Is there value in VMAT-2 inhibitors for tardive dyskinesia?

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IS THERE VALUE IN VMAT-2 INHIBITORS FOR TARDIVE DYSKINESIA?

Samantha Vogel, PharmD
PGY2 Psychiatric Pharmacy Resident
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Objectives

• Describe tardive dyskinesia (TD)
• Identify at risk patients for TD
• Outline current management strategies
• Assess use of vesicular monoamine transporter-2 (VMAT-2) inhibitors in treating TD
• Recommend treatment plan for a patient with TD

Patient Case:

• HPI: SV is a 34 year old Hispanic female who presents to your mental health clinic for medication management. She states she began experiencing slight involuntary movements of the tongue and jaw 7 months ago which have progressed into marked movements of the tongue and jaw, grimacing, and moderate choreic movements of the upper limbs.


Patient Case (part I):

• She has been stable on her current medication regimen for the past 6 years, however 12 months ago her risperidone was increased from 4 mg to 6 mg:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Reason for discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone 6 mg PO daily</td>
<td></td>
</tr>
<tr>
<td>Sertraline 100 mg PO daily</td>
<td></td>
</tr>
<tr>
<td>Metformin ER 1000 mg PO daily</td>
<td>Acetaminophen 325 mg PO PRN</td>
</tr>
</tbody>
</table>

• Previous psychiatric medication trials:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Reason for discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol 15 mg PO daily</td>
<td>Acute dystonic reaction</td>
</tr>
<tr>
<td>Olanzapine 20 mg PO daily</td>
<td>Weight gain, breakthrough psychosis</td>
</tr>
<tr>
<td>Quetiapine 600 mg PO qHS</td>
<td>Weight gain, sedation</td>
</tr>
<tr>
<td>Aripsiprazole 10 mg PO daily</td>
<td>Akathisia</td>
</tr>
<tr>
<td>Duloxetine 60 mg PO daily</td>
<td>Insomnia</td>
</tr>
</tbody>
</table>

BACKGROUND

Drug-Induced Movement Disorders

Extrapyramidal Symptoms (EPS)

Acute

Akathisia

Dystonia

Parkinsonism

Chronic

Tardive Dyskinesia (TD)
Tardive Dyskinesia (TD)

- Iatrogenic
  - Dopamine receptor blocking agents (DRBA)
  - >3 months of drug exposure
- Choreoathetoid movement disorder
  - Heterogeneous, involuntary movements
  - Non-rhythmic, repetitive, and purposeless
- Insidious onset
  - Varying severity
  - Chronic course may wax and wane
- Potentially irreversible

Tardive Spectrum

- Classic TD (oro-bucco-lingual sterotypy)
  - Lip smacking or pursing
  - Facial grimacing
  - Tongue movements
  - Can progress to trunk and limbs
- Atypical TD
  - Tremor, akathisia, or dystonia
  - May present as combination

Presentation

Abnormal Involuntary Movement Scale (AIMS)

- Used to detect TD and follow severity over time
- 12 item clinician administered and scored test
- Items 1-10 are rated from 0-4
  - Items 1-4 assess orofacial movements
  - Items 5-7 assess extremity and truncal movements
  - Items 8-10 assess global severity and patient awareness
- Items 11-12 assess teeth and denture status

Diagnosis

- DSM-5
  - Involuntary athetoid or choreiform movements
  - Lasting at least a few weeks
  - Developed in association with the use of a neuroleptic (DRBA) for at least a few months
  - May also appear after discontinuation, change, or reduction in dosage of neuroleptic medications

- Schooler-Kane
  - Three cumulative months DRBA exposure
  - AIMS of ≥3 on one item, or AIMS of ≥2 on multiple items
  - Exclusion of other diagnoses

Agents that Cause TD

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Known Offenders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical Antipsychotics (First generation)</td>
<td>Chlorpromazine, haloperidol</td>
</tr>
<tr>
<td>Atypical Antipsychotics (Second generation)</td>
<td>Aripiprazole, olanzapine, quetiapine, risperidone</td>
</tr>
<tr>
<td>Anticholinergics/antihistamines</td>
<td>Benztropine</td>
</tr>
<tr>
<td>Antiepileptic agents</td>
<td>Carbamazepine, phenobarbital, phenytoin</td>
</tr>
<tr>
<td>Antiparkinson agents</td>
<td>Levodopa, bromocriptine</td>
</tr>
<tr>
<td>Gastrointestinal agents</td>
<td>Metoclopramide, droperidol, prochlorperazine</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>Lithium</td>
</tr>
<tr>
<td>SSRI/SNRIs</td>
<td>Citalopram, duloxetine</td>
</tr>
<tr>
<td>Tricyclic Antidepressants</td>
<td>Amitriptyline, amoxapine, doxepin</td>
</tr>
</tbody>
</table>
Epidemiology

- Cumulative annual incidence with antipsychotic exposure = 5%
  - Typical antipsychotics: 8.5%
  - Atypical antipsychotics: 3.1%
- May persist for years or decades
- Spontaneous remission ranges from 6-22%

