Tardive Dyskinesia: A Movement Towards Better Treatment Strategies?

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February 20th, 2018
Objectives

- Identify risk factors and medications that contribute to the development of tardive dyskinesia
- Select a drug-therapy plan to mitigate the development of tardive dyskinesia in a patient presenting with early symptoms
- Describe a patient that may benefit from one of the novel therapies approved for the treatment of tardive dyskinesia
Types of Extrapyramidal Symptoms (EPS)

- **Akathisia**: Minutes to hours
  - Restlessness, excessive movements

- **Dystonia**: Hours to days
  - Abnormal, prolonged muscle contraction

- **Parkinsonism**: Days to weeks
  - Parkinsonian tremor, muscular rigidity

- **Tardive Dyskinesia**: 3 to 6 months
  - Involuntary, rapid, repetitive movements (typically orofacial)
Tardive Dyskinesia, DSM-V Definition

“Involuntary athetoid or choreiform movements (lasting at least a few weeks) generally of the tongue, lower face and jaw, and extremities (but sometimes involving the pharyngeal, diaphragmatic, or trunk muscles) developing in association with the use of a neuroleptic medication for at least a few months.”

• Anxiety and stress can exacerbate symptoms
• Can develop mixed drug-induced movement disorders
  • Important to note the time of onset and what the actual movement is
• Can potentially be life-threatening (diaphragm movement)
• Overall Diagnosis: Onset, movement, no other cause
Screening with AIMS

• AIMS (Abnormal Involuntary Movement Scale)
  • Developed by the US National Institute of Mental Health

• NOT used for diagnosis

• Can be used as a structured way to screen patients and follow progress over time (classify presence/severity)
  • Used in clinical trials for new agents
  • Every 3 months for specific symptoms (every 6-12 months for screening)

• Other screening tools exist (DISCUS)
**AIMS**

- Rates dyskinetic movements in 7 body regions
- Score 0-4 in each region:
  - 0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe

<table>
<thead>
<tr>
<th>I FACIAL &amp; ORAL MOVEMENTS</th>
<th>II EXTREMITIES MOVEMENTS</th>
<th>III TRUNK MOVEMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Muscles of Facial Expression</strong> e.g. movements of forehead, eyebrows, periorbital area, cheeks, including frowning, blinking, smiling, grimacing</td>
<td>5. <strong>Upper (arms, wrists, hands, fingers)</strong> Include choreic movements (i.e. rapid objectively purposeless, irregular, spontaneous) athetoid movements. DO NOT INCLUDE TREMOR (i.e. repetitive, regular, rhythmic)</td>
<td>7. <strong>Neck, shoulders and hips</strong> Rocking, twisting, squirming, pelvic gyrations</td>
</tr>
<tr>
<td>2. <strong>Lips and Perioral Area</strong> e.g. puckering, pouting, smacking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. <strong>Jaw</strong> Biting, clenching, chewing, mouth opening, lateral movement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. <strong>Tongue</strong> Rate only increases in movement both in and out of mouth. NOT inability to sustain movement. Darting in and out of mouth</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Correll CU. *J Clin Psych* 2017
**AIMS – Outside of the Body Regions**

- Severity
- Impact
- Awareness
- Rule out dental causes

| IV GLOBAL JUDGEMENT |  
|---------------------|---
| 8. Severity of abnormal movements overall |  
| 9. Incapacitation due to abnormal movements |  
| 10. Patient’s awareness of abnormal movements. Rate only patients report:  
  - No Awareness = 0  
  - Aware, no distress = 1  
  - Aware, mild distress = 2  
  - Aware, moderate distress = 3  
  - Aware, severe distress = 4 |  

| V DENTAL STATUS |  
|----------------|---
| 11. Current problems with teeth and/or dentures |  
| 12. Are dentures usually worn |  
| 13. Endentia? |  
| 14. Do movements disappear with sleep? |  

Very important to complete **throughout** the visit!
Videos of Tardive Dyskinesia

• Severe
• Moderate
• Mild
Pathophysiology – Basal Ganglia

Tardive Dyskinesia

= Dopamine (DA)
= DA receptor
= DA receptor antagonist (drug)
= Sensitized DAR
Pathophysiology – Basal Ganglia

