MOVING TOWARD THE FUTURE: NEW DEVELOPMENTS IN THE MANAGEMENT OF TARDIVE DYSKINESIA
Learning Objectives

• Apply a systematic approach to assessing suspected drug-induced movement disorders

• 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 treatment options
What is Dyskinesia?

- **Dyskinesia**
  - Hyperkinetic movement disorder
  - Abnormal involuntary movements
    - Nonrhythmic
      - Rapid
        - Suppressible
          - Tics
        - Non-suppressible
          - Chorea; Myoclonus
      - Sustained
        - Dystonia
      - Slow
        - Athetosis
    - Rhythmic
      - 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)

Vijayakumar D, Jankovic J. Drugs 2016;76(7):759-77; Vijayakumar D, Jankovic J. Drugs 2016;76(7):779-87.
Tardive syndromes

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

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

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

Classic tardive dyskinesia
Stereotypic oro-bucco-lingual, digital or truncal movements

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

Tardive tic
Involves brief movements that occur repeatedly and without warning

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

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
Dopamine supersensitivity?

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

Dopamine supersensitivity?

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

• Aberrant spine formation
  − D2 receptors on necks; glutamate receptors on heads

• 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?

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

- Genes coding for D2 and D3 receptors
  - DRD2
  - DRD3

- Genes related to GABAergic pathway
  - COMT
  - SLCA11
  - GABRB2
  - GABRC3

- Catechol-O-methyltransferase gene

- Cytochrome P450 gene

- Related to NMDA receptors
  - GRIN2A

- 5HT2A receptors gene
  - HTR2A
  - Val66Met

- Polymorphism in brain-derived neurotrophic factor (BDNF) gene has been shown to predict a good response to Ginkgo biloba

- Manganese superoxide dismutase (an enzyme that eliminates free radicals) gene
  - MnSOD

- Oxidative stress-related genes
  - GSTM1
  - GSTP1
  - NQO1
  - NOS3

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What Do We Know About the Genetics of Tardive Dyskinesia?

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Genes have also been linked to response to treatment

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Vijayakumar D, Jankovic J. Drugs 2016;76(7):779-87;
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 1 month of cumulative exposure in older patients
- During exposure to DRBAs
- After 2 months of withdrawal of depot agent

Symptoms should persist for longer than a month

Vijayakumar D, Jankovic J. Drugs 2016;76(7):779-87.
## Diagnostic Criteria for TD

<table>
<thead>
<tr>
<th>Source</th>
<th>Exposure</th>
<th>Severity threshold</th>
<th>Duration</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schooler-Kane (1982)</td>
<td>≥3 months</td>
<td>AIMS items: ≥3 in one area or ≥2 in 2 areas</td>
<td>Persistent ≥3 months</td>
<td>Dx of exclusion</td>
</tr>
<tr>
<td>Glazer et al. (1993)</td>
<td>≥3 months</td>
<td>AIMS items: ≥3 total with at least one ≥2 in 1 area</td>
<td>Persistent ≥2 exams</td>
<td>Dx of exclusion</td>
</tr>
<tr>
<td>DSM-IV (1994) 333.82</td>
<td>≥3 months; ≥1 month if ≥60 years</td>
<td>Involuntary movements</td>
<td>≥4 weeks</td>
<td>Dx of exclusion</td>
</tr>
<tr>
<td>DSM-5 (2013) 333.85 (G24.01)</td>
<td>At least few months</td>
<td>Involuntary movements</td>
<td>≥8 weeks</td>
<td></td>
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</tbody>
</table>

DSM = *Diagnostic and Statistical Manual of Mental Disorders*; Dx = diagnosis; APA = American Psychiatric Association

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
  - 1/5 of patients treated with SGAs showed this “rare” side effect
- In four studies, 7.2% prevalence with SGA reported in patients without prior FGA treatment

Mean TD Prevalence

<table>
<thead>
<tr>
<th>Treatment</th>
<th>TD Prevalence</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>FGA</td>
<td>30.0%</td>
<td>26.4%–33.8%</td>
</tr>
<tr>
<td>SGA</td>
<td>20.7%</td>
<td>16.6%–25.4%</td>
</tr>
</tbody>
</table>

