Overview of Pediatric Movement Disorders

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• **Teva** (SD-809 for Tourette/HD/TD, pridopidine for HD)
• **Neurocrine** (Valbenazine for Tourette)
• Kyowa, ADAMAS, NIH, MJFF, Intec, Biotie (Parkinson disease)
• Axovant (Dementia with Lewy bodies)

Personal Biases
• Clinical investigator
• Tics without copralalia

Off label uses will be discussed
Objectives

1. Identify basic semiology and diagnostic criteria for pediatric movement disorders that are commonly seen in psychiatric practice.
2. Discuss key management considerations for pediatric movement disorders
3. Explain when to consider referral of pediatric movement disorder patients
Common in Psychiatry

• Primary or Secondary
  – Chorea, Dystonia, Myoclonus, Tremor
  – Tics and Tourette’s
  – Stereotypies

• Drug-Induced
  – Tremor
  – Parkinsonism
  – Tardive dyskinesia

• Psychogenic disorders
Enhanced Physiological Tremor

- Higher Frequency (8-12 Hz)
- Action tremor (Postural and/or kinetic)
- Iatrogenic causes include:
  - Beta-agonists, theophylline
  - SSRIs, TCAs
  - Lithium
  - VPA
  - Cyclosporine, tacrolimus
- Treat w dose reduction or β-blockers
Serootonin Syndrome
Dystonia: definition/etiology

A syndrome of **sustained** muscle contractions, frequently causing **twisting** and repetitive movements or abnormal **postures**.

May be characterized by a sensory trick

- **Subtypes**
  - Generalized, multifocal, hemidystonia
  - Focal (limb, cranial, cervical)
  - Segmental (craniocervical)

- With AAO<26, consider Genetic Etiologies
  - GTP-CH (Segawa disease)= dopa-responsive
  - DYT1, DYT6
Tardive Syndromes

• Risk is proportional to dose and duration of agents that reduce D2 receptor activity
  – Antagonist, inverse agonist or partial agonist

• Diagnosis requires prolonged exposure
  – 3 months (1 if age 60+)

• Screen w AIMS (or “modified AIMS”)
  – Assess all body regions, including tongue
  – Assess for emergence with distraction
DDX: Antipsychotic side effects

- Parkinsonism
- Akathisia
- Withdrawal emergent symptoms
- Tardive Syndromes
  - Stereotypies
  - Dystonia
  - Akathisia
  - Chorea
  - Tics
  - Tremor
TD Treatment options

- Reduce or D/C APS
- Switch to lower potency agent, clozapine
- Botulinum toxin, DBS
- Off label/limited evidence
  - Amantadine, zonisamide


Rationale for VMAT-2 inhibitors

- Tetrabenazine
  Depletes dopamine by blocking presynaptic vesicular storage
- Little risk of tardive dyskinesia, metabolic syndrome
- Post-dose peak contributes to fatigue/somnolence (50%), akathisia, insomnia, depression, anxiety
- Novel approaches can improve area under the curve
Valbenazine- approved for TD

- Prodrug of the alpha isomer of tetrabenazine
- Slow rate of metabolism to active metabolite allows QD dosing
- FDA approved for TD
  - 40 and 80 mg doses
- SE profile vs placebo
  - Somnolence
    - 5.3 vs 3.9%
  - Akathisia, dry mouth
    - 3.3 vs 1.3%


FIGURE 3. Percentage of Participants Receiving Valbenazine or Placebo Who Had a ≥50% Improvement in AIMS Dyskinesia Score (Intent-to-Treat Population)\textsuperscript{a}

- Placebo
- Valbenazine, 40 mg/day
- Valbenazine, 80 mg/day

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Placebo</th>
<th>Valbenazine, 40 mg/day</th>
<th>Valbenazine, 80 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Week 4</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Week 6</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
</tr>
</tbody>
</table>

\textsuperscript{a}
SD-809 (deutetetetrabenazine)

- Deuterium slows degradation of active metabolites
- Allows BID dosing
- Approved for HD chorea (24-48mg/d)
- Under review for TD (PDUFA 8/30/2017)
- SE=placebo in TD
- Slightly higher rate of somnolence (11 vs 6%) in HD chorea
- No worsening of mood or parkinsonism


Acute Dystonia

• **Prophylaxis:** *Short term* treatment with bentropine 2mg/d for one week
  – Reduces risk when using typical antipsychotics

• **Causes:**
  – DRBs, TCA’s, MAOIs, SSRIs, SNRI

• **Treatment:**
  – Withdraw offending agent
  – Treat with antihistamine/anticholinergic
Stereotypies

• Semi-rhythmic repetitive movement
• Motor
  – Hand rubbing, rocking, prancing
• Vocal
  – humming
• Developmental/degenerative disorders
  – Autistic Spectrum
  – Pervasive developmental delay
  – Rett syndrome
• Tardive
Tic Characteristics

1. Mimic normal coordinated movement
2. Occur out of a background of normal motor activity
3. Not constantly present
4. Vary in intensity
5. Lack rhythmicity
6. Voluntarily suppressible
7. Usually characterized by a premonitory sensation
• Tic Video examples (available open access; please go to reference website to stream).
# Key Features Differentiating Tics from Other Hyperkinetic Movement Disorders

<table>
<thead>
<tr>
<th>Movