Does Your Patient Have Tardive Dyskinesia?
Recognition and Treatment for Improving Quality of Life
Faculty

Jason P. Caplan, MD, FAPA, FACLP
Chair of Psychiatry
St. Joseph’s Hospital & Medical Center
Professor of Psychiatry
Creighton University School of Medicine
Phoenix, AZ
Disclosures

Jason P. Caplan, MD, FAPA, FAclrP serves as a speaker for Neurocrine Biosciences and Acadia Pharmaceuticals. Dr. Caplan also serves as an advisory board member for Alkermes and as a speaker and consultant for Avanir Pharmaceuticals.
Learning Objectives

1. Outline the pathophysiology and risk factors for tardive dyskinesia (TD);
2. Describe the clinical manifestations and diagnosis of TD;
3. Recognize the impact of TD on the patient’s quality of life;
4. Discuss the efficacy and safety of treatment options for TD.
Pre-test ARS Question 1

Pre-T1: How often do you prescribe dopamine receptor blocking agents (including antipsychotics like aripiprazole, quetiapine, olanzapine, or risperidone) in your practice?

1. Never
2. Rarely
3. Occasionally
4. Frequently
5. Very frequently
Pre-test ARS Question 2

Pre-T2: Please rate your confidence in your ability to recognize tardive dyskinesia in your patient population:

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Pre-test ARS Question 3

Pre-T3: Please rate your confidence in your ability to manage tardive dyskinesia in your patient population:

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Tardive Dyskinesia

- Delayed-onset movement disorder associated with any dopamine receptor blocking agent
- Frequently irreversible
- Movements may involve a variety of body areas:
  - Face
  - Eyes
  - Mouth/lips/tongue
  - Trunk
  - Arms/hands/fingers
  - Legs/feet/toes
Dopamine Receptor Blocking Agents (DRBAs)

Antipsychotics

- First generation (typical) including:
  - Chlorpromazine
  - Haloperidol
  - Fluphenazine
- Second generation (atypical) including:
  - Quetiapine
  - Olanzapine
  - Aripiprazole
  - Risperidone
- Non-psychotropics
  - Metoclopramide
Uses of “antipsychotics”

**Used on-label for:**
- Schizophrenia
- Bipolar disorder
- Major depressive disorder

**Have been used off-label for:**
- Behavioral and psychiatric symptoms of dementia
- Anxiety disorders
- Insomnia
Increased use of DRBAs

- >400% increase over last 25 years
- 15 million prescriptions/year in early 1990s
- 66 million prescriptions/year in 2017
Pre-test ARS Question 4

Pre-T4: In the United States, approximately what percentage of antipsychotics are prescribed by primary care providers?

1. 7%
2. 17%
3. 27%
4. 37%
5. 47%
Use in Primary Care

- 37% of antipsychotic prescriptions written by primary care physicians
- 6% by nurse practitioners and physician assistants
- 8% by all other specialties
- 49% by psychiatrists
How Common is it?

- **Annual incidence**
  - 5.5% for patients on first-generation agents
    - ~one in 18 patients
  - 3.9% or patients on second-generation agents
    - ~one in 26 patients

Does it get Better?

- Data is variable:
  - With continued DRBA exposure: 2.5% remission rate
  - With permanent discontinuation of DRBAs: 12-22% remission rate

- In the best case scenario, 78% of patients with TD will not experience remission even if the DRBA is permanently discontinued
Differential Diagnosis

❖ DRBA-induced movement disorders
  - Acute vs tardive

❖ Acute
  - Acute dystonia
  - Akathisia
  - Drug-induced Parkinsonism

❖ Tardive
  - Tardive dyskinesia
  - Neuroleptic withdrawal emergent dyskinesia
Acute Disorders

- Acute dystonia
  - Minutes to hours after first dose or increased dose
  - Dystonic posturing of limbs
  - Torticollis
  - Oculogyric crisis
  - Treated with IM anticholinergics