Increasing dose = masking effects

Stopping drug = all receptors available, significant risk of movement disorders
Drugs Causing Tardive Dyskinesia

1st generation antipsychotics
5-30% Incidence

2nd generation antipsychotics
0.8-20% Incidence

Partial Dopamine Agonist
Aripiprazole*

Anti-emetics
1-15% Incidence (likely much lower)

*Warning for TD but controversial evidence to support it may improve TD
Risk Factors for Tardive Dyskinesia

- Duration of treatment, total daily dose
- Mood Disorders – Depression, Bipolar, Anxiety
- “Drug holidays” – stopping and starting treatment
- Female > male
- Advanced age
  - Five times higher risk in elderly, more often irreversible
- Comorbidities: Diabetes, alcoholism/substance abuse, iron deficiency, HIV, cognitive impairment
- History of extrapyramidal reaction
Patient Case

• JP is a 25 year old woman who was diagnosed with schizophrenia approximately 2 months ago. She was started on haloperidol at that time and is currently taking 15 mg daily.

• Her past medical history includes drug-induced Parkinsonism, for which she takes benztropine, and alcohol use disorder
Question 1:

In patient JP specifically, which is **not** considered a risk factor for TD development?

- A. Haloperidol use
- B. Female
- C. Duration of anti-psychotic therapy
- D. Substance abuse history
- E. History of drug-induced Parkinsonism
Management Overview

Prevention

- 1st vs. 2nd generation antipsychotics
- Use lowest effective dose
- Avoid “drug holidays”
- Screening tools – prompt recognition
  - Irreversible in 80% of patients

Treatment of early/reversible causes

- Change to agent with lower risk
  - Olanzapine, quetiapine, risperidone, clozapine
- Off-label treatments (low evidence)
  - Clonazepam, amantadine, tetrabenazine
- FDA approved treatments (new)
Changing Antipsychotics

Gradually switch from a 1st to a 2nd generation antipsychotic

Olanzapine, quetiapine, risperidone, (not clozapine)
Clozapine – Details

- Prolonged onset of effect with rebound TD if clozapine is stopped
- Limited evidence of varying quality – case reports, older studies

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Design (n = patients)</th>
<th>Clozapine Dose</th>
<th>AIMS score reduction</th>
</tr>
</thead>
</table>
| Gerbino (1980)| Uncontrolled N = 24   | 900mg/day      | • All saw 50% reduction of AIMS score  
                                         • 7/24 had 100% remission at 4 weeks |
| Littrell (1993)| Uncontrolled N = 12     | Unknown        | • All saw 60% reduction by 1 month, 94% reduction by 4 months |
| Simpson (1978)| Single-blind N = 7     | 523-775mg/day  | • All saw >50% reduction by 12 weeks |
## AAN Guidelines – Adjunctive Off-label Treatment Options

<table>
<thead>
<tr>
<th>Agent</th>
<th>Description</th>
<th>Evidence</th>
</tr>
</thead>
</table>
| Clonazepam  | • **MOA**: indirect GABA agonist  
• Benefit in 37% of patients vs. placebo but tolerance developed in >50% after 5 months | Moderate |
| Amantadine  | • **MOA**: Blocks N-methyl-D-aspartate receptors  
• Average 15-22% reduction in AIMS score compared to placebo in two small trials  
• Pro-dopaminergic tone, potential psychosis | Weak     |
| Tetrabenazine | • **MOA**: Reversible vesicular monoamine transporter 2 inhibitor (reduces synaptic levels of dopamine)  
• 1:1 mix of enantiomers – one is a dopamine receptor antagonist - can induce parkinsonism  
• Short half-life, poorly tolerated, suicidality warning | Weak     |
Patient Case

- JP returns to your clinic 6 months later and states she feels her schizophrenia is well controlled with haloperidol.
- She has not trialed any other antipsychotics aside from haloperidol in her first 8 months of treatment.
- You notice a slight, but persistent, tongue protrusion motion in JP and ask to perform the AIMS assessment.
- She scores a 3 (moderate) on the facial and oral movements section but doesn’t show any other symptoms.
Question 2:

For patient JP, what is the most appropriate treatment strategy to pursue in order to prevent further development of tardive dyskinesia?

- A. Increase the dose of haloperidol
- B. Switch to clozapine
- C. Switch to clonazepam
- D. Switch to olanzapine
- E. Add on clonazepam
Valbenazine

- Brand name: Ingrezza®
- FDA approved for TD
  April 11\textsuperscript{th}, 2017
- Oral capsule
- 40mg once daily, increase to 80mg daily after one week
Mechanism of Action – VMAT2 Inhibitors

- VMAT2 – Vesicular monoamine transporter 2

Before Treatment

After Treatment

- VMAT2 transporter
- DA reuptake transporter
- VMAT2 inhibitor
KINECT 3 Trial – Valbenazine

- Randomized, double-blind, placebo-controlled, parallel-group

- Adults with schizophrenia, schizoaffective disorder ≥3 months + Tardive dyskinesia ≥3 months

- N=76
  - Valbenazine 40mg daily

- N=80
  - Valbenazine 80mg daily

- N=78
  - Placebo

- Concomitant psychiatric medications allowed if stable regimen for ≥30 days. Changes “discouraged”

- Excluded if other diagnosis of an involuntary movement disorder

Hauser et al. Am J Psychiatry 2017
Population

• Mean AIMS score was 10 (range 0-20)
• Baseline disease
  • 66.1% schizophrenia/schizoaffective disorder
  • 33.9% mood disorder
• Concomitant medications
  • 76.7% second generation antipsychotics
  • 16.7% first generation antipsychotics
• All baseline testing for psychiatric diseases indicated stable psychiatric disease
Primary Endpoint – AIMS Score Reduction

-0.1
-1.9*
-3.0**
-3.2**

Baseline Week 2 Week 4 Week 6 Week 48 Week 52

(washout)

AIMS Score Change From Baseline

Placebo
Valbenazine, 40mg
Valbenazine, 80mg

*P<0.01
**P<0.001

48 week extension

Hauser et al. Am J Psychiatry 2017
Factor et al. J Clin Psychiatry 2017
Secondary Outcome

- Clinical Global Impression of Change – Tardive Dyskinesia (CGI-TD) score
  - Rates overall change in tardive dyskinesia via observation (patient, practitioner)
  - Score 0-7 ranging from “very much worse” to “very much improved”
- Scores were not statistically significantly different between 80mg and placebo group
  - 40mg group was therefore not assessed

Conclusion: Valbenazine 80mg daily was well tolerated and statistically significantly improved tardive dyskinesia compared to placebo
ARM-TD Trial - Deutetrabenazine

- Randomized, double-blind, parallel-group study, 12 weeks

DRA treatment for ≥3 months + Tardive dyskinesia ≥3 months + AIMS score ≥6

Randomize

N=58
Deutetrabenazine 12mg/day Titrated weekly*

N=59
Placebo

Psych Disorder %

<table>
<thead>
<tr>
<th>Disorder</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia/Schizoaffective</td>
<td>68.4</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>23.1</td>
</tr>
<tr>
<td>Depression</td>
<td>25.6</td>
</tr>
</tbody>
</table>

*Mean daily dose achieved was 38.8mg/day

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Secondary Outcome: Deutetrabenazine Placebo P-value

CGIC treatment success 48.2% 40.4% Not significant

CGIC = Clinical Global Impression of Change

Conclusion: Deutetrabenazine may be an efficacious and well-tolerated treatment for abnormal movements in TD
AIM-TD Trial (Fixed Dose Trial) - Deutetrabenazine

- Randomized, double-blind, placebo-controlled, 12 weeks

DRA = dopamine receptor antagonist

<table>
<thead>
<tr>
<th>Randomize</th>
<th>12mg daily</th>
<th>24mg daily</th>
<th>36mg daily</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=75</td>
<td>N=74</td>
<td>N=75</td>
<td>N=74</td>
<td></td>
</tr>
</tbody>
</table>

Psych Disorder %

- Schizophrenia/Schizoaffective disorder: 60%
- Bipolar disorder: 17%
- Depression: 19%
- Other: 4%

Anderson et al. *Lancet* 2017
AIM-TD – Primary Outcome

Change in AIMS Score

- Placebo
- 12mg
- 24mg
- 36mg

Baseline Week 2 Week 4 Week 8 Week 12

AIMS Score Change

-3.5 -3.0 -2.5 -2.0 -1.5 -1.0 -0.5 0

-1.4

-2.1 p=0.217

-3.2 p=0.003

-3.3 p=0.001

Anderson et al. Lancet 2017

CGIC = Clinical Global Impression of Change
AIM-TD - Outcomes and Conclusion

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Placebo</th>
<th>12mg</th>
<th>24mg</th>
<th>36mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGIC treatment success</td>
<td>26%</td>
<td>28% (p=0.734)</td>
<td>49% (p=0.014)</td>
<td>44% (p=0.059)</td>
</tr>
</tbody>
</table>

**Conclusion:** Deutetrabenazine dosing regimens could be individualized to each patient’s response and tolerability.
## Safety (%)

<table>
<thead>
<tr>
<th>Safety</th>
<th>Valbenazine</th>
<th>Placebo</th>
<th>Deutetrabenazine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>5.3</td>
<td>3.9</td>
<td>13.8</td>
<td>10.2</td>
</tr>
<tr>
<td>Akathisia</td>
<td>3.3</td>
<td>1.3</td>
<td>5.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>2.6</td>
<td>5.3</td>
<td>0.0</td>
<td>1.7</td>
</tr>
<tr>
<td>D/C due to AE</td>
<td>80mg: 6.3, 40mg: 5.6</td>
<td>5.3</td>
<td>1.7</td>
<td>3.4</td>
</tr>
</tbody>
</table>

- Deutetrabenazine is contraindicated in suicidal patients/untreated depression due to trials done in Huntington’s Disease – not seen here.
- Package insert: avoid in congenital long QT or arrhythmias with long QT
  - No clinically relevant changes in ECG’s

D/C = Discontinuation
AE = Adverse Event

Hauser et al. *Am J Psychiatry* 2017
Fernandez et al. *Am Acad of Neurology* 2017
# New Agent Comparison

<table>
<thead>
<tr>
<th></th>
<th>Valbenazine</th>
<th>Deutetrabenazine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Once daily, one titration</td>
<td></td>
<td>• Twice daily, weekly titration</td>
</tr>
<tr>
<td>• Miss &gt;7 days must re-titrare</td>
<td></td>
<td>• Miss &gt;7 days must re-titrare</td>
</tr>
<tr>
<td><strong>Dose Adjustments</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CrCl &lt; 30 mL/min – not recommended</td>
<td></td>
<td>• No renal recommendations</td>
</tr>
<tr>
<td>• Moderate to severe hepatic impairment → 40mg daily</td>
<td></td>
<td>• C/I in hepatic dysfunction</td>
</tr>
<tr>
<td><strong>PGx</strong></td>
<td>CYP2D6 PM or 2D6 strong inhibitor use – decrease dose</td>
<td></td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Strong CYP3A4 inducer – avoid</td>
<td></td>
<td>• C/I with MAOIs</td>
</tr>
<tr>
<td>• Strong CYP3A4 inhibitor – 40mg max</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PM = poor metabolizer  
C/I = Contraindicated  
MAOi = monoamine oxidase inhibitor
## Cost Information

<table>
<thead>
<tr>
<th>Valbenazine Capsules</th>
<th>Cost (30 capsules)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40mg</td>
<td>$6,330.00</td>
</tr>
<tr>
<td>80mg</td>
<td>$7,470.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Deutetrabenazine Tablets</th>
<th>Cost (60 tablets – BID drug)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6mg</td>
<td>$3,945.60</td>
</tr>
<tr>
<td>9mg</td>
<td>$4,438.80</td>
</tr>
<tr>
<td>12mg</td>
<td>$5,918.40</td>
</tr>
</tbody>
</table>

- Currently require prescribing through specialty pharmacies in order to navigate approval processes and co-pays
Question 3:

• JP presents to your clinic with significantly worsened TD
• Looking over her chart you see that she has tried haloperidol, olanzapine, quetiapine, and is now treated with clozapine
• She claims her schizophrenia is well controlled but the TD symptoms in her face and arms are greatly impacting her quality of life as she cannot keep a job for more than a week
• You perform the AIMS assessment on her and unfortunately calculate a worsened AIMS score of 14
Question 3:

What is the best way to manage JP’s tardive dyskinesia symptoms?

