Diagnosis and Treatment of Tardive Syndrome

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Drug-Induced Movement Disorders

movement disorders caused by anti-dopaminergics aka. extrapyramidal syndrome (EPS)

EPS
- acute/subacute: dystonia, akathisia, neuroleptic malignant syndrome
- dose-dependent: parkinsonism, drug-induced tremor
- delayed: tardive syndrome
Anti-Dopaminergic Drugs

Dopamine Depletors (DD): presynaptic
metyrosine – tyrosine hydroxylase
reserpine – VMAT 1&2 (vesicular monoamine transporter)
benazines – VMAT 2

Dopamine Receptor Blockers (DRB): postsynaptic
typical neuroleptics
atypical neuroleptics
anti-emetics

DD & DRB → acute/subacute EPS
dose-dependent EPS
DRB → tardive syndrome
Tardive Syndrome

onset when on anti-dopaminergic: > 1 month of exposure

onset when off anti-dopaminergic: “unmasked” phenomenon mostly within 6 months occasionally 6-12 months never > 12 months

▪ idiosyncratic: no safe threshold, risk ↑ as duration ↑
▪ prevalence ≈ 5-20 %
▪ risk factors
  - duration
    - typical > atypical neuroleptics
  - dosage
  - female > male
  - older > younger
  - drug holidays & interruptions

▪ natural history: non-progressive, spontaneous remission possible
History of Tardive Syndrome

paroxysmal dyskinesia as the effect of Megaphen \((Schönecker 1957)\)

- reserpine
- chlopromazine
- tardive dyskinesia \((Faurbye 1964)\)
- clozapine
- quetiapine
- olanzapine

Dopamine Receptor Blockers: typical vs atypical neuroleptics

risk of EPS $\approx$ binding affinity to D2 receptor

<table>
<thead>
<tr>
<th>Region</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Striatum</td>
<td>15</td>
<td>53</td>
<td>390</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>Striatum</td>
<td>0.82</td>
<td>360</td>
<td>39</td>
<td>2.1</td>
<td>0.44</td>
</tr>
<tr>
<td>Accumbens</td>
<td>2.5</td>
<td>22</td>
<td>&gt;500</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Frontal</td>
<td>2600</td>
<td>710</td>
<td>&gt;830</td>
<td>7100</td>
<td>21</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>570</td>
<td>0.98</td>
<td>56</td>
<td>2.1</td>
<td>&gt;5000</td>
</tr>
</tbody>
</table>

“atypicalness”: clozapine >>> quetiapine >> olanzapine > risperidone
Dopamine Receptor Blockers: newer neuroleptics

<table>
<thead>
<tr>
<th>Drug</th>
<th>EPS</th>
<th>metabolic syndrome (weight gain, diabetes, etc)</th>
<th>QTc prolongation</th>
</tr>
</thead>
<tbody>
<tr>
<td>clozapine</td>
<td>+/-</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>quetiapine</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>olanzapine</td>
<td>+</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>aripiprazole (Abilify)</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>ziprasidone (Geodon)</td>
<td>+</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>iloperidone (Fanapt)</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>lurasidone (Latuda)</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>asenapine (Saphris)</td>
<td>+++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>paliperidone (Invega)</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>cariprazine (Vraylar)</td>
<td>++</td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>
Pimavanserin (Nuplazid): a novel antipsychotic

- approved in 2016 for Parkinson disease with psychosis
- inverse agonist of serotonin 5-HT$_{2A}$ receptor
- no appreciable affinity to dopaminergic D2 receptor (Ki >300 nM)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Adverse Reactions in Placebo-Controlled Studies of 6-Week Treatment Duration and Reported in ≥2% and &gt;Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of Patients Reporting Adverse Reaction</td>
<td>NUPLAZID 34 mg</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>N=202</td>
</tr>
<tr>
<td>Nausea</td>
<td>7%</td>
</tr>
<tr>
<td>Constipation</td>
<td>4%</td>
</tr>
<tr>
<td>General disorders</td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>7%</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>2%</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>Hallucination$^a$</td>
<td>5%</td>
</tr>
<tr>
<td>Confusional state</td>
<td>6%</td>
</tr>
</tbody>
</table>
Dopamine Receptor Blockers: central vs peripheral anti-emetics

<table>
<thead>
<tr>
<th></th>
<th>prochlorperazine (Compazine)</th>
<th>metoclopramide (Reglan)</th>
<th>promethazine (Phenergan)</th>
<th>trimethobenzamide (Tigan)</th>
<th>domperidone (Motilium)</th>
</tr>
</thead>
<tbody>
<tr>
<td>blood-brain barrier</td>
<td>+</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>risk of EPS</td>
<td>+</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
Tardive Syndrome

- classic tardive dyskinesia
- tardive dystonia
- tardive akathisia
- tardive pain (focal akathisia)
- tardive chorea (withdrawal emergent syndrome)
- tardive myoclonus?
  - tremor?
  - tics?
  - parkinsonism??

