MOVING ALONG: MANAGING TARDIVE DYSKINESIA
Learning Objectives

• Explore the hypothesized neurobiological bases of tardive dyskinesia

• Implement treatment strategies for the management of tardive dyskinesia
What is tardive dyskinesia?

• Involuntary **choreoathetoid** movements usually associated with lower facial and distal extremity musculature (truncal movements also possible)
  – **Chorea**: Quick, irregular, non-stereotyped 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
Tardive Dyskinesia Prevalence in Second-Generation Antipsychotic Use

- TD prevalence is higher in patients treated with first-generation antipsychotics (FGAs).
- Recent meta-analysis compared TD prevalence in FGAs vs. second-generation antipsychotics (SGAs) users.

<table>
<thead>
<tr>
<th>FGA Treatment</th>
<th>SGA Treatment</th>
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<tbody>
<tr>
<td>30.0%</td>
<td>20.7%</td>
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<tr>
<td>95% CI = 26.4%–33.8%</td>
<td>95% CI = 16.6%–25.4%</td>
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TD rates significantly lower with SGA treatment

41 Studies (N = 11,493)
Q = 9.17, P = 0.0024

Tardive Dyskinesia Prevalence in Second-Generation Antipsychotic Use

• 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 was reported in patients without prior FGA treatment

Dopamine Supersensitivity?

Dopamine Supersensitivity?

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

Dopamine Supersensitivity?

This upregulation may lead to tardive dyskinesia

= D2 antagonist

Nigrostriatal pathway

May contribute, but has lots of problems

Probably a 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 scientific evidence
  - May offer avenues for clinical 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

Treatment Options for Tardive Dyskinesia

• Slowly taper off an offending dopamine receptor blocking agent (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

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

Three Ways to Block VMAT2 With Three Benazines

1. Tetrabenazine—not approved for TD in the United States
2. Valbenazine—FDA-approved for the treatment of TD, April 2017
3. Deutetra benazine—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
• Deutetra benazine and valbenazine are established as effective treatments of TD (Level A)

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 is rapidly converted to dihydrotetrabenazine $\alpha$, $\beta$ enantiomers in a ratio of 1:1. Metabolites are metabolized via CYP2D6. Requires mandatory CYP2D6 genotyping for doses >50 mg/day.

Valbenazine

- Designed to deliver metabolite in a controlled fashion

\[
\begin{align*}
\text{Valbenazine} & \quad \text{Valbenazine} \\
\text{ONH} & \quad \text{ONH} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O}
\end{align*}
\]

- 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

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, \(d=0.90\)

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 adverse effect (AE)
  - Valbenazine (all doses), 10.9%; placebo, 4.2%
  - May be due to depletion of monoamines in people with higher plasma levels of valbenazine

O’Brien et al. Movement Disord 2015;30:1681-7; Hauser RA et al. Neurology 2016;86(16)(suppl PL02.003);
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

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

**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

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>
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<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>
<tr>
<td>• Deutetrabenazine • Valbenazine</td>
<td>• Clonazepam • Ginkgo biloba</td>
<td>• Amantadine • Tetrabenazine • Pallidal deep brain stimulation (intractable TD)</td>
<td>• Withdrawing causative agents • Switching from typical to atypical DRBA</td>
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Summary

• Tardive dyskinesia (TD) remains a serious risk of antipsychotics and other dopamine receptor blocking agents

• TD often persists even after medication is discontinued

• There are several different hypotheses as to why TD occurs

• VMAT2 inhibitors have demonstrated efficacy and two are FDA-approved for TD
A 43-year-old with tardive dyskinesia (TD) has been taking tetrabenazine to treat his symptoms. Tetrabenazine is approved in the United States for the treatment of which movement disorder?

1. Huntington’s disease
2. Tardive dyskinesia
3. Parkinson’s disease
4. All of the above
Frank has been taking valbenazine for the treatment of tardive dyskinesia. In a 6-week, double-blind, phase II trial of valbenazine for tardive dyskinesia, what percentage of patients showed a response (at least 50% improvement) on the Abnormal Involuntary Movement Scale (AIMS)?

1. 19%
2. 29%
3. 39%
4. 49%
Which medication(s) does/do not require CYP2D6 genotyping?

1. Valbenazine
2. Tetrabenazine
3. Deutetrabenazine
4. 1 and 3