Risk Factors

- Organic brain damage
- D2 receptor occupancy
- Negative symptoms of schizophrenia
- Older age
- Diabetes mellitus
- Female sex
- Genetics
- Concomitant affective disorder
- Early development of EPS

Patient Case (part II):

- Based on SV's history and current medication list, what are her risk factors for TD?
  - Diabetes mellitus
  - D2 receptor occupancy
  - Concomitant affective disorder
  - Female sex
  - Early development of EPS

- Which assessment tool would be most useful to determine if SV has TD?
  A. Mini-Mental Status Examination (MMSE)
  B. Abnormal involuntary movement scale (AIMS)
  C. Barnes Akathisia Rating Scale (BARS)

Pathophysiology of TD

- Mesocortical pathway
- Mesolimbic pathway
- Nigrostriatal pathway

Pathophysiology cont.

- DRBA
- Dopamine receptor blockade
- Upregulation and increased sensitivity at postsynaptic dopamine receptors
- Dysfunctional GABAergic and glutamatergic neurons
- Maladaptive synaptic plasticity
- Direct oxidative damage from increased dopamine metabolism

Consequences of TD

- Increased social stigmatization
- Negative impact on daily functioning
- Poor treatment adherence
- Lower rates of symptom remission in patients with schizophrenia
- Higher rates of relapse
- Longer hospitalizations
- Cognitive impairments
- Increased mortality
TREATMENT OPTIONS

Goals of Treatment

Prevent worsening of TD

Resolve symptoms of TD

Prevent recurrence of TD

Maintain clinical stability

Approach to Treatment

<table>
<thead>
<tr>
<th>Option</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue current therapy** b</td>
<td>• Reduced risk of psychotic relapse</td>
<td>• Reduced likelihood of TD reversibility</td>
</tr>
<tr>
<td></td>
<td>• Up to 30% will have spontaneous reduction in TD</td>
<td></td>
</tr>
<tr>
<td>Discontinue agent or reduce dose c</td>
<td>• Discontinuation or dose reduction may provide improvement in TD in 37% of patients</td>
<td>• Complete resolution uncommon • Increased risk of relapse</td>
</tr>
<tr>
<td>Switch agent*</td>
<td>• Switching from first generation AP to second generation AP may reduce TD</td>
<td>• TD likely to persist or fluctuate • Increased risk of relapse</td>
</tr>
<tr>
<td>Initiate adjunctive agent** e</td>
<td>• Multiple agents may benefit TD symptoms</td>
<td>• Small studies with varied results</td>
</tr>
<tr>
<td></td>
<td>• Can be used with AP treatment</td>
<td></td>
</tr>
</tbody>
</table>

Drug Targets

Development of TD

Improve TD

Upregulation and increased sensitivity at postsynaptic dopamine receptors

Tetrabenazine

Reserpine

Amanadine

Clonazepam

Dysfunctional GABAergic and glutamatergic neurons

Amanadine

Maladaptive synaptic plasticity

Ginkgo biloba

Direct oxidative damage from increased dopamine metabolism

Vitamin E

Adjunctive Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amanadine</td>
<td>• 100-400 mg daily for 2-7 weeks</td>
</tr>
<tr>
<td></td>
<td>• Reduced AIMS by 25-32% in two studies</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>• 2-3.5 mg daily</td>
</tr>
<tr>
<td></td>
<td>• Improved TD by 37% after 12 weeks but waned with long-term use</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>• 240 mg daily for 12 weeks</td>
</tr>
<tr>
<td></td>
<td>• 51% of patients had &gt;50% reduction of AIMS score</td>
</tr>
<tr>
<td></td>
<td>• Positive effect continued after medication was withdrawn</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>• 1,200-1,600 IU daily</td>
</tr>
<tr>
<td></td>
<td>• Several studies reporting mixed results in improving TD</td>
</tr>
<tr>
<td>Reserpine</td>
<td>• 0.75-1.25 mg daily</td>
</tr>
<tr>
<td></td>
<td>• Positive effect but peripheral side effects limited use</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>• 25-200 mg daily in various studies</td>
</tr>
<tr>
<td></td>
<td>• Reports of akathisia, parkinsonism, and depression with suicidal ideation</td>
</tr>
</tbody>
</table>

Guideline Consensus

| APA 2010       | • Switch to an atypical antipsychotic or reduce the dose                 |
|                | • Vitamin E may reduce the risk of development of tardive dyskinesia    |
| WFSBP 2012     | • Switch to clozapine                                                   |
|                | • Consider application of vitamin E therapy                            |
|                | • ECT, deep brain stimulation, or pallidotomy for severe cases          |
| AAN 2013       | • Amanadine, ginkgo biloba, and tetrabenazine should be considered for TD|
|                | • Insufficient evidence to support withdrawal or switch of current antipsychotic |
VESICULAR MONOAMINE TRANSPORTER-2 (VMAT-2) INHIBITORS

VMAT-2 Pharmacology

- Reversible inhibitor of VMAT-2
- Selective to central nervous system
- Inhibits release of monoamines from cytoplasmic vesicles into the synaptic cleft
- Increases monoamine metabolism
- Minimal/no affinity for VMAT1, dopaminergic, serotonergic, adrenergic, histaminergic or muscarinic receptors

VMAT-2 Pharmacology cont.

