Tardive Dyskinesia or “TD” as it is typically known to Psychiatrists and people who work in Mental Health Settings

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What is Tardive Dyskinesia?

- Tardive - late or delayed onset
- Dyskinesia - abnormal, involuntary, mostly irregular and non-rhythmic, low frequency, “chorea” “athetoid” and “dystonic” neuromuscular movements
- Chorea- rapid, fast, jerky, semi purposive, mostly non-rhythmic
- Athetoid- slow and sinuous, writhing, and small amplitude
- Dystonia: sustained, slow muscular contractions or muscular spasms

Where in the body would one see these TD neuromuscular movements?

- Head/Orofacial/Tongue: lips, jaws, face and eye muscles
- Hands: thumb and fingers
- Feet and ankle: may be big toe, sometimes other toes, and ankle
- Trunk and Torso, Neck and Shoulders, less common: pelvic
- Rare: Pharyngeal muscles (swallowing issues), Intercostal or Diaphragmatic muscles (breathing issues)
Clinical Features and Presentations of TD

• Facial grimacing, smiling, frowning
• Constant chewing, side to side jaw thrusting, jaw clenching
• Frequent eye blinking
• Tongue protrusions in and out of the mouth or against the cheek ("Flycatcher’s Tongue" or the “Bon-Bon” sign)
• Frequent lip smacking
• Frequent pursing and puckering of the lips
• Piano fingers and Leg movements, e.g. frequent foot tapping, crisscrossing of legs, walking in place (e.g. in the med or food line)
• Neck & Trunk & Pelvic Torsion Movements including Dystonia
Other Tardive Movement Disorders

- **Tardive Dystonia** (often seen as sustained muscular contractions of the neck, trunk, pelvis, jaw, facial and eye muscles, impacting gait and normal activities of daily living)
- **Tardive or Persistent Akathisia** (often seen objectively as fidgetiness, restlessness, crisscrossing of the legs, pacing the room and corridors instead of sitting, and sometimes acute akathisia persists or akathisia may onset late (Tardive: weeks to months later).
- These can co-exist with Tardive Dyskinesia

What could TD be mistaken for?
(Differential Diagnosis)

- Parkinsonian Symptoms – especially Tremors, stiffness, rigidity, shuffling gait, diminished arm swing, these symptoms can be caused by antipsychotic drugs
- Tremors from several causes including antipsychotic drugs or Lithium, and other medications
- Rabbit Syndrome
- Neurological Disorders – Huntington’s Chorea, Wilson’s Disease
- Mannerisms, Stereotypies
- Tics including in Tourette’s syndrome
- Several less common neuropsychiatric or neurological disorders
Differentiating Drug Induced Parkinsonism from Tardive Dyskinesia

- **Parkinsonism**
  - Tremor
  - Rhythmic and regular movements
  - Recent start or increase in dosage of high potency D2 blocker
  - Rigidity and cogwheeling
  - Anticholinergics and amantadine generally effective as Rx or lowering the dosage or discontinuation of the antipsychotic agent

- **Tardive Dyskinesia**
  - No Tremor
  - Irregular and Non-rhythmic
  - Not necessarily, typically long exposure to D2 blockers
  - No rigidity or cogwheeling
  - No impact of anticholinergics on TD, some data to suggest these drugs could worsen TD

Differentiating Orofacial Tardive Dyskinesia from Rabbit Syndrome

- **Orofacial TD**
  - Irregular, Non-rhythmic lip, tongue, facial, jaw and eye muscle movements
  - Anticholinergic Medications - No effect, could worsen TD
  - Approved VMAT2 Inhibitors can improve TD

- **Rabbit Syndrome**
  - Rhythmic movement, like a tremor of the upper lip (Rabbit)
  - May be seen early or late in treatment with Antipsychotic Rx
  - Responds to anticholinergic medications or lowering of the antipsychotic medication (if feasible)
Incidence (New cases) of Tardive Dyskinesia

• In those 18 to 50 years receiving First Generation Antipsychotic Medications
  - Annual Incidence Rates: 5% 1st Year, 10% 2nd Year, 15% 3rd Year, and approx. 20% 4th Year.
  - 23 to 26% in Years 5 and 6
  - Prevalence: Approx: 25%, Approx: 21% in SGA and 30% in FGA
  - TD onsets sooner and at higher rates in those > 50 Years, and even higher rates among those over 65 years (typically seen in nursing homes, assisted living, residential settings, state facilities, etc.)
  - Many have mild TD, some go onto have Moderate or Severe TD

