EMERGING TREATMENT OPTIONS FOR TARDIVE DYSKINESIA
Learning Objectives

Apply a systematic approach to assessing suspected adverse drug effects

Discuss the diagnosis and management of TD and comorbid disorders in psychiatric patients

Individualize treatment choices, giving consideration to efficacy, safety, long-term data, and unique patient characteristics

Formulate appropriate treatment regimens considering the emergence of new investigative agents
What Is Dyskinesia?

Dyskinesia

Hyperkinetic movement disorder

Abnormal involuntary movements

Nonrhythmic

Rhythmic

Rapid

Sustained

Slow

Suppressible

Suppressible

Non-suppressible

Tics

Dystonia

Athetosis

Chorea Myoclonus

Tremors

Vijayakumar D, Jankovic J. Drugs 2016;76(7):779-87;
Types of Dyskinesia

Drug-induced

• Levodopa-induced dyskinesia
• Antipsychotic-induced dyskinesia
• Dopamine receptor blocking agents (DRBAs)
Classic tardive dyskinesia
Stereotypic oro-bucco-lingual, digital or truncal movements

Tardive akathisia
An inner sense of restlessness, causing an inability to be still

Tardive tic
Involves brief movements that occur repeatedly and without warning

Tardive dystonia
Sustained muscle contraction, causing abnormal posture
Focal, segmental, or generalized dystonia

Tardive tremor
Shaking movements, usually noticed in the hands and arms

Tardive myoclonus
Quick muscle jerks that cannot be controlled, usually affecting the upper extremities

Tardive syndromes
- Delayed onset
- Abnormal movements
- Caused by exposure to DRBAs

Vijayakumar D, Jankovic J. Drugs 2016;76(7):779-87;
Aquino C, Lang A. Parkinsonism Related Disord 2014;20(suppl 1):S113-7;
What Is Tardive Dyskinesia?

- Involuntary choreoathetoid movements usually associated with lower facial and distal extremity musculature (truncal movements also possible)
  - Chorea: Quick, irregular, non-stereotype movements
  - Athetosis: Slow, writhing, serpentine movements
- Not associated with direct sensory problems
- Of considerable clinical, medical, and legal concern because of potential persistence despite drug discontinuation
Characteristic Distribution of TD
Dopamine Supersensitivity?

Blockade of D2 receptors in the nigrostriatal dopamine pathway causes them to upregulate

This upregulation may lead to tardive dyskinesia

May contribute, but lots of problems

Probably better model for withdrawal-emergent dyskinesia

Other Mechanism(s) of Drug-Induced TD

• Abnormal synaptic plasticity
  – Chronic blockade of D2 receptors provokes maladaptive plasticity in corticostriatal transmission

• Neuronal degeneration hypothesis
  – Oxidative and/or excitotoxic damage from free radicals
  – Considerable basic science evidence
  – May offer avenues for clinical treatment

What Do We Know About the Genetics of Tardive Dyskinesia?

Genes have also been linked to response to treatment.

Polymorphisms in genes have been shown to influence the risk for TD.

Variances in other genes have also been linked to TD.

- Genes coding for D2 and D3 receptors: DRD2, DRD3
- Genes related to GABAergic pathway: SLCA11, GABRB2, GABRC3, COMT
- Catechol-O-methyl-transferase gene
- GRIN2A Related to NMDA receptors
- HTR2A 5HT2A receptors gene
- MnSOD Manganese superoxide dismutase (an enzyme that eliminates free radicals) gene
- Oxidative stress-related genes: NOS3, GSTM1, GSTP1, NQO1
- Polymorphism in brain-derived neurotrophic factor (BDNF) gene has been shown to predict a good response to Ginkgo biloba: Val66Met

Tardive Dyskinesia: Delayed Onset

Tardive Dyskinesia can occur in patients...