LITERATURE REVIEW

What is the role of VMAT-2 inhibitors in TD treatment?

Definitions

- **LS Mean AIMS change** – least squares average change in AIMS score from baseline
- **% Responders** – Patients who experienced a reduction of 50% or more in AIMS score
- **CGIC/CGIC-TD** – Clinical Global Impression of Change; Clinician based assessment of improvement before and after treatment on a 7-point Likert scale
- **PGIC** – Patient Global Impression of Change; Patient based assessment of improvement before and after treatment on a 7-point Likert scale

VALBENAZINE (Ingrezza™)

**KINECT 2**

**Objective**
- Assess efficacy, tolerability, and safety of VBZ

**Design**
- Phase II, RDBPC, multi-center, dose-titration study
- Duration: 6 weeks + 2 weeks follow-up

**Inclusion**
- Male & female adults with moderate or severe TD by AIMS
- Diagnosis of schizophrenia, schizoaffective disorder, mood disorder with neuroleptic-induced TD (defined by DSM-IV), or GI disorder with metoclopamide-induced TD
- Stable on concomitant meds for before & during study

**Interventions**
- VBZ 25 mg daily; escalated by 25 mg every 2 weeks to maximum of 75 mg daily
- Placebo; identical escalation strategy as active group
- VBZ 40 mg daily; escalated by 25 mg every 2 weeks to maximum of 75 mg daily
- Placebo; identical escalation strategy as active group

**Study Drug Exposure (N=89)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>VBZ</th>
<th>Pbo</th>
<th>P-value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary (N=89)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIMS change at 6 weeks (LS mean)</td>
<td>-2.6</td>
<td>-0.2</td>
<td>0.0005 (&lt;3.7, -1.1)</td>
</tr>
<tr>
<td>Responders (%)</td>
<td>49</td>
<td>18</td>
<td>&lt;0.002 (n/a)</td>
</tr>
<tr>
<td><strong>Secondary (N=89)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-TD score at 6 weeks (LS mean)</td>
<td>2.2</td>
<td>3.1</td>
<td>&lt;0.0001 (&lt;1.2, -0.5)</td>
</tr>
<tr>
<td>PGIC score at 6 weeks (LS mean)</td>
<td>2.6</td>
<td>3.3</td>
<td>0.0011 (&lt;1.1, -0.3)</td>
</tr>
<tr>
<td><strong>Safety (N=100)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall incidence of side effects (%)</td>
<td>49</td>
<td>33</td>
<td>n/a</td>
</tr>
</tbody>
</table>

**KINECT 3**

**Objective**
- Evaluate the efficacy, safety, and tolerability of valbenazine for tardive dyskinesia

**Design**
- Phase III, RDBPC, multi-center, fixed-dose study
- Duration: 6 weeks

**Inclusion**
- Male & female adults with moderate or severe TD by AIMS
- Diagnosis of schizophrenia, schizoaffective disorder, mood disorder with neuroleptic-induced TD (defined by DSM-IV), or GI disorder with metoclopamide-induced TD
- Stable on concomitant meds for before & during study

**Interventions**
- VBZ 40 mg daily
- VBZ 80 mg daily
- Placebo
KINECT 3 Results

Primary Outcome: LS Mean Change From Baseline in AIMS Among Participants Receiving VBZ or Placebo

<table>
<thead>
<tr>
<th>Time of Assessment</th>
<th>AIMS Mean Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.1</td>
</tr>
<tr>
<td>Week 2</td>
<td>-2.2, P=0.001</td>
</tr>
<tr>
<td>Week 4</td>
<td>-3.5, P=0.001</td>
</tr>
<tr>
<td>Week 6</td>
<td>-4.2, P=0.001</td>
</tr>
</tbody>
</table>

KINECT 3 Results cont.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>VBZ 40 mg</th>
<th>P-value</th>
<th>VBZ 80 mg</th>
<th>P-value</th>
<th>Pbo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary (N=225)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIMS change at 6 weeks (LS mean) Responders (%)</td>
<td>-1.9</td>
<td>0.002</td>
<td>3</td>
<td>&lt;0.001</td>
<td>0.1</td>
</tr>
<tr>
<td>Secondary (N=225)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-TD score at 6 weeks (LS mean)</td>
<td>2.9</td>
<td>0.074</td>
<td>2.9</td>
<td>0.056</td>
<td>3.2</td>
</tr>
<tr>
<td>PGIC score at 6 weeks (LS mean)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Safety (N=227)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akathisia (%)</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Dry mouth (%)</td>
<td>7</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Somnolence (%)</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Suicidal ideation (%)</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

