
Reflections and Closing Remarks
Adjourn