- After 3 months of cumulative exposure to DRBAs
- After 1 month of withdrawal of oral agent
- After 2 months of withdrawal of depot agent
- During exposure to DRBAs
- After 1 month of cumulative exposure in older patients

Symptoms should persist for longer than a month

Vijayakumar D, Jankovic J. Drugs 2016;76(7):779-87.
Epidemiology of Tardive Dyskinesia

Approximately 20–50% of patients receiving antipsychotics develop TD

Risk Factors

• Duration or cumulative antipsychotic exposure

• Potency of antipsychotic

• Older age is consistently found to be a risk factor for TD
  • Geriatric patients: increased movement disorders, even in neuroleptic-naïve patients
    – TD rates of 26–31% after 1 year of exposure to FGA
    – TD rates of 2.5% after 1 year of exposure to atypical antipsychotic (risperidone, quetiapine)

• Children: higher TD rates in patients taking haloperidol

Tardive Dyskinesia Prevalence in Second-Generation Antipsychotic Use

- TD prevalence higher in patients treated with first-generation antipsychotics (FGAs)

- Recent meta-analysis comparison of TD prevalence in FGAs versus second-generation antipsychotics (SGAs) users

- However, SGAs still show risk of TD
  - One-fifth of patients treated with SGAs showed this “rare” side effect

Tardive Dyskinesia: Other Risk Factors

• Early onset of psychosis
• Presence of mood disorder
• Acute EPS/akathisia
• Treatment with anticholinergics
• Negative symptoms, cognitive symptoms
• Comorbid substance abuse
• Sex: female, especially post-menopausal
• Ethnicity?
• 5% of medication-naïve schizophrenia patients exhibit spontaneous movements

Abnormal Involuntary Movement Scale (AIMS)

• 12-item clinician-rated scale to assess severity of dyskinesias
• With FGA, examine for TD at least every 6 months
• With Second Generation Antipsychotics SGA, examine for TD every 12 months
• Patients at high risk of EPS:
  • examine for TD every 3 months with FGA
  • examine for TD every 6 months with SGA

### Abnormal Involuntary Movement Scale (AIMS)

**Rate Highest Severity Observed**

<table>
<thead>
<tr>
<th>Facial &amp; Oral Movements</th>
<th>Extremity Movements</th>
<th>Trunk Movements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Muscles of Facial Expression</strong></td>
<td><strong>2. Lips and Perioral Area</strong></td>
<td><strong>5. Upper (arms, wrists, hands, fingers)</strong></td>
</tr>
<tr>
<td>e.g. movements of forehead, eyebrows, periorbital area. Include frowning, blinking, and grimacing of upper face</td>
<td>e.g. puckering, pouting, and smacking</td>
<td>Include choreic movements (rapid, objectively purposeless, irregular, spontaneous) and athetoid movements (slow, irregular, complex, serpentine). DO NOT include tremor (repetitive, regular, rhythmic).</td>
</tr>
<tr>
<td>e.g. biting, clenching, chewing, mouth opening, and lateral</td>
<td>Rate only increase in movements both in and out of mouth, NOT inability to sustain movement.</td>
<td>e.g. lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot.</td>
</tr>
<tr>
<td><strong>7. Neck, shoulders, hips</strong></td>
<td><strong>Trunk Movements</strong></td>
<td></td>
</tr>
<tr>
<td>e.g. rocking, twisting, squirming, pelvic gyrations. Include diaphragmatic movements.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Movement Ratings:**
- 0 = none
- 1 = minimal
- 2 = mild
- 3 = moderate
- 4 = severe
Abnormal Involuntary Movement Scale (AIMS)
Instructions for Performing Exam

1. Ask patient whether there is anything in his/her mouth (i.e., gum, candy, etc.) and if there is, to remove it
2. Ask patient about the current condition of his/her teeth
   • Ask patient if he/she wears dentures
   • Do teeth or dentures bother patient now?
3. Ask patient whether he/she notices any movements in mouth, face, hands, or feet
   • If yes, ask to describe and to what extent they currently bother patient or interfere with his/her 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.
Abnormal Involuntary Movement Scale (AIMS) Instructions for Performing Exam

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, hips included

11. Ask patient to extend both arms outstretched in front with palms down
    • Observe trunk, legs, and mouth

12. Have patient walk a few paces, turn, and walk back to chair
    • Observe hands and gait
    • Do this twice
Impact on Quality of Life

