Tardive Syndromes
Overview and Management

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Conflicts of Interest & Unapproved uses

Honoraria: Karger Press; Cambridge University Press; Medlink
Consultant & research funding: none in recent years, but reimbursement in past years from Acadia Pharm and other companies making anti-psychotic medications

Unapproved uses: botulinum; deep brain stimulation; amantadine; ginkgo; baclofen; anticholinergics;
Objectives

• To summarize the key pathophysiological theories of tardive syndromes
• To review the phenomenology of the main tardive syndromes
• To discuss approaches to management of TD and other tardive syndromes, with a focus on non-VMAT2 inhibition (which will be covered by Dr Factor)
Tardive dyskinesia (DSM V [G24.01])

• 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 neuroleptic medication for at least a few months and persisting beyond 4-8 weeks”

• Symptoms may develop after a shorter period in older persons. In some patients, movements of this type may appear after discontinuation, or after change or reduction in dosage, of neuroleptic medications, in which case the condition is called neuroleptic withdrawal-emergent dyskinesia. Because withdrawal-emergent dyskinesia is usually time-limited, lasting less than 4-8 weeks, dyskinesia that persists beyond this window is considered to be tardive dyskinesia.
Other definitions

• There are many other definitions of tardive syndromes:
• All require exposure to dopamine receptor blocking drugs
• Variable period of exposure and variable minimum duration
• All describe the various syndromes or include any new movement disorder

Note: movement disorders associated with non-dopamine receptor blocking drugs should be considered “TD-like” rather than TD.
Other *DSM V* tardive syndromes

- Tardive dystonia
- Tardive akathisia
Tardive syndromes

- Dyskinesia- choreoathetoid movements, most commonly involving the mouth
- Stereotypies
- Akathisia- restlessness (often perceived as anxiety)
- Dystonia- sustained dystonia involving any body parts
- Myoclonus
- Tics
- Pain
- Tremor
- Parkinsonism?????
| Facial and Oral Movements | 1. **Muscles of Facial Expression**  
| e.g. movements of forehead, eyebrows, periorbital area, cheeks, including frowning, blinking, smiling, grimacing | 0 1 2 3 4 | 0 1 2 3 4 | 0 1 2 3 4 | 0 1 2 3 4 |
| 2. **Lips and Perioral Area**  
| e.g., puckering, pouting, smacking | 0 1 2 3 4 | 0 1 2 3 4 | 0 1 2 3 4 | 0 1 2 3 4 |
| 3. **Jaw**  
| e.g. biting, clenching, chewing, mouth opening, lateral movement | 0 1 2 3 4 | 0 1 2 3 4 | 0 1 2 3 4 | 0 1 2 3 4 |
| 4. **Tongue**  
| Rate only increases in movement both in and out of mouth. NOT inability to sustain movement. Darting in and out of mouth. | 0 1 2 3 4 | 0 1 2 3 4 | 0 1 2 3 4 | 0 1 2 3 4 |
| Extremity Movements | 5. **Upper (arms, wrists, hands, fingers)**  
| Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous) athetoid movements (i.e., slow, irregular, complex, serpentine). DO NOT INCLUDE TREMOR (i.e., repetitive, regular, rhythmic) | 0 1 2 3 4 | 0 1 2 3 4 | 0 1 2 3 4 | 0 1 2 3 4 |
| 6. **Lower (legs, knees, ankles, toes)**  
| e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot. | 0 1 2 3 4 | 0 1 2 3 4 | 0 1 2 3 4 | 0 1 2 3 4 |
| Trunk Movements | 7. **Neck, shoulders, hips**  
| e.g., rocking, twisting, squirming, pelvic gyrations | 0 1 2 3 4 | 0 1 2 3 4 | 0 1 2 3 4 | 0 1 2 3 4 |
Problems in the study of Tardive Syndromes

• Early difficulties in recognition (historical)
  • All the movements seen were described, in detail, in pre-neuroleptic times
  • Unlike other drug side effects, tardive dyskinesia improved with higher doses
  • Patients often had agnosia for the movements

• Difficulties in epidemiology
  • Confounds due to anti-psychotic medications which vary over time and place
  • “Natural history” is unknown

• Difficulties in treatment
  • VMAT2 trials have been of Tardive Dyskinesia, measured on the AIMS. Akathisia was not studied. Unclear if dystonia or other syndromes were included.
Pre-neuroleptic observations

Kraepelin 1919 observed (in different patients):

Wrinkling of the forehead, distortion of the corners of the mouth, irregular movements of the tongue and lips, smacking and clicking with the tongue, sudden protrusions

Other reports:

Peculiar facial grimacing, esp of the mouth...twisting her mouth when talking..sometimes making pouting motion with lips

There was much facial grimacing, frowning, jutting the lower jaw forward and forming his mouth in the shape of a snout

There were a fair number of mannerisms and facial movements, the most notable one being flipping of the lower lip