• A. D/C clozapine and restart haloperidol
• B. D/C clozapine and start valbenazine 40mg daily
• C. Continue clozapine and start valbenazine 40mg daily
• D. D/C clozapine and start deutetrabenazine 24mg twice daily
• E. Continue clozapine and start deutetrabenazine 24mg twice daily
New Agents Place in Therapy

1. Gradually switch from a 1st to a 2nd generation antipsychotic
2. Try a different 2nd generation antipsychotic
3. Transition to clozapine

- Add on a VMAT2 Inhibitor
- Add on a VMAT2 Inhibitor

Study patients: Stable psychiatric disease, normal organ function, average AIMS of 10, no suicidal ideation in the last 6 months
Supplemental Slides
Deutetrabenazine - Structure

- Deuterium – naturally occurring, nontoxic, form of hydrogen
- Stabilizes rates of metabolism = decreased plasma fluctuations, less side effects due to peak concentrations
# Drugs Causing Tardive Dyskinesia (continued)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Drugs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergics</td>
<td>Procyclidine, orphenadrine, benzhexol</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>SSRIs (fluoxetine, sertraline), TCAs (amitriptyline, doxepin), MAOIs (phenelzine, rasagiline)</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Phenytoin &gt; carbamazepine, lamotrigine</td>
</tr>
<tr>
<td>Antiparkinson agents</td>
<td>Levodopa, bromocriptine</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>Lorazepam, clonazepam (usually withdrawal related, reversible)</td>
</tr>
<tr>
<td>Mood Stabilizers</td>
<td>Lithium</td>
</tr>
</tbody>
</table>

*TD is less common with these agents, usually when used in combination or in a patient with multiple risk factors for a long period of time.*

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**Notes:**
- SSRIs (selective serotonin reuptake inhibitors)
- TCAs (Tricyclic antidepressants)
- MAOIs (monoamine oxidase inhibitors)

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**References:**
- Cornett EM. Ochsner Journal 2017
- Chen JJ. US Pharm 2007
Diagnosis: Schooler-Kane Criteria

Must meet all 3 criteria

1. At least 3 months of antipsychotic exposure (continuous or discontinuous)

2. Exhibit abnormal, involuntary movements of moderate or greater severity in 1 or more body regions
   • Or mild severity in 2 or more body regions (according to AIMS scale)

3. Must be free of other conditions that may cause abnormal, involuntary movements
   • Huntington’s, Parkinson’s, Tourette’s, Wilson’s, hypoglycemia, dentures/no teeth, blind
DISCUS Score

- DISCUS (Dyskinesia Identification System: Condensed User Scale)
- Similar screening tool - used at Mayo Clinic
- 3 pre-requisites to use:
  - At least 3 months total cumulative antipsychotic drug exposure
  - Score a total of at least 5 points with the tool
  - Other conditions not responsible for the movements
DISCUS Score

- More specific movements assessed
- Neither tool correlates a certain score with diagnosis
  - Used more to track progress

<table>
<thead>
<tr>
<th>Category</th>
<th>Items</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>1. Tics .......................... 2. Grimaces..........................</td>
<td>0 1 2 3 4 NA</td>
</tr>
<tr>
<td>Eyes</td>
<td>3. Blinking .........................</td>
<td>0 1 2 3 4 NA</td>
</tr>
<tr>
<td>Oral</td>
<td>4. Chewing/Lip Smacking ...... 5. Puckering/Sucking Thrusting Lower Lip</td>
<td>0 1 2 3 4 NA</td>
</tr>
<tr>
<td>Head/ Neck/ Trunk</td>
<td>10. Retrocollis/Torticollis .... 11. Shoulder/Hip Torsion ...........</td>
<td>0 1 2 3 4 NA</td>
</tr>
<tr>
<td>Upper Limb</td>
<td>12. Athetoid/Myokymic Finger-Wrist-Arm 13. Pill Rolling ............</td>
<td>0 1 2 3 4 NA</td>
</tr>
<tr>
<td>Lower Limb</td>
<td>14. Ankle Flexion/ Foot Tapping 15. Toe Movement .....................</td>
<td>0 1 2 3 4 NA</td>
</tr>
</tbody>
</table>
Novel Therapy Summary

- Mainly studied in patients with schizophrenia and schizoaffective disorder
  - Stable disease, stable therapy, exclusion of patients with other underlying disorders contributing to movement
  - No active suicidal ideation within past 6 months
  - Normal QTc and renal/hepatic function