KINECT 3-Extension

Objective: To assess long term efficacy of valbenazine

Design: Phase III, DBPC, multi-center, fixed-dose, extension study

Duration: 42 weeks of extended treatment + 4 weeks treatment-free follow-up

Inclusion: Patients who completed first 6 weeks of KINECT 3 study

Placebo patients randomized to treatment groups

Interventions: VBZ 40 mg daily

VBZ 80 mg daily

KINECT 3-Extension Results

Outcome                  | VBZ 40 mg | VBZ 80 mg | Pbo |
--------------------------|-----------|-----------|-----|
Primary (N=225)           |           |           |     |
AIMS change at 48 weeks (LS mean) | -3.0   | -4.8     | -   |
AIMS change at 52 weeks (LS mean) | +1.6   | +3.6     | -   |
Responders at 48 weeks (%) | 28       | 52       | -   |
Secondary (N=198)         |           |           |     |
Schizophrenia/Schizoaffective |         |           |     |
CGI-TD score at 6 weeks (LS mean) | 2.9    | 3.0       | 3.2 |
CGI-TD score at 48 weeks (LS mean) | 2.4    | 2.2       | 2   |
CGI-TD score at 52 weeks (LS mean) | 3.3    | 3.4       | 3.6 |
Mood disorder             |           |           |     |
CGI-TD score at 6 weeks (LS mean) | 2.9    | 2.7       | 3.2 |
CGI-TD score at 48 weeks (LS mean) | 2.2    | 2.0       | 2   |
CGI-TD score at 52 weeks (LS mean) | 2.8    | 3.6       | 3.6 |

KINECT 4

Safety and Tolerability Study of VBZ in Subjects with Tardive Dyskinesia: Results of a Long-term, open-label, multi-center, fixed-dose study.

Objective: To evaluate safety and tolerability of VBZ

Design: Phase III, open-label, multi-center, fixed-dose study

Duration: 48 weeks of treatment

Inclusion: Male & female adults with moderate or severe TD by AIMS

Diagnosis of schizophrenia, schizoaffective disorder, or mood disorder with neuroleptic-induced TD (defined by DSM-IV)

Stable on concomitant meds for before & during study

Interventions: VBZ 40 mg daily

VBZ 80 mg daily

Results: Completed March 2017 (publication pending)
Assess long-term safety and tolerability of valbenazine
Assess emergence of EPS symptoms with valbenazine treatment

Once DBZ

High percentage of patients on VBZ, including 40 mg or VBZ 80 mg daily
No serious adverse events related to VBZ, including TD reappeared after medication was withdrawn
Duration PGIC
Stable on antipsychotic
Patients in KINET 2, KINET 3, KINETC 3-Extension, and KINET 4
No information on VBZ effect in bipolar disorder
Determine efficacy
Some patients received shorter
Male & female adults with TD and DRBA treatment for ≥3 months

DEUTETRABENAZINE
(Austedo™)

DEUTETRABENAZINE
(Austedo™)

Pooled Analyses

KINECT Series: Conclusion

Strengths

Limitations

Blinded central reviewers
Animated effect based on diagnosis and concomitant medications
Rapid titration schedule to effective dose
Extended treatment with washout period
Robust criteria for % responders

High percentage of patients on anticholinergic medications
No information on VBZ effect in different AIMS domains
No data on functional improvement
PGIC not included in later studies
Some patients received shorter treatment duration

Conclusion

Once-daily VBZ significantly reduced AIMS across diagnoses, antipsychotic use, and TD severity for up to 48 weeks
Minimally improved CGI-TD scores
No serious adverse events related to VBZ, including EPS
TD reappeared after medication was withdrawn

ARM-TD


Objective

Design

Inclusion

Interventions

Results

Common side effects: somnolence (9.1%), urinary tract infection (10.7%), and headache (12.4%)
Serious adverse events occurred in 12.6%
6.1% required dose reduction
TD: Tardive dyskinesia; AIMS: Abnormal Involuntary Movement Scale

Limitations

No data on functional improvement
PGIC not included in later studies
Some patients received shorter treatment duration

DEUTETRABENAZINE
(Austedo™)

ARM-TD Results

Arm-TD Results cont.

Outcome

DBZ

Pbo

Demographics (N=117)

(N=58)

(N=59)

Age (y)

56

53

Male gender (%)

50

46

Duration of TD (y)

6

6

Disease category (%)

Schizophrenia

50

49

Schizoaffective disorder

19

19

Bipolar disorder

21

25

Depression

30

22

AIMS score (mean)

10

10

AIMS score ≥ 6 (%)

83

83

Concomitant Medications (N=117)

Depamine receptor blocking agent (%)

>80

>80

Outcome

DBZ

Pbo

P-value (95% CI)

Primary (N=113)

(AIMS change at 12 weeks (LS mean)

-3.0

-1.6

0.019 ( -2.6, -0.2)

Responders (%) 49

18

0.002 (n/a)

Secondary (N=113)

Treatment success based on CGIIC (%)

48

40

NSD

Treatment success based on PGIC (%)

43

30

NSD

Safety (N=117)

(AIMS change at 12 weeks (LS mean)