Severity of TD

Quality of life

Vijayakumar D, Jankovic J. Drugs 2016;76(7):779-87.
Expected Course of Tardive Dyskinesia

• Long-term studies of the course of TD provide a wide range of remission rates (0–73%)\(^1-4\)
  – Most report remission rates below 25%

• After discontinuation of the causing DRBAs, the rate of remission is low
  – Even with atypical antipsychotics, reversibility rates remain low as only 20.5%\(^5\)

Is Tardive Dyskinesia Preventable?

• Inform patients of risk of developing TD before initiating treatment
• Use agents with less risk of TD
  – Risk increases with potency of D2 binding
• Patients should be monitored periodically for the development of TD
• Early recognition
  – Systematic evaluation including rating scales

Bhidayasiri R et al. Neurology 2013;81:463-9;
Vijayakumar D, Jankovic J. Drugs 2016;76(7):779-87.
Switching Antipsychotics to Address Tardive Dyskinesia

• Dopamine antagonism can mask dyskinesia

• Severe TD
  - Switch to clozapine

• Mild to moderate TD on conventional antipsychotic
  - Switch to atypical antipsychotic *if possible*

• Mild to moderate TD on atypical antipsychotic
  - No clear evidence

Treatment Options for Tardive Dyskinesia

• Slowly taper off an offending DRBA *if possible*
  
• VMAT2 inhibitors
  - Reserpine
  - Tetrabenzaine
  - Valbenazine
  - Deutetramazine

• Other:
  - Amantadine
  - Gingko biloba?
  - GABA agonist medications
Vesicular Monoamine Transporter (VMAT)

- Protein integrated into the membrane of synaptic vesicles of presynaptic neurons
- Transports monoamine neurotransmitters (DA, 5HT, NE, epinephrine, histamine) into vesicles
- 2 forms: VMAT1 and VMAT2
  - VMAT1: expressed mainly in peripheral nervous system
  - VMAT2: expressed mainly in monoaminergic cells of the CNS

Kenney C, Jankovic J. Expert Rev Neurother 2006;6(1):7-17;
Shen V et al. Tremor Other Hyperkinetic Movements 2013;3. doi:10.7916/D8BK1B2D;
VMAT2 Inhibition in Tardive Dyskinesia

vmat2

tardive dyskinesia

psychosis

tardive dyskinesia
Reserpine and Psychiatry

• 1954: first reported to be effective for schizophrenia
  - Adverse effects limited use; replaced soon thereafter with chlorpromazine, which had improved efficacy and tolerability

• 1955: noted to be effective for Huntington's chorea

• 1956: Delay and Deniker reported extrapyramidal adverse effects from reserpine

# Tetrabenazine (TBZ) vs. Reserpine

<table>
<thead>
<tr>
<th>Pharmacological properties</th>
<th>TBZ</th>
<th>Reserpine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Selectively binds VMAT2</td>
<td>Binds VMAT1 and VMAT2</td>
</tr>
<tr>
<td>Inhibition</td>
<td>Reversible</td>
<td>Irreversible</td>
</tr>
<tr>
<td>VMAT2 binding site</td>
<td>Inside the vesicle</td>
<td>Outside the vesicle</td>
</tr>
<tr>
<td>Duration</td>
<td>Hours</td>
<td>Days</td>
</tr>
<tr>
<td>Peripheral monoamine depletion</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Causes orthostatic hypotension or gastrointestinal side effects</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Tetrabenazine: Efficacy and Safety

- TBZ has been shown to reduce TD symptoms by 54%\(^1\)
  - Approved in US in 2008 for Huntington's disease

- Studies have shown improvement of symptoms in 70–71% of patients treated with TBZ\(^2,3\)

- Level C recommendation from American Academy of Neurology (AAN)\(^4\)

- Common side effects associated with TBZ include:\(^5\)
  - Drowsiness
  - Parkinsonism
  - Akathisia
  - Depression