- Tardive Dyskinesia
  - In studies – moderate-severe classification, average AIMS score of approximately 10 at baseline
  - AIMS scores improved, quality of life scores varied in significance

- Potentially applicable situations:
  - Cannot change current antipsychotic therapy
  - Failure of several other management strategies for tardive dyskinesia
  - Life-threatening tardive dyskinesia symptoms
  - Cost is not a barrier to the patient (financial assistance programs, etc.)
Tardive Dyskinesia Epidemiology

Overall Prevalence (patients taking antipsychotics) 25.3%

1\textsuperscript{st} generation antipsychotics: 30%

2\textsuperscript{nd} generation antipsychotics: 20.7%

Never exposed to 1\textsuperscript{st} generation: 7.2%

• Another study showed onset of 5.4% with 1\textsuperscript{st} generation (haloperidol) and 0.8% with 2\textsuperscript{nd} generation

• There are still patients on 1\textsuperscript{st} generation drugs!
Types of Movement Disorders

- **Akathisia**
  - Restlessness, excessive movements

- **Dystonia**
  - Abnormal, prolonged muscle contraction

- **Neuroleptic-induced parkinsonism**
  - Parkinsonian tremor, muscular rigidity post medication

- **Tardive Dyskinesia**
  - Involuntary, rapid, repetitive movements (typically orofacial)

**EPS** (Extrapyramidal Symptoms)
Onset

• Acute – within hours to days of exposure
• Subacute – weeks after drug exposure
• Tardive – months to years after drug exposure
  • Can be mild initially → progressively severe causing disability, disfigurement
• Anxiety and stress can exacerbate symptoms
• Can develop mixed drug-induced movement disorders
  • Important to note the time of onset and what the actual movement is
Drugs Causing Tardive Dyskinesia

<table>
<thead>
<tr>
<th>1st generation antipsychotics (“Typical”)</th>
<th>2nd generation antipsychotics (“Atypical”)</th>
<th>Partial Dopamine Agonist</th>
<th>Anti-emetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Olanzapine</td>
<td>Aripiprazole</td>
<td>Metoclopramide</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Quetiapine</td>
<td></td>
<td>Prochlorperazine</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>Risperidone</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clozapine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cornett EM. *Ochsner Journal* 2017
Chen JJ. *US Pharm* 2007
Reversible?

Patients with TD

80% Irreversible

20% Change Agent

Reversible

Duration Age Severity

If not, only ~10% of patients will improve

Chen JJ. US Pharm 2007
Implications of TD for the Patient

- Social impairment
  - Social isolation and stigma
  - Unemployment
- Functional impairment (more severe)
  - Chewing, speaking, swallowing
  - Dental and oral cavity damage
- May lead to drug discontinuation
  - Worsening of psychiatric disease
- Poor quality of life, increased mortality
- Potentially life-threatening (case reports)
Management Overview

1. Prevention
   - 1st vs. 2nd generation antipsychotics
   - Use lowest effective dose
   - Avoid “drug holidays”

2. Prompt Recognition
   - Screening tools
   - Change drugs – first generation to second generation
   - Change dose

3. Treatment of early/reversible causes
   - Old treatments (low evidence) – AAN guidelines
   - New treatments
# American Academy of Neurology Guidelines

- **Recommendations regarding TD treatment**

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| Insufficient      | - Withdrawal of dopamine blocking agents  
                   - **Switching to atypical antipsychotics**  
                   - Treating with atypical antipsychotics (mask symptoms instead of treating, may cause TD also)  
                   - Acetazolamide, reserpine, a-methyldopa, dopamine agonists, cholinergic/anti-cholinergics, buspirone  
                   - Antioxidants: vitamin E, melatonin |
| Weak              | - Amantadine, tetrabenazine |
| Moderate          | - Ginkgo biloba (data limited to inpatient schizophrenia patients)  
                   - Clonazepam (short term treatment – 3 months) |
Valbenazine (Ingrezza®)

Indications
• Tardive dyskinesia in adults

Route/Dose
• Oral capsule
• 40mg once daily, increase to 80mg once daily after 1 week
• Consider continuing 40mg in some patients based on response and tolerability