48

36

n/a

Overall incidence of side effects (%) 48

36

n/a

DBZ: Deutetrabenazine; Pbo: Placebo; TD: Tardive dyskinesia; AIMS: Abnormal Involuntary Movement Scale

NSD: No significant difference; CGIIC: Clinical Global Improvement in Change; PGIC: Patient Global Improvement in Change; NSD: No significant difference

Robust criteria for % responders

DEUTETRABENAZINE
(Austedo™)

Limitations

No data on functional improvement
PGIC not included in later studies
Some patients received shorter treatment duration

Conclusion

Once-daily VBZ significantly reduced AIMS across diagnoses, antipsychotic use, and TD severity for up to 48 weeks
Minimally improved CGI-TD scores
No serious adverse events related to VBZ, including EPS
TD reappeared after medication was withdrawn

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(Austedo™)

KINECT Series: Conclusion

Strengths

Limitations

Blinded central reviewers
Animated effect based on diagnosis and concomitant medications
Rapid titration schedule to effective dose
Extended treatment with washout period
Robust criteria for % responders

High percentage of patients on anticholinergic medications
No information on VBZ effect in different AIMS domains
No data on functional improvement
PGIC not included in later studies
Some patients received shorter treatment duration

Conclusion

Once-daily VBZ significantly reduced AIMS across diagnoses, antipsychotic use, and TD severity for up to 48 weeks
Minimally improved CGI-TD scores
No serious adverse events related to VBZ, including EPS
TD reappeared after medication was withdrawn
AIM-TD

**Objective**
- Assess efficacy, safety, and tolerability of fixed doses of Deutetrabenazine for TD

**Design**
- Phase III, RDBPC, multi-center, fixed-dose study
- Duration: 4 weeks titration + 8 weeks maintenance treatment + 1 week washout
- Stratified by DBRA use at baseline

**Inclusion**
- Male & female adults with TD and DBRA treatment for ≥3 months (≥1 month if patient was 60 or older)
- AIMS ≥ 6 at screening and baseline
- Stable on antipsychotic medication use (i.e., no strong anticholinergic medications)

**Interventions**
- DBZ 12 mg, 24 mg, or 36 mg daily
- Placebo; identical escalation strategy as active group

**ARM-TD and AIM-TD Conclusions**

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Specified specific AIMS score at screening and baseline</td>
<td>- Placebo effect seen with AIMS score in both studies</td>
</tr>
<tr>
<td>- Stringent requirement for concomitant medication use (i.e., no strong anticholinergic medications)</td>
<td>- No long-term follow-up after study medication was stopped</td>
</tr>
<tr>
<td>- No comment on functional improvement</td>
<td>- Patients with AIMS ≥ 6 included</td>
</tr>
</tbody>
</table>

**Conclusion**
- Deutetrabenazine 24 mg and 36 mg daily of provided a significant reduction in TD
- Deutetrabenazine was safe and well tolerated
- Long-term efficacy and safety is not established

**Comparison of VMAT-2 Inhibitors**

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Valbenazine (Ingrezza™)</th>
<th>Deutetrabenazine (Austedo™)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-80 mg daily (with or without food)</td>
<td>6-48 mg daily (with food)</td>
<td></td>
</tr>
</tbody>
</table>

**Cost of VMAT-2 Inhibitors**

<table>
<thead>
<tr>
<th>Valbenazine</th>
<th>Deutetrabenazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>AWP Monthly Cost</td>
<td>$12,660 ($460 of 12 mg)</td>
</tr>
<tr>
<td>Estimated annual cost</td>
<td>$151,920</td>
</tr>
</tbody>
</table>

**Manufacturer**
- Neurocrine

**Acquisition**
- Specialty pharmacies only

**Patient/Provider Support?**
- Yes – INRACE™ Support Program

**AIM-TD Results**

**Outcome**

<table>
<thead>
<tr>
<th>Duration</th>
<th>P-value</th>
<th>DBZ 12 mg</th>
<th>P-value</th>
<th>DBZ 24 mg</th>
<th>P-value</th>
<th>DBZ 36 mg</th>
<th>P-value</th>
<th>Pbo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>(N=222)</td>
<td>(N=55)</td>
<td>(N=74)</td>
<td>(N=74)</td>
<td>(N=72)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIM change at 12 weeks*</td>
<td>-2.1</td>
<td>0.217</td>
<td>-3.2</td>
<td>0.003</td>
<td>-3.3</td>
<td>0.001</td>
<td>-4.4</td>
<td>1.4</td>
</tr>
</tbody>
</table>