- Akathisia
  - Hours to days after first dose or increased dose
  - Motoric restlessness
  - “can’t sit still”
  - Treated with beta-blocker
Neuroleptic Withdrawal Emergent Dyskinesia

- Onset after discontinuation or lowered dose of a neuroleptic
- Resolves spontaneously within three months
Drug-induced Parkinsonism vs. Tardive Dyskinesia

- **Drug-induced Parkinsonism**
  - “classical music”
  - Steady resting tremor
  - Shuffling gait
  - Bradykinesia
  - “pill rolling” hands

- **Tardive dyskinesia**
  - “be-bop jazz”
  - Unpredictable arrhythmic movements
  - “piano playing” hands
 Movements of TD

- **Head/Face/Mouth**
  - Chewing
  - Jaw thrusting
  - Tongue movements
  - Cheek bulging
  - Lip smacking, puckering, or pursing
  - Frowning/grimacing
  - Blinking

- **Trunk**
  - Twisting
  - Shoulder shrugging
  - Rocking/swaying

- **Limbs**
  - Finger flicking
  - “Piano playing” movements
  - Dystonic extension of toes or fingers
  - Foot tapping
Classic TD
Piano Playing Fingers
Facial movements, foot tapping
Life-threatening TD

- Involvement of the pharynx
  - Aspiration risk
- Involvement of the diaphragm
Pre-test ARS Question 5

Pre-T5: Which of the following patients would be considered highest risk for the development of TD due to prescription of an antipsychotic?

1. 24 year-old African-American man with schizophrenia
2. 68 year-old Caucasian woman with treatment-resistant depression
3. 55 year-old Asian man with schizoaffective disorder
4. 20 year-old Caucasian woman with schizophrenia
5. They are all of equal risk
Who’s at risk?

**Patient Factors**
- Women
- Increased age
- Substance use (including tobacco, alcohol, illicit drugs)
- Primary mood disorder (i.e., patients receiving DRBAs for something other than schizophrenia/schizoaffective disorder)
- Diabetes mellitus

**Treatment Factors**
- Potency of DRBA used
- Time of exposure
- Drug-induced Parkinsonism
- Exposure to anticholinergics
Standard of Care according to APA Practice Guideline

- Must document monitoring of patients on DRBAs for TD

- Low risk patients
  - On a second generation agent – once a year
  - On a first generation agent – every six months

- High risk patients
  - On a second generation agent – every six months
  - On a first generation agent – every three months
Abnormal Involuntary Movement Scale (AIMS) Exam

- Hard-backed armless chair
- Shoes and socks off
- Discard gum or candy
- Watch for movements in systematic way
  - Head/face/neck
  - Torso/upper extremities
  - Lower extremities
- Don’t let one area distract you from the others
- Employ distraction techniques to minimize suppression
# AIMS Exam