What about TD in the era of the Newer Antipsychotic Medications

• 57 head to head, Randomized Clinical Trials, 118 Treatment Arms
• 32 First Generation Rx Arms, 86 Second Generation Rx Arms
• 32 FGA – SGA Comparisons, and 35 SGA-SGA Comparisons
  • AND:
    • 6.5% Annualized Incidence Rate in FGA and 2.6% in SGA Arms
    • Importantly: No Dose Effect seen in FGA Rx arms
    • Among Non-Clozapine SGAs – Olanzapine had a lower risk
    • No Difference between Clozapine and other SGAs (mainly olanzapine)

Risk Factors Associated with TD

1. Prolonged Exposure to Dopamine Receptor Antagonist Medications, Antipsychotic Medications, Metoclopramide (Preoperative and GI medicine)
2. Age ≥ 50 years, and especially > 65 years, elderly often in Senior Community Residential Settings
3. Post-menopausal women, ≥ 50 years
4. Diagnosis of Mood Disorders – Major Depression, Bipolar Disorder, Persons with previous brain injury, or CNS “insults”
5. ? Anticholinergic Medications
6. Diabetes Mellitus

Examination for TD

- Most commonly used scale: Abnormal Involuntary Movement Scale – AIMS
Additional Tips for AIMS Examination

- Observe in waiting area and during walk back to office for tremors, shuffling gait or loss of arm swing (i.e. Parkinsonian symptoms) but also Tardive movements
- Role Play "stick out your tongue for 10 secs" Like so. “Raise your arm and touch each finger to your thumb”, Like so.
- Keep a conversation going during “activation” (or distraction) e.g. the tongue in mouth or tongue sticking out instructions, or hands outstretched palms facing down, and at the same time watch other parts of the body, face, hands, jaws, neck, and feet, same during walking, etc.
- Even though the AIMS is designed for TD assessment, hints of Parkinsonian Sx can be picked up during walking, tremors, or examining for rigidity
- Need good daylight or well light office or use a flashlight for the mouth and tongue especially if there is inadequate lighting
- If you need to examine the feet without socks, prepare the patients ahead of time e.g. during phone/text/email/health portal reminders for the next clinic visit
Scoring the AIMS Scale

• Complete the examination procedure before making ratings. For the movement ratings (the 7 items in 3 categories, Face and Oral, Upper and Lower Extremities, Trunk), rate the highest severity observed. 0 = none, 1 = minimal (may be extreme normal), 2 = mild, 3 = moderate, and 4 = severe. Rate the highest score even if it seen only for a short time during the examination, in other words: don’t try and “average”. Score: Range from 0 to 28.

• According to the original AIMS instructions, one point is subtracted if movements were seen only on activation, but of late, this convention has been dropped, so it is recommended that you give the highest score in each body area seen during your examination.

• Hint: if the tongue breaks out of the mouth beyond the teeth, score a 3 (Moderate) is reasonable.

Munetz and Benjamin 1988 Hospital and Community Psychiatry
Schooler-Kane Research Diagnostic Criteria for TD

- 3 Criteria
- Antipsychotic Drug Usage for ≥ 3 months (does NOT have to be continuous Rx)
- Of the first 7 items on the AIMS, one or more items is marked ≥ 3 (Moderate or greater)
- OR
- Of the first 7 items, **two different bodily areas** on AIMS is marked ≥ 2 (Mild or greater)
- Abnormal Involuntary Movements are not explained by other causes

Schooler & Kane, DC for TD. Arch Gen Psychiatry 1982
Based on Schooler-Kane RDC for TD, we use some terms for the Progression or lack of Progression for TD

- **Probable TD** (meets Schooler-Kane-3 criteria)
- **Masked Probable TD** (antipsychotic is reintroduced or increased in dosage and masks TD, i.e. no longer seen)
- **Transient TD** (on a second examination, within 3 months, no TD movements are seen)
- **Withdrawal TD** (seen on taper or stoppage of antipsychotic medication but is no longer seen after 3 months of withdrawal of antipsychotic)
- **Persistent TD** (meets probable TD even after 3 months of stoppage of antipsychotic or even if continuing antipsychotic medication)
- **Masked Persistent TD** on reintroduction of antipsychotic or increased dosage, TD no longer seen

Schooler & Kane, DC for TD. Arch Gen Psychiat. 1982

What Criteria should we use to diagnose TD in Clinical Practice?