**Secondary | (N=222) |
| AIM change at 12 weeks* | 28 | 0.734 | 49 | 0.014 | 44 | 0.059 | 26 | 0.217 |

**Study | N | Duration | Interventions | AIMS | CGIC | PGIC |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>KINET 2</td>
<td>89</td>
<td>6 wks</td>
<td>Valbenazine 25 mg – 75 mg</td>
<td>✔</td>
<td>✔</td>
<td>n/a</td>
</tr>
<tr>
<td>KINET 3</td>
<td>225</td>
<td>6 wks</td>
<td>Valbenazine 40 mg</td>
<td>✔</td>
<td>✔</td>
<td>n/a</td>
</tr>
<tr>
<td>KINET 3-ext.</td>
<td>225</td>
<td>48 wks</td>
<td>Valbenazine 40 mg</td>
<td>✔</td>
<td>✔</td>
<td>n/a</td>
</tr>
<tr>
<td>ARM-TD</td>
<td>113</td>
<td>12 wks</td>
<td>Deutetrabenazine</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>AIM-TD</td>
<td>222</td>
<td>12 wks</td>
<td>Deutetrabenazine 12 mg</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Deutetrabenazine 24 mg</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deutetrabenazine 36 mg</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Statistically significant, p≤0.05

**9/16/2017**
Treating TD in Patients with Stable Psychiatric Diagnoses

Patient Case (part III):
- After reducing her dose of risperidone back to 4 mg, SV returns to your clinic in 6 weeks. On a repeat AIMS she scores a 14 (indicating a 1 point improvement). SV states she is becoming increasingly upset regarding her TD and has had to recently quit her job.
- Would you consider a VMAT-2 inhibitor?
- What must you consider before prescribing a VMAT-2 inhibitor?

Future Questions
- How do changes in AIMS score correlate to functional improvement?
- What does TD progression look like with medication noncompliance or after treatment is stopped?
- What is the feasibility for long-term use given the current cost of VMAT-2 inhibitors?
- Will we ever see head-to-head trials with previously studied agents such as ginkgo biloba or amantadine?

Conclusion
- VMAT-2 inhibitors demonstrate significant improvement in AIMS in patients with moderate to severe TD
- VMAT-2 inhibitors can be considered for patients impaired by TD in whom dose reductions or adjunctive agents do not provide relief
- All patients should be counseled on risk of TD before AP initiation and with ongoing AP use
- At minimum, all patients should be assessed yearly for TD

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  Clinical Pharmacy Specialist – Psychiatry
  Seton Shoal Creek Hospital

- Lisa Mican, PharmD, BCPP
  Clinical Pharmacy Specialist – Psychiatry
  Austin State Hospital

Evaluator:
- Cynthia A. Gutierrez, PharmD, MS, BCPP
  Clinical Pharmacy Specialist – Mental Health
  South Texas Veterans Health Care System
IS THERE VALUE IN VMAT-2 INHIBITORS FOR TARDIVE DYSKINESIA?

Samantha Vogel, PharmD
PGY2 Psychiatric Pharmacy Resident
Seton Healthcare Family
The University of Texas College of Pharmacy
Appendices

A. Abbreviations
B. Patient Case – SV
C. Abnormal Involuntary Movement Scale (AIMS)
D. Treating TD in Patients with Stable Psychiatric Diagnoses Algorithm
### A. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAN</td>
<td>American Academy of Neurology</td>
</tr>
<tr>
<td>AIMS</td>
<td>Abnormal Involuntary Movement Scale</td>
</tr>
<tr>
<td>AP</td>
<td>Antipsychotic</td>
</tr>
<tr>
<td>APA</td>
<td>American Psychiatric Association</td>
</tr>
<tr>
<td>CGIC</td>
<td>Clinical Global Impression of Change</td>
</tr>
<tr>
<td>CGI-TD</td>
<td>Clinical Global Impression of Change – Tardive Dyskinesia</td>
</tr>
<tr>
<td>DBZ</td>
<td>Deutetrabenazine</td>
</tr>
<tr>
<td>DRBA</td>
<td>Dopamine Receptor Blocking Agent</td>
</tr>
<tr>
<td>DSM-5</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>ECT</td>
<td>Electroconvulsive Therapy</td>
</tr>
<tr>
<td>EPS</td>
<td>Extrapyramidal Symptoms</td>
</tr>
<tr>
<td>PBO</td>
<td>Placebo</td>
</tr>
<tr>
<td>PGIC</td>
<td>Patient Global Impression of Change</td>
</tr>
<tr>
<td>RDBPC</td>
<td>Randomized, Double Blind, Placebo Controlled</td>
</tr>
<tr>
<td>SNRI</td>
<td>Serotonin-Norepinephrine Reuptake Inhibitor</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective Serotonin Reuptake inhibitor</td>
</tr>
<tr>
<td>TD</td>
<td>Tardive Dyskinesia</td>
</tr>
<tr>
<td>VBZ</td>
<td>Valbenazine</td>
</tr>
<tr>
<td>VMAT</td>
<td>Vesicular Monoamine Transporter</td>
</tr>
<tr>
<td>WFSBP</td>
<td>World Federation of Societies of Biological Psychiatry</td>
</tr>
</tbody>
</table>
B. Patient Case – SV

**HPI:** SV is a 34 year old Hispanic female who presents to your mental health clinic for medication management. She states she began experiencing slight involuntary movements of the tongue and jaw 7 months ago which have progressed into marked movements of the tongue and jaw, grimacing, and moderate choreic movements of the upper limbs.