<table>
<thead>
<tr>
<th>FACIAL / ORAL MOVEMENT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. MUSCLES of FACIAL EXPRESSION - movements of forehead, eyebrows, cheeks, periorbital area [include frowning, blinking, smiling, grimacing].</td>
<td>3</td>
</tr>
<tr>
<td>2. LIPS &amp; PERIORAL AREA - puckering, pouting, lip smacking.</td>
<td>3</td>
</tr>
<tr>
<td>3. JAW - biting, clenching, chewing, mouth opening, lateral movement.</td>
<td>4</td>
</tr>
<tr>
<td>4. TONGUE - rate increase in movement, both in / out of mouth [not inability to sustain movement].</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EXTREMITY MOVEMENT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5. UPPER (Arms, Wrist, Hands, Fingers) - Choreic Movements [rapid, objectively purposeless, irregular, spontaneous]; Athetoid Movements [slow, irregular, complex, serpentine]. Do’t include Tremor [repetitive, regular, rhythmic].</td>
<td>0</td>
</tr>
<tr>
<td>6. LOWER (Legs, Knees, Hands, Toes) - lateral knee movement, foot tapping, heel dropping, foot squirming, foot inversion / eversion.</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TRUNK</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>7. NECK, SHOULDERS, HIP - rocking, twisting, squirming, pelvic gyrations.</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GLOBAL JUDGMENT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>8. SEVERITY OF ABNORMAL MOVEMENTS</td>
<td>4</td>
</tr>
<tr>
<td>9. INCAPACITY DUE TO ABNORMAL MOVEMENTS</td>
<td>2</td>
</tr>
<tr>
<td>10. PATIENT'S AWARENESS OF ABNORMAL MOVEMENTS (rate only Resident's Report ) - 0 = Aware / No Distress; 2 = Aware / Mild Distress; 3 = Aware / Moderate Distress; 4 = Aware / Severe Distress.</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DENTAL STATUS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>11. DOES RESIDENT USUALLY WEAR DENTURES?</td>
<td>YES</td>
</tr>
<tr>
<td>12. CURRENT TEETH / DENTURE PROBLEMS?</td>
<td>YES</td>
</tr>
</tbody>
</table>
Sequelae of TD and Impact on Quality of Life

Complications of TD include:

- Oral/dental
  - Ulceration/infection of tongue, cheeks, and lips
- Impairment of speech
- Respiratory
  - Disturbances of rate, depth, and rhythm of breathing
  - Snorting, grunting, gasping
- Swallowing
- Weight loss

Jeste DV et al. Schizophr Bull. 1993; 19:303-315
Pre-test ARS Question 6

Pre-T6: According to the RE-KINECT study, approximately what percentage of patients with TD did not have symptoms involving their head/face/neck?:

1. 2%
2. 5%
3. 10%
4. 25%
5. 33%
Sequelae of TD and Impact on Quality of Life

- Re-KINECT study
- Study of 739 patients
  - Exposed to at least one antipsychotic for at least 3 months
  - 37 different outpatient practices across the US
  - Actively screened for TD
- 28% screened positive for TD
  - Primary diagnoses of:
    - Schizophrenia
    - Anxiety disorders
    - Bipolar disorder
    - Schizoaffective disorder
    - Major depressive disorder
Sequelae of TD and Impact on Quality of Life

- Body area affected:
  - Head/face/neck: 66.0%
  - Arms/hands/fingers: 59.1%
  - Legs/feet/toes: 42.4%
  - Trunk: 20.9%

- >50% had at least 2 areas affected
Sequelae of TD and Impact on Quality of Life

<table>
<thead>
<tr>
<th></th>
<th>Screened out for TD</th>
<th>Screened in for TD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobility: walking</td>
<td>32.8</td>
<td>41.8</td>
</tr>
<tr>
<td>Self-care: washing/dressing</td>
<td>20.9</td>
<td>32.5</td>
</tr>
<tr>
<td>Usual activities: work/study/leisure</td>
<td>46.8</td>
<td>51.0</td>
</tr>
<tr>
<td>Pain/discomfort</td>
<td>56.5</td>
<td>63.9</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td>72.5</td>
<td>76.7</td>
</tr>
</tbody>
</table>

Percentage of patients scoring at least 2 (“slight problems”) on 5-point scale of EuroQOL-5 Dimension-5 Level (ED-5D-5L) scale
Pre-test ARS Question 7

Pre-T7: Evidence-based medicine supports the use of which of the following approaches for managing TD?