- On the basis of the AIMS examination, you can use the 3 Schooler-Kane criteria for probable TD
- **OR**
  - You can use a score of Moderate or Greater (≥3) on the AIMS, i.e. item 8, overall Global Severity of Movements
  - The two approved VMAT2 inhibitors (Valbenazine and Deutetrabenazine) were assessed in RCTs for FDA approval in those patients with Moderate or greater severity TD. Blinded Centralized Video Ratings of AIMS were scored
Social and Functional Implications of TD, the AIMS does not really get much into this aspect

1. Many patients do not know they “have it” until relatives, friends, doctors or clinicians or co-workers point it out, but many DO.
2. Impacts Mobility, Activities, Self Care
3. Embarrassment
4. Not fitting in as people may “avoid” those with severe TD
5. Overall Quality of Life
6. Getting back to work, school or major roles in life may be hard
7. Pharyngeal or Respiratory Muscle TD can impact swallowing and breathing could be a serious concern

How often should we do the AIMS?

- At least annually in patients on SGAs, and every 6 months for FGAs, more often if a patient is showing movement of scores from 0 (none) to 1 (doubtful) to 2 (mild)
- In those above 50 years, every 3 to 6 months, and more often if scores move from 0 to 2
- In those above 65 years, every 3 months
- More often in those with risk factors: diabetes, need anticholinergic drugs for parkinsonian symptoms, post-menopausal women, children and adults with antipsychotic drugs for Tics/Tourette’s, and in intellectual disability settings
- Electronic Health Records Reminders could be very helpful
Tremors alongside Tardive dyskinesia

Can TD coexist with Tremors or other Extrapyramidal Side Effects (EPS) or Tardive Akathisia or Tardive Dystonia?
Yes!
The Management and Treatment of Tardive Dyskinesia

Over the Years – Low Quality or Inadequate Evidence

1. Lower the dose of the antipsychotic medication
2. Taper and stop the antipsychotic medication
3. Increase the dose of the antipsychotic medication (? Masking TD)
4. Drug holidays (some evidence this strategy may worsen TD)
5. Switch to newer second generation agents
6. What about Clozapine: some evidence from small studies of benefit for moderate/severe TD including dystonia (but is it Rxing or masking or not causing?)

Over the Years – 2 – Low Quality or Inadequate Evidence and/or no difference from Placebo

1. Vitamin E – Dose: 1200 to 1600 International Units per day, 13 Randomized Studies
2. Benzodiazepines
3. Anticholinergic agents (some reports suggest worsening TD)
4. Cholinergic Drugs (e.g. Deanol, Lecithin, Galantamine, Rivastigmine, Donepezil)
5. Calcium Channel Blockers
6. Pyridoxal 5 Phosphate
7. Branched Chain Amino Acids (Tarvil)
8. Melatonin
9. So many others! Including ECT and Hypnosis

https://www.cochrane.org/evidence
Search term: Tardive Dyskinesia

https://www.cochrane.org/evidence
Search term: Tardive Dyskinesia
The Management and Treatment of Tardive Dyskinesia – 3

- Gingko Biloba (EGb-761, standardized extract from leaves)
- Moderate Grade Evidence but one controlled study (n= 157)
- Benefits reported
- No details of any side effects

https://www.cochrane.org/evidence
Search term: Tardive Dyskinesia

The Management and Treatment of Tardive Dyskinesia – 4

- VMAT2 Inhibitor Medications (Vesicular Monoamine Transporter Inhibitors – Type 2)
- Tetrabenazine (Rx of Chorea associated with Huntington’s Disease) Off Label Use in Tardive Dyskinesia
- FDA Approved VMAT2 Medications – Two medications approved to date for Tardive Dyskinesia
  - Valbenazine (Brand: Ingrezza®) April 2017
  - Duetetabenazine (Brand: Austedo®) August 2017
Vesicular Monoamine Transporter Inhibitor – Type 2 (VMAT2) – Mechanism of Action Schematic

Valbenazine - Change in AIMS from Baseline by Visit, Study 1304

Source: Reviewer-created, using Study 1304 analysis dataset A_AIMS.XPT. Error bars represent standard error of the mean. CFB = change from baseline.
Valbenazine - LS mean change from baseline in AIMS dyskinesia total score through 6 weeks (ITT population)\(^1\)\(^-\)\(^3\)


Valbenazine - Percent of patients with specified magnitude of AIMS total score improvement at the end of Week 6\(^1\)\(^,\)\(^3\)\,*

Valbenazine – Change in AIMS from Baseline by Visit, Full Study Duration by Central Video Raters, Study 1304

Source: Primary reviewer-created, using Study 1304 analysis dataset A_AIMS.XPT. Subjects who received placebo and were re-randomized to valbenazine after 6 weeks are grouped with the 40 mg and 80 mg treatment groups for Weeks 8-52. Data from early termination visits were excluded. Each error bar is constructed using 1 standard error from the mean.