**Medications:** She has been stable on her current medication regimen for the past 6 years, however 12 months ago her risperidone was increased from 4 mg to 6 mg:

- Risperidone 6 mg PO daily
- Metformin ER 1000 mg PO daily
- Sertraline 100 mg PO daily
- Acetaminophen 325 mg PO PRN

Previous psychiatric medication trials:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Reason for discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol 15 mg PO daily</td>
<td>Acute dystonic reaction</td>
</tr>
<tr>
<td>Olanzapine 20 mg PO daily</td>
<td>Weight gain; breakthrough psychosis</td>
</tr>
<tr>
<td>Quetiapine 600 mg PO qHS</td>
<td>Weight gain, sedation</td>
</tr>
<tr>
<td>Aripiprazole 10 mg PO daily</td>
<td>Akathisia</td>
</tr>
<tr>
<td>Duloxetine 60 mg PO daily</td>
<td>Insomnia</td>
</tr>
</tbody>
</table>
## C. 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.

<table>
<thead>
<tr>
<th>Facial and Oral Movements</th>
<th>1. Muscles of Facial Expression</th>
<th>0 1 2 3 4</th>
<th>0 1 2 3 4</th>
<th>0 1 2 3 4</th>
<th>0 1 2 3 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>e.g. movements of forehead, eyebrows, periorbital area, cheeks, including frowning, blinking, smiling, grimacing</td>
<td>RATER 1 2 3 4</td>
<td>RATER 1 2 3 4</td>
<td>RATER 1 2 3 4</td>
<td>RATER 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>2. Lips and Perioral Area</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>e.g., puckering, pouting, smacking</td>
<td>RATER 1 2 3 4</td>
<td>RATER 1 2 3 4</td>
<td>RATER 1 2 3 4</td>
<td>RATER 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>3. Jaw</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>e.g. biting, clenching, chewing, mouth opening, lateral movement</td>
<td>RATER 1 2 3 4</td>
<td>RATER 1 2 3 4</td>
<td>RATER 1 2 3 4</td>
<td>RATER 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>4. Tongue</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>Rate only increases in movement both in and out of mouth. NOT inability to sustain movement. Darting in and out of mouth.</td>
<td>RATER 1 2 3 4</td>
<td>RATER 1 2 3 4</td>
<td>RATER 1 2 3 4</td>
<td>RATER 1 2 3 4</td>
</tr>
<tr>
<td>Extremity Movements</td>
<td>5. Upper (arms, wrists,, hands, fingers)</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>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)</td>
<td>RATER 1 2 3 4</td>
<td>RATER 1 2 3 4</td>
<td>RATER 1 2 3 4</td>
<td>RATER 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>6. Lower (legs, knees, ankles, toes)</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot.</td>
<td>RATER 1 2 3 4</td>
<td>RATER 1 2 3 4</td>
<td>RATER 1 2 3 4</td>
<td>RATER 1 2 3 4</td>
</tr>
<tr>
<td>Trunk Movements</td>
<td>7. Neck, shoulders, hips</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>e.g., rocking, twisting, squirming, pelvic gyrations</td>
<td>RATER 1 2 3 4</td>
<td>RATER 1 2 3 4</td>
<td>RATER 1 2 3 4</td>
<td>RATER 1 2 3 4</td>
</tr>
<tr>
<td>Global Judgments</td>
<td>8. Severity of abnormal movements overall</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>9. Incapacitation due to abnormal movements</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>10. Patient’s awareness of abnormal movements</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>Rate only patient’s report No awareness 0</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>Aware, no distress 1</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>Aware, mild distress 2</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>Aware, moderate distress 3</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td></td>
<td>Aware, severe distress 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Dental Status</td>
<td>11. Current problems with teeth and/or dentures?</td>
<td>No Yes</td>
<td>No Yes</td>
<td>No Yes</td>
<td>No Yes</td>
</tr>
<tr>
<td></td>
<td>12. Are dentures usually worn?</td>
<td>No Yes</td>
<td>No Yes</td>
<td>No Yes</td>
<td>No Yes</td>
</tr>
<tr>
<td></td>
<td>13. Edentia?</td>
<td>No Yes</td>
<td>No Yes</td>
<td>No Yes</td>
<td>No Yes</td>
</tr>
<tr>
<td></td>
<td>14. Do movements disappear in sleep?</td>
<td>No Yes</td>
<td>No Yes</td>
<td>No Yes</td>
<td>No Yes</td>
</tr>
</tbody>
</table>

**CODE**

- 0 = None
- 1 = Minimal (may be extreme normal)
- 2 = Mild
- 3 = Moderate
- 4 = Severe
Description

The entire test can be completed in about 10 minutes. The AIMS test has a total of twelve items rating involuntary movements of various areas of the patient's body. These items are rated on a five-point scale of severity from 0–4. The scale is rated from 0 (none), 1 (minimal), 2 (mild), 3 (moderate), 4 (severe). Two of the 12 items refer to dental care. The patient must be calm and sitting in a firm chair that doesn't have arms, and the patient cannot have anything in his or her mouth. The clinician asks the patient about the condition of his or her teeth and dentures, or if he or she is having any pain or discomfort from dentures.