1. Diphenhydramine
2. Benztropine
3. Valbenazine
4. Switch to a second-generation antipsychotic
5. High-dose vitamin E
Folklore of Treating TD

- Change the dose/agent
  - From 2018 consensus statement:
  - Data are insufficient to support treatment by withdrawing causative agents or switching from typical to atypical DRBA (level U)

- Anticholinergics
  - From benztropine package insert:
  - Benztropine is indicated as an adjunct in the treatment of Parkinsonism and is useful in the control of extrapyramidal disorders (other than TD) due to neuroleptic drugs
  - Antiparkinsonian agents do not alleviate the symptoms of TD, and in some instances may aggravate them
  - Benztropine is not recommended for use in patients with TD
Other Things we’ve Tried:

- Clonazepam (Level B)
- Gingko biloba (Level B)
- Amantadine (Level C)
- Vitamin E (Level U)
Pre-test ARS Question 8

Pre-T8: What is the primary mechanism of action of the VMAT2 inhibitors?

1. Inhibition of the synthesis of dopamine
2. Inhibition of the packaging of recycled dopamine for re-release
3. Stimulation of the enzymes that break down excess dopamine
4. Conversion of dopamine to an inactive form
5. Down-regulation of post-synaptic dopamine receptors
TD Pathophysiology

[Diagram showing the process involving VMAT2, dopamine, and dopamine receptors transporters]
Vesicular Monoamine Transporter Type-2 (VMAT2) Inhibitors

- Tetrabenazine (Xenazine)
- Deutetrabenazine (Austedo)
- Valbenazine (Ingrezza)
Tetrabenazine

- VMAT2 reversible inhibitor
- Treatment used for schizophrenia in the 1970s; obtained FDA approval in 2009 for Huntington’s disease
- Is **NOT** FDA approved for treatment of tardive dyskinesia
- Requires dosing titration and TID dosing
- Numerous adverse effects limit its clinical use; some serious and potentially fatal:
  - Sedation, parkinsonism, EPS, dysphagia, hypotension, neuroleptic malignant syndrome
  - **Depression, suicidality [BOXED WARNING]**
Deutetrabenazine

- VMAT2 reversible inhibitor
- Tetrabenazine with hydrogen replaced with deuterium at primary sites of metabolism
- Deuterium is “heavy hydrogen” – shortens the bond and slows metabolism
- Lengthens half-life so deutetrabenazine can be dosed BID instead of TID for tetrabenazine.
- FDA-approved for both Tardive Dyskinesia (8/30/17) and Huntington’s disease (4/4/17)
Deutetrabenazine

- **Dose Availability:** 6 mg, 9 mg, 12 mg tablets
- **Tardive Dyskinesia Treatment**
  - Initiate at 6 mg po twice daily, titrate up at weekly intervals by 6 mg per day to a tolerated dose that reduces chorea or tardive dyskinesia, up to a maximum daily dose of 48 mg (24 mg po twice daily)
- **Take with food**
- **If patient is on any other QT-prolonging medication, check EKG if increasing from 24 mg**
- **Avoid use in patients with congenital long QT syndrome or arrhythmias associated with prolonged QT interval**
- **Contraindicated in hepatic impairment**
Deutetrabenazine

**WARNING: DEPRESSION AND SUICIDALITY IN PATIENTS WITH HUNTINGTON’S DISEASE**

Deutetrabenazine can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease. Anyone considering the use of Deutetrabenazine must balance the risks of depression and suicidality with the clinical need for treatment of chorea. Closely monitor patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior. Patients, their caregivers, and families should be informed of the risk of depression and suicidality and should be instructed to report behaviors of concern promptly to the treating physician.

Particular caution should be exercised in treating patients with a history of depression or prior suicide attempts or ideation, which are increased in frequency in Huntington's disease. Deutetrabenazine is contraindicated in patients who are suicidal, and in patients with untreated or inadequately treated depression [see Contraindications (4) and Warnings and Precautions (5.1)].
Deutetrabenazine

Adverse Reactions in Patients with Huntington's Disease (Study 1) Experienced by at Least 4% of patients on Deutetrabenazine and with a Greater Incidence than on Placebo

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Deutetrabenazine (N=45) %</th>
<th>Placebo (N=45) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Contusion</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