Adverse Reactions in 3 valbenazine (INGREZZA) Placebo-Controlled Studies of 6-week Treatment Duration Reported at ≥2% and >Placebo

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>INGREZZA (n=243) (%)</th>
<th>Placebo (n=149) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>10.9%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>5.4%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>4.1%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.4%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.7%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.6%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.5%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Metabolics</td>
<td>2.3%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

*Within each adverse reaction category, the observed adverse reactions are listed in order of decreasing frequency.

Deutetrabenazine -
Mean change and
treatment response
rates based on AIMS
score from baseline to
week 12 in the
modified intention-to-
treat population

(A) Least-squares mean
c change from baseline to
weeks 2, 4, 8, and 12. Error
bars represent SEs. p values all
represent
difference vs placebo

(B) Treatment response rates
based on percentage
reduction in
AIMS score from baseline to
week 12 for all treatment
groups

www.thelancet.com/psychiatry
Vol 4 August 2017
Deutetrabenazine - Percent of Patients with Specified Magnitude of AIMS Total Score Improvement at the End of Week 12 (Study 1)

Adverse Reactions Reported in ≥2% of Patients Treated With Deutetrabenazine (AUSTEDO) in TD Studies

Once patients were titrated to their maintenance dose, the following adverse events were no longer reported:

- Dry mouth, nausea, hypertension (AIM-TD)
- Somnolence and dry mouth (ARM-TD)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>AUSTEDO (n=37)</th>
<th>Facet (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2%</td>
<td>7%</td>
</tr>
<tr>
<td>Weight increased</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Depression/Depressive disorder</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Akathisia</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Comparison of Valbenazine and Deutetrabenazine

Valbenazine
• Once a Day dosing
• With or Without Food
• 40 mg/day for first week and then 80 mg/day (Capsules)
• AE > 4% and twice placebo; Somnolence 10.9 vs 4.2%,

Deutetrabenazine
• Twice a day dosing
• With Food
• 6 mg bid for first week, and then weekly increase by 6 mg to 36 to 48 mg/day (Tablets)
• AE > 4% and twice placebo; Nasopharyngitis 4 vs 2%, and Insomnia 4 vs 1%

Poor Metabolizers and Hepatic CYP Drug-Drug Interactions

Valbenazine
• Poor CYP 2D6 Metabolizers: Max Dose 40 mg/day
• Strong CYP 2D6 or CYP 3A4 inhibitor: Max Dose 40 mg/day
• Paroxetine & Fluoxetine can elevate levels
• Phenytoin, carbamazepine, rifampicin can lower levels (strong 3A4 inducers)
• Digoxin Levels can go up
• Avoid with MAOIs

Deutetrabenazine
• Poor CYP 2D6 Metabolizers: Max Dose of 36 mg/day
• Strong CYP 2D6 inhibitor: Max Dose of 36 mg/day
• Paroxetine & Fluoxetine can elevate levels
• Digoxin has not been studied
• MAOIs contraindicated
No Head to Head Comparisons of Valbenazine and Deutetrabenazine at this point

- Decisional Uncertainty of Which Treatment to Initiate?
- Shared Decision Making
  - Choice Talk: Diagnosis of TD, Severity Category: Mild, Moderate or Severe, and then monitor reaction, offer choices and monitor reaction
  - Option Talk: Assess knowledge, list options, and listen to preferences, review harms and benefits, support decision, and summarize
  - Decision Talk: Focus and Elicit Preferences, Shift towards Decision, Review and act, Check Insurance Coverage, Specialty Pharmacy Rx
Key Messages

- Monitor for TD with AIMS in any patient receiving Antipsychotics
- Recommend training and experience in AIMS examinations
- If Moderate or Greater Severity TD, offer Treatment Choices, and document Shared Decision Making Approach including any refusal to consider and/or try VMAT2 inhibitor medications
- Intervals for AIMS should be determined based on individual patients, risk factors and other clinical considerations
- If movement disorder appears something other than TD consider Movement Disorder Neurology referral

References

- https://www.cochrane.org/evidence Search term: Tardive Dyskinesia, accessed Nov 1, 2021