Dose Adjustments
• CrCl < 30 mL/min – not recommended
• Moderate to severe hepatic impairment (Child-Pugh class B or C) – 40mg daily

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Valbenazine (continued)

**PK**
- Hydrolysis to active metabolite
- Major CYP3A4 substrate, minor CYP2D6 substrate
- Excretion: 60% urine, 30% feces

**Drug Interactions**
- Strong CYP3A4 – avoid use
- Strong CYP3A4 inhibitors – 40mg once daily
- Strong CYP2D6 inhibitors – no adjustment recommended, but may need to decrease dose

**Clinical Pearls**
- May prolong QT interval – avoid in congenital long QT syndrome or arrhythmias (though not seen in clinical trials)
- EKG before starting if at risk
Deutetrabenazine (Austedo®)

Indications
- Treatment of tardive dyskinesia in adults
- Treatment of chorea associated with Huntington disease

Route/Dose
- Oral tablet, given with food
- Initial: 6mg twice daily, titrate weekly in increments of 6mg
- Maximum: 48mg/day (two divided doses if 12mg or more)

Dose Adjustments
- Renal: no recommendations
- Hepatic: contraindicated in hepatic dysfunction
- CYP2D6 PM or 2D6 strong inhibitor use – 18-36mg max dose

PM = poor metabolizer
Deutetrabenazine (continued)

**PK**
- Extensive hepatic metabolism to active metabolites
- CYP2D6 further metabolizes
- Excretion 75-86% urine, 10% feces
- 9-10 hour half-life

**Drug Interactions**
- Contraindicated with or within 14 days of an MAOi
- CYP2D6 PM have increased drug metabolites = need decreased dose

**Clinical Pearls**
- If doses missed for >7 days, re-titrate
- May worsen suicidal ideation
- Monitor EKG for QT prolongation (>24mg/day, patients at risk)
Conclusions

Valbenazine 80mg daily was well tolerated and significantly improved tardive dyskinesia in patients with schizophrenia, schizoaffective disorder, or a mood disorder compared to placebo

• Kinect-3 extension studies – 48 weeks, no placebo comparison

• Safety/tolerability
  • No changes in psychiatric stability
  • 14.7% discontinuation due to AE
  • AE: UTI (6.1%), headache (5.8%), somnolence (5.2%)
  • No notable ECG changes occurred – 81% of patients had concomitant QT prolonging medications

• Efficacy
  • AIMS continued change of 4.8 (from 3.2) in 80 mg group
  • Percent with ≥50% AIMS score change: 52% (from 40%)
  • AIMS scores worsened with D/C of drug 4 weeks later
Safety (Valbenazine)

<table>
<thead>
<tr>
<th>Adverse Events (No p-values)</th>
<th>Valbenazine (doses combined)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>5.3%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Akathisia</td>
<td>3.3%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3.3%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>2.6%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2.6%</td>
<td>1.3%</td>
</tr>
<tr>
<td>D/C due to AE</td>
<td>80mg: 6.3%, 40mg: 5.6%</td>
<td>5.3%</td>
</tr>
</tbody>
</table>

• No clinically relevant changes in lab parameters, ECG’s, or psychiatric stability

**Conclusion:** Valbenazine 80mg daily was well tolerated and statistically significantly improved tardive dyskinesia compared to placebo.
### ARM-TD Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Deutetrabenazine (%)</th>
<th>Placebo (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGIC treatment success</td>
<td>48.2%</td>
<td>40.4%</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety (No p-values)</th>
<th>Deutetrabenazine (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>13.8</td>
<td>10.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6.9</td>
<td>8.5</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6.9</td>
<td>1.7</td>
</tr>
<tr>
<td>Akathisia</td>
<td>5.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>1.7</td>
<td>0.0</td>
</tr>
<tr>
<td>Depression/suicidal ideation</td>
<td>0.0</td>
<td>1.7</td>
</tr>
</tbody>
</table>

**Conclusion:** Deutetrabenazine may be an efficacious and well-tolerated treatment for abnormal movements in TD.

CGIC = Clinical Global Impression of Change

Fernandez et al. *Am Acad of Neurology* 2017
Secondary Outcomes (continued)

% of Patients with ≥50% AIMS Score Improvement

Conclusion: Valbenazine 80mg daily was well tolerated and statistically significantly improved tardive dyskinesia compared to placebo