One or more adverse reaction resulted in a reduction of the dose of study medication in 7% of patients in Study 1. The most common adverse reaction resulting in dose reduction in patients receiving Deutetrabenazine was dizziness (4%). Agitation led to discontinuation in 2% of patients treated with Deutetrabenazine in Study 1.
### Deutetrabenazine

**Adverse Reactions in 2 Placebo-Controlled Tardive Dyskinesia Studies (Study 1 and Study 2) of 12-week Treatment on Deutetrabenazine Reported in at Least 2% of Patients and Greater than Placebo**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Deutetrabenazine (N=279) %</th>
<th>Placebo (N=131) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Depression/Dysthymic disorder</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Akathisia/Agitation/Restlessness</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

One or more adverse reaction resulted in a reduction of the dose of study medication in 4% Deutetrabenazine-treated patients and in 2% of placebo-treated patients.
Valbenazine

- Highly-selective reversible VMAT2 inhibitor
- Orally active agent with metabolite also a highly selective VMAT2 inhibitor
- FDA-approved for Tardive Dyskinesia on 4/11/17
Valbenazine

- Dose Availability: 40 mg, 80 mg capsule
- Tardive dyskinesia Treatment
  - Initiate at 40 mg po daily; increase to 80 mg po daily after one week
  - Can maintain at 40 mg if moderate or severe hepatic impairment or if used with strong CYP3A4 inhibitors
- Take with or without food
- Avoid use in patients with congenital long QT syndrome or arrhythmias associated with prolonged QT interval
- “Degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing.”
## Verbenalin

Adverse Reactions in 3 Placebo-Controlled Studies of 6-week Treatment Duration Reported at >2% and >Placebo

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Valbenazine (n=262) (%)</th>
<th>Placebo (n=183) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence (somnolence, fatigue, sedation)</td>
<td>10.9%</td>
<td>4.2%</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticholinergic effects (dry mouth, constipation, disturbance in attention, vision blurred, urinary retention)</td>
<td>5.4%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Balance disorders/fall (fall, gait, disturbance, dizziness, balance disorder)</td>
<td>4.1%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Headache</td>
<td>3.4%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Akathisia (akathisia, restlessness)</td>
<td>2.7%</td>
<td>0.5%</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.3%</td>
<td>2.1%</td>
</tr>
<tr>
<td><strong>Musculoskeletal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2.3%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

*Within each adverse reaction category, the observed adverse reactions are listed in order of decreasing frequency.*
POST-TEST QUESTIONS
Post-test ARS Question 1

Post-T1: In the United States, approximately what percentage of antipsychotics are prescribed by primary care providers?

1. 7%
2. 17%
3. 27%
4. 37%
5. 47%
Post-test ARS Question 2

Post-T2: Which of the following patients would be considered highest risk for the development of TD due to prescription of an antipsychotic?

1. 24 year-old African-American man with schizophrenia
2. 68 year-old Caucasian woman with treatment-resistant depression
3. 55 year-old Asian man with schizoaffective disorder
4. 20 year-old Caucasian woman with schizophrenia
5. They are all of equal risk
Post-test ARS Question 3

Post-T3: According to the RE-KINECT study, approximately what percentage of patients with TD did not have symptoms involving their head/face/neck?:

1. 2%
2. 5%
3. 10%
4. 25%
5. 33%
Post-test ARS Question 4

Post-T4: Evidence-based medicine supports the use of which of the following approaches for managing TD?

1. Diphenhydramine
2. Benztropine
3. Valbenazine
4. Switch to a second-generation antipsychotic
5. High-dose vitamin E
Post-test ARS Question 5

Post-T5: What is the primary mechanism of action of the VMAT2 inhibitors?:

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2. Inhibition of the packaging of recycled dopamine for re-release
3. Stimulation of the enzymes that break down excess dopamine
4. Conversion of dopamine to an inactive form
5. Down-regulation of post-synaptic dopamine receptors