Metabolism of Tetrabenazine

Tetrabenazine (−)-1

Rapidly converted to dihydrotetrabenazine α, β enantiomers in a ratio of 1:1

Metabolites are metabolized via CYP2D6

Requires mandatory CYP2D6 genotyping for doses >50 mg/day

Evidence Suggests That Binding of the TBZ Metabolites to VMAT2 is Stereospecific

TBZ Enantiomers (±)-1

TBZ: tetrabenazine
DHTZB: dihydrotetrabenazine

Highest Binding Affinity for VMAT2

(±)-α-DHTBZ

(2R,3R,11bR)-DHTBZ (+)-2

K_i: 3.96

DHTBZ Metabolites

(−)-α-DHTBZ

(2S,3S,11bS)-DHTBZ (-)-2

K_i: 23,700

(+)−β-DHTBZ

(2S,3R,11bR)-DHTBZ (+)-3

K_i: 13.4

(−)-β-DHTBZ

(2R,3S,11bS)-DHTBZ (-)-3

K_i: 2,460

VMAT2 Binding Affinity

Valbenazine

• Designed to deliver metabolite in a controlled fashion

\[
\begin{align*}
\text{Valbenazine} & \rightarrow \text{(+) -} \alpha - \text{DHTBZ} \\
\end{align*}
\]

• Limited off-target receptor binding

• FDA approved for the treatment of TD, April 2017
  - Initial dose 40 mg/day, after 1 week increase dose to 80 mg/day
  - No need for CYP2D6 genotyping

**Valbenazine: Selective VMAT2 Inhibitor**

Cumulative Proportion of Responders During 6-Week, Double-Blind, Phase II Trial

Central Video Rater AIMS Dyskinesia Total Score Responder Analysis at Week 6
(ITT Analysis Set)

Response: at least 50% improvement in AIMS
Placebo n=44, NBI-98854 n=45.

Valbenazine Efficacy
KINECT 3 AIMS Outcomes at Week 6

Change from baseline in the severity of TD symptoms assessed by the Abnormal Involuntary Movement Scale (AIMS) through week 6

AIMS score (least squares [LS] mean change from baseline to week 6, MMRM):

- Valbenazine 40 mg -1.9 vs. -0.1 placebo; p<0.05; effect size, d=0.52
- Valbenazine 80 mg -3.2 vs. -0.1 placebo; p<0.001; effect size, d=0.90

AIMS at week 6 for the valbenazine 80 mg dose was reduced 3.1 points more than placebo (p<0.001)

Valbenazine Safety and Tolerability

• PK profile permits once-daily dosing
• Psychiatric status remained stable
• Improved TD regardless of the use or type of concomitant AP
• Somnolence is the most common treatment-related AE
  - Valbenazine (all doses), 10.9%; placebo, 4.2%
  - May be due to depletion of monoamines in people with higher plasma levels of valbenazine

Valbenazine Appears Safe and Well-Tolerated Long-Term

• Data pooled from 3 long-term studies with valbenazine (up to 48 weeks) in adults with TD

• 66.5% of patients experienced treatment-emergent adverse events (TEAEs), but only about 14.7% discontinued the drug due to AEs

• Patients with schizophrenia:
  - urinary tract infection (6.1%)
  - headache (5.8%)
  - somnolence (5.2%)

• Patients with mood disorders:
  - headache (12.4%)
  - urinary tract infection (10.7%)
  - somnolence (9.1%)

Deutetrabenazine

- Deutetrabenazine is a selective VMAT2 inhibitor
- Deuteration is the replacing of hydrogen atoms with deuterium on a compound
  - No change in shape, size, charge, or target pharmacology of small molecules
  - Chemical bond C-D is 8x stronger
  - Prolongs half-life and improved PK

FDA Approved for Tardive Dyskinesia on August 30, 2017
- Initial dose 12 mg/day in two divided doses
- Titrate at weekly intervals by 6 mg/day based on reduction of tardive dyskinesia and tolerability
- Maximum recommended daily dosage of 48 mg (24 mg twice daily)
- No need to CYP2D6 genotyping