She was twitching her body about, making aimless jerking motions with her arms
“Natural” history

- 37% remission rate in review of 285 studies....Jeste 1982
- 14% remission after mean 3.1 years (off neuroleptics)....Zutshi 2014
- 11/12 improved ....Quicken 1977
- 1 of 49 better. ...Morgenstern
- 14 year follow up (on neuroleptic): improved AIMS but worse Parkinsonism (53 in-patients).******
Pathophysiology

• “Hyperdopaminergic” theory
• Dopamine synaptic plasticity
• Dopamine terminal loss
• Striatal tissue loss
• Serotonin and glutamate receptor maladapts
• Oxidative stress leading to neurodegeneration
• Genetic
Challenges in management strategy

• Most patients require lifelong treatment with DRBD

• The “natural” history of TS is unknown and unpredictable, whether remaining on antipsychotic or not
Treatment varies with the syndrome

• Dyskinesia, stereotypy, akathisia or tremor

• Dystonia

• Other
Treating tardive dyskinesia, stereotypies or akathisia

1. Attempt DRBD discontinuation or replacement with less DRBD potency (quetiapine or clozapine). Work with psychiatrist.
   * warn patient of possible worsening
2. Add VMAT2 inhibitor and titrate as indicated, aiming for reasonable therapeutic goal.
3. Add a secondary drug, based on your experience and comfort level, and your patient’s
4. If severe, consider Gpi deep brain stimulation
Tardive Dystonia

• Attempt to discontinue DRBD
• If antipsychotic cannot be stopped or dystonia does not improve, use clozapine.
• If clozapine cannot be used, use quetiapine for psychosis
• Botulinum toxin, if appropriate
• VMAT2 inhibitors, anticholinergics, baclofen
• Gpi deep brain stimulation
### Table 4  Second-tier drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Trial number and total N</th>
<th>Dose</th>
<th>Common adverse effects</th>
<th>Evidence level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td>Weak NMDA (N-methyl-D-aspartate) receptor antagonist</td>
<td>3 randomized trials N = 44</td>
<td>100 mg TID</td>
<td>Insomnia, Constipation, Dizziness</td>
<td>C</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>GABAergic–GABA&lt;sub&gt;A&lt;/sub&gt; receptors</td>
<td>1 randomized trial N = 19</td>
<td>4.5 mg</td>
<td>Sedation, Ataxia</td>
<td>B</td>
</tr>
<tr>
<td><em>Ginkgo biloba</em> extract (EGB-761)</td>
<td>Antioxidant</td>
<td>1 randomized trial N = 157</td>
<td>240 mg per day</td>
<td>None</td>
<td>B</td>
</tr>
<tr>
<td>Drug</td>
<td>Mechanism</td>
<td>Trial number and total $N$</td>
<td>Daily dose (mg)</td>
<td>Common adverse effects</td>
<td></td>
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<tr>
<td>Levetiracetam</td>
<td>Synaptic vesicle protein 2A: inhibition of synaptic vesicle release, N-type calcium channel blockade</td>
<td>1 randomized trial $N = 50$</td>
<td>Up to 3000</td>
<td>Sedation, Nervousness, Headache, Nasal congestion</td>
<td></td>
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<tr>
<td>Piracetam</td>
<td>N-type calcium channel blockade</td>
<td>1 randomized trial $N = 40$</td>
<td>4800</td>
<td>Drowsiness, Insomnia, Anxiety, Weight gain</td>
<td></td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>Antioxidant</td>
<td>2 randomized trials $N = 60$</td>
<td>400</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Melatonin</td>
<td>Antioxidant</td>
<td>2 randomized trials $N = 35$</td>
<td>10-20</td>
<td>None</td>
<td></td>
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<tr>
<td>Baclofen</td>
<td>GABAergic–GABAB receptors</td>
<td>3 randomized trial $N = 71$</td>
<td>Up to 90</td>
<td>Dizziness, Insomnia, Nausea, Drowsiness</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>Beta-blocker</td>
<td>1 randomized trial $N = 4$ Other studies $N = 71$</td>
<td>Up to 80</td>
<td>Lightheadedness, Fatigue, Nightmares</td>
<td></td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Binds to the GABA–benzodiazepine receptor complex</td>
<td>1 open trial $N = 3$</td>
<td>10-20</td>
<td>Sedation</td>
<td></td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Sodium and T-type calcium channel blocker</td>
<td>1 open trial $N = 11$</td>
<td>50-100</td>
<td>Loss of appetite, Weight loss, Dizziness, Headache</td>
<td></td>
</tr>
</tbody>
</table>
Special cases

- Parkinsonism in a patient with tardive syndrome
- Medically emergent need to reduce tardive movements
- Tardive syndrome in a patient with idiopathic Parkinson’s disease
- Non-compliant patient
Factor SA. Management of Tardive Syndrome: Medications and Surgical Treatment
Neurotherapeutics 2020; Oct; 17(4): 1664-1712