**tardive dyskinesia in a broader sense = tardive syndrome**
**tardive dyskinesia in a narrower sense → one of many types of tardive syndrome**
Classic Tardive Dyskinesia

- repetitive, stereotyped and rhythmic - tardive stereotypy

  - face, mouth, tongue: oral-buccal-lingual dyskinesia (OBLD)
    - "flycatcher’s tongue"
  - limbs: distal > proximal
    - "piano-playing fingers"
  - abdominal and pelvic dyskinesia
  - vocal dyskinesia

- absent during voluntary movements
- psychosocial impact >>> physical impact
Tardive Dystonia

- proximal > distal

  - mouth – oromandibular dystonia (OMD)
  - axial – retrocollis, opistotonus, rotation of shoulders & extension of elbows

- most common cause of secondary dystonia

- phenomenologically indistinguishable from idiopathic dystonia
Tardive Akathisia

- subjective restless feeling & objective restless movements
- phenomenologically indistinguishable from akathisia of acute EPS
- focal tardive akathisia(tardive pain): oral or pelvic
Diagnosis

1. history of exposure to DRB
2. phenomenology of movements consistent with tardive syndrome
3. excluding other etiologies

“double dyskinesia”: an underlying hyperkinetic movement disorder + tardive syndrome

“pseudo-tardive dyskinesia”: consistent phenomenology, but caused by other etiologies
Treatment — continue DRBs or not

- spontaneous remission after discontinuation of DRBs
  33 % in classic tardive dyskinesia
  12 % in tardive dystonia
  8 % in tardive akathisia  (*Burke* 1989)

- does continuing DRBs worsen tardive syndrome?

- does symptomatic treatment of tardive syndrome change its natural course?
  ???
Treatment – classic tardive dyskinesia

- to treat or not to treat
- dopamine depletors (tetrabenazine > reserpine > metyrosine)

- benazines – reversible VMAT2 inhibitor
  short half-life & less peripheral adverse effects
- reserpine – irreversible VMAT1&2 inhibitor
  long half-life & more peripheral adverse effects
- metyrosine – low potency

- GABAergics (benzodiazepines, vaproate, baclofen)

- may be worsened by anticholinergics- different from acute EPS!
**VMAT2 Inhibitors- benazines**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approval Date</th>
<th>Approved Indication</th>
<th>Risk of Depression</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetrabenazine (Xenazine)</td>
<td>2008</td>
<td>Huntington chorea</td>
<td>+++ (19%)</td>
<td>bid-tid</td>
</tr>
<tr>
<td>Deutetrabenazine (Austedo)</td>
<td>2017</td>
<td>Huntington chorea</td>
<td>+ (2-4%)</td>
<td>bid</td>
</tr>
<tr>
<td>Valbenazine (Ingrezza)</td>
<td>2017</td>
<td>Tardive dyskinesia</td>
<td>- (&lt;1%)</td>
<td>qd</td>
</tr>
</tbody>
</table>
Treatment – tardive dystonia

- anticholinergic responders
- dopamine-depletor responders
  - baclofen
  - botulinum toxin injection
  - deep brain stimulation of globus pallidus internus (GPi DBS)
Treatment – tardive akathisia

- not responsive to anticholinergics - different from acute EPS
- responsive to dopamine depletors: benazines
  - gabapentin
  - clonidine
  - opioids
  - amantadine
Mechanism of Tardive Syndrome

- mechanism – denervation hypersensitivity
- pathology – no obvious morphological changes
  subtle biochemical abnormalities
  \((\text{Christensen 1970, Jellinger 1977, Harrison 1999})\)

- genetics – dopamine D2 or D3 receptors polymorphism
  \((\text{Steen 1997, Segman 1999, Kishida 2004})\)

- animal models
  rodents – acute EPS but no tardive syndrome
  primates – tardive syndrome
  no obvious morphological changes
  subtle biochemical changes

- functional imaging – no changes in dopaminergic transmission
Conclusions

- Think thrice before starting DRB and use safer ones if possible.

- Diagnosis of tardive syndrome is straightforward, but don’t forget about double or pseudo-tardive dyskinesia.

- Tailor treatment to the type of tardive syndrome.

- Always communicate with the physician who started DRB!