Pharmacokinetics of Deutetrabenazine

Mean Plasma Concentration
TOTAL alpha + beta (n=24-25)

- Deutetrabenazine, 15 mg, Fed
- Deutetrabenazine, 15 mg, Fasted
- Tetrabenazine, 25 mg, Fasted

Anderson et al. Poster presented at: American Psychiatric Association Annual Meeting; May 2016; Atlanta, GA.
Deutetrabenazine: Phase III Randomized ARM-TD Dose-Finding Trial

Double-blind, placebo-controlled, parallel-group study

At Week 12

Placebo group (n=59)
Decrease in mean AIMS: 1.6 (SE=0.46)

Deutetrabenazine group (n=58)
Decrease in mean AIMS: 3.0 (SE=0.45)

p=0.019

AEs: somnolence, headache

AIMS: Abnormal Involuntary Movement Scale.

Deutetrabenazine: Phase III Randomized AIM-TD Fixed-Dose Trial

At Week 12

- **Placebo group**
  - mean AIMS: -1.4 points (SE=0.41)

- **Deutetrabenazine 12 mg/d**
  - mean AIMS: -2.1 points (SE=0.42)

- **Deutetrabenazine 24 mg/d**
  - mean AIMS: -3.2 points (SE=0.45)

- **Deutetrabenazine 36 mg/d**
  - mean AIMS: -3.3 points (SE=0.42)

AIMS: Abnormal Involuntary Movement Scale.

* p=0.006 for 24 mg/day and 0.032 for 36 mg/day
** p=0.003 for 24 mg/day and 0.018 for 36 mg/day
*** p=0.012 for 24 mg/day and 0.008 for 36 mg/day
**** p=0.003 for 24 mg/day and 0.001 for 36 mg/day

Deutetrabenazine: Intention-to-Treat Analysis

Significant Reductions in Abnormal Involuntary Movements

- CGIC at week 12
- Treatment success was defined as a rating of “much improved” or “very much improved” on the CGIC
- Deutetrabenazine at doses of 24 mg/day and 36 mg/day were efficacious and well tolerated

3 Ways to Block VMAT2 with 3 Benazines

1. Tetrabenazine – not approved
2. Valbenazine – FDA approved for the treatment of TD, April 2017
3. Deutetrabenazine – FDA approved for the treatment of TD, August 2017
   • No head to head studies
   • All share the same fundamental mechanism
   • Major differences are in pharmacokinetics
   • Differences in efficacy or safety not yet well established
   • Advantages and disadvantages?
Other Evidence-Based Therapies

• Clonazepam
  – Probably effective in decreasing TD symptoms short term (approximately 3 months; efficacy wanes by 6 months)

• Amantadine
  – Reduced TD when used conjointly with a neuroleptic during the first 7 weeks (1 positive study; short-term use only)

• Botulinum toxin injections for focal dystonia symptoms

Other Evidence-Based Therapies

Extract of Ginkgo biloba (Egb-761)

- Potent antioxidant possessing free radical-scavenging activities

Inpatients with schizophrenia and TD

<table>
<thead>
<tr>
<th>Condition</th>
<th>EGb-761 (240 mg/d)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>78</td>
<td>79</td>
</tr>
</tbody>
</table>

After 12 weeks of treatment

<table>
<thead>
<tr>
<th>Decrease in mean AIMS:</th>
<th>2.13 (± 1.75)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.10 (± 1.69)</td>
</tr>
</tbody>
</table>

Some efficacy, but data is limited to inpatients with schizophrenia

Summary

• Tardive dyskinesia still exists and remains a serious risk of APs and other DRBAs
  – Risk still present with SGAs
  – Rarely reversible, even after discontinuing the causing agent

• Better genetic predictors are needed

• 3 ways to block VMAT2 with 3 benazines

• VMAT2 inhibitors have shown efficacy at reducing TD symptoms
  – Deutetrabenazine - *FDA approved for the treatment of TD, August 2017*
  – Valbenazine - *FDA approved for the treatment of TD, April 2017*