TD rates significantly lower with SGA treatment

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: 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

• Regardless of DRBA choice and symptomatic profile, regular TD screening using the AIMS should be **implemented routinely**
• 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

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%\(^5\)

Vinuela A et al. Tremor Other Hyperkinet Mov (N Y). 2014;4:282;
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

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
  - Tetrabenazine
  - Valbenazine
  - Deutetrabenazine
- Other:
  - Gingko biloba
  - GABA agonists (e.g., Clonazepam)
  - Amantadine
Other Evidence-Based Therapies

• **Gingko biloba**
  - Positive study of gingko extract n=157 in China

• **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 (one 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

- EGb-761 (240 mg/d)  
  n = 78
- Placebo  
  n = 79

Decrease in mean AIMS:

- After 12 weeks of treatment
  - EGb-761: 2.13 (± 1.75)
  - Placebo: -0.10 (± 1.69)

Some efficacy, but data is limited to inpatients with schizophrenia

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
- Two 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
Reserpine and Psychiatry

- 1954: first reported to be effective for schizophrenia
  - Adverse effects in 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: 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)\(^4,6\)

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

## Tetrabenazine Historical Approval

<table>
<thead>
<tr>
<th>Country</th>
<th>Diagnosis</th>
<th>Approval Year</th>
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<tbody>
<tr>
<td>United States</td>
<td>Huntington’s chorea</td>
<td>2008</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Huntington’s chorea</td>
<td>2007</td>
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<tr>
<td>Germany</td>
<td>Huntington’s chorea and tardive dyskinesia</td>
<td>2007</td>
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<tr>
<td>Italy</td>
<td>Organic movement disorder and tardive dyskinesia</td>
<td>2007</td>
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<tr>
<td>France</td>
<td>Huntington’s chorea and hemiballismus</td>
<td>2005</td>
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<td>Israel</td>
<td>Organic movement disorder and tardive dyskinesia</td>
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<td>Portugal</td>
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<td>2003</td>
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<td>Canada</td>
<td>Organic movement disorder and tardive dyskinesia</td>
<td>1995</td>
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<td>Denmark</td>
<td>Hypermobilities</td>
<td>1980</td>
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<td>Australia</td>
<td>Organic movement disorder and tardive dyskinesia</td>
<td>1979</td>
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<td>New Zealand</td>
<td>Organic movement disorder and tardive dyskinesia</td>
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<td>Ireland</td>
<td>Organic movement disorder (tardive refused)</td>
<td>1971</td>
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<tr>
<td>UK</td>
<td>Organic movement disorder and tardive dyskinesia</td>
<td>1971</td>
</tr>
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</table>
Metabolism of Tetrabenazine

Tetrabenazine (-1)

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

Metabolites are metabolized via CYP2D6

Re经济s 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: dihydrotebenazine

**Highest binding affinity for VMAT2**

(+)−α-DHTBZ
(2R,3R,11bR)-DHTBZ (+)-2

K_i: 3.96

(−)−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

Valbenazine

• Designed to deliver metabolite in a controlled fashion

Valbenazine

• 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

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 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 three 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

Tetrabenazine

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

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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

Mean Change in AIMS Score

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

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.

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

Three Ways to Block VMAT2 With Three Benazines

1. Tetrabenazine – *not approved in the United States*

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, but differences in efficacy or safety not yet well established
- Deutetrabenazine and valbenazine are established as effective treatments of TD (Level A)

American Academy of Neurology (AAN): Updated Recommendations for Treatment of Tardive Syndrome

<table>
<thead>
<tr>
<th>Level A</th>
<th>Level B</th>
<th>Level C</th>
<th>Level U</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>must be recommended as treatment</strong></td>
<td><strong>should be considered as treatment</strong></td>
<td><strong>might be considered as treatment</strong></td>
<td>insufficient evidence to support or refute</td>
</tr>
</tbody>
</table>
| • Deutetrabenazine  
  • Valbenazine | • Clonazepam  
  • Ginkgo biloba | • Amantadine  
  • Tetrabenazine  
  • Pallidal deep brain stimulation (intractable TD) | • Withdrawing causative agents  
  • Switching from typical to atypical DRBA |

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

• Three ways to block VMAT2 with three 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*