The remaining 10 items refer to body movements themselves. In this section of the test, the clinician or rater asks the patient about body movements. The rater also looks at the patient in order to note any unusual movements first-hand. The patient is asked if he or she has noticed any unusual movements of the mouth, face, hands or feet. If the patient says yes, the clinician then asks if the movements annoy the patient or interfere with daily activities. Next, the patient is observed for any movements while sitting in the chair with feet flat on the floor, knees separated slightly with the hands on the knees. The patient is asked to open his or her mouth and stick out the tongue twice while the rater watches. The patient is then asked to tap his or her thumb with each finger very rapidly for 10–15 seconds, the right hand first and then the left hand. Again the rater observes the patient's face and legs for any abnormal movements.

After the face and hands have been tested, the patient is then asked to flex (bend) and extend one arm at a time. The patient is then asked to stand up so that the rater can observe the entire body for movements. Next, the patient is asked to extend both arms in front of the body with the palms facing downward. The trunk, legs and mouth are again observed for signs of TD. The patient then walks a few paces, while his or her gait and hands are observed by the rater twice.

Results

The total score on the AIMS test is not reported to the patient. A rating of 2 or higher on the AIMS scale, however, is evidence of tardive dyskinesia. If the patient has mild TD in two areas or moderate movements in one area, then he or she should be given a diagnosis of TD. The AIMS test is considered extremely reliable when it is given by experienced raters.

If the patient's score on the AIMS test suggests the diagnosis of TD, the clinician must consider whether the patient still needs to be on an antipsychotic medication. This question should be discussed with the patient and his or her family. If the patient requires ongoing treatment with antipsychotic drugs, the dose can often be lowered. A lower dosage should result in a lower level of TD symptoms. Another option is to place the patient on a trial dosage of Clozapine (Clozaril), a newer antipsychotic medication that has fewer side effects than the older neuroleptics.
Examination Procedure

Either before or after completing the examination procedure, observe the patient unobtrusively at rest (e.g., in the waiting room).

The chair to be used in this examination should be a hard, firm one without arms. Have the person remove their shoes and socks.

1. Ask the patient whether there is anything in his or her mouth (such as gum or candy) and, if so, to remove it.
2. Ask about the "current" condition of the patient's teeth. Ask if he or she wears dentures. Ask whether teeth or dentures bother the patient "now".
3. Ask whether the patient notices any movements in his or her mouth, face, hands, or feet. If yes, ask the patient to describe them and to indicate to what extent they "currently" bother the patient or interfere with activities.
4. Have the patient sit in chair with hands on knees, legs slightly apart, and feet flat on floor. (Look at the entire body for movements while the patient is in this position.)
5. Ask the patient to sit with hands hanging unsupported -- if male, between his legs, if female and wearing a dress, hanging over her knees. (Observe hands and other body areas).
6. Ask the patient to open his or her mouth. (Observe the tongue at rest within the mouth.) Do this twice.
7. Ask the patient to protrude his or her tongue. (Observe abnormalities of tongue movement.) Do this twice.
8. Ask the patient to tap his or her thumb with each finger as rapidly as possible for 10 to 15 seconds, first with right hand, then with left hand. (Observe facial and leg movements.)
9. Flex and extend the patient's left and right arms, one at a time.
10. Ask the patient to stand up. (Observe the patient in profile. Observe all body areas again, hip included.)
11. Ask the patient to extend both arms out in front, palms down. (Observe trunk, legs, and mouth.)
12. Have the patient walk a few paces, turn, and walk back to the chair. (Observe hands and gait.) Do this twice.

Source: National Institute of Mental Health
D. Algorithm - Treating TD in Patients with Stable Psychiatric Diagnoses

Is chronic DRBA use necessary?

- Yes
  - Continue current treatment and assess severity and functional impairment of TD
    - Absent or minimal impairment in function
    - Moderate or severe impairment in function
      - Consider dose reduction + follow-up AIMS in 3 months
      - Consider dose reduction + follow-up AIMS in 1 month
    - Improvement of TD?
      - Yes
        - Add ginkgo biloba 120 mg BID OR, Amantadine 100 mg daily + follow-up AIMS in 1 month
        - Improvement of TD?
          - Yes
            - Baseline EKG + Consider VMAT-2 inhibitor + Follow-up AIMS in 1 month
          - No
            - Baseline EKG + Consider VMAT-2 inhibitor + Follow-up AIMS in 1 month
        - Improvement of TD?
          - Yes
            - Baseline EKG + Consider VMAT-2 inhibitor + Follow-up AIMS in 1 month
          - No
            - Baseline EKG + Consider VMAT-2 inhibitor + Follow-up AIMS in 1 month

- No
  - Discontinue DRBA + follow-up AIMS in 3 months
  - Continue TD management and follow-up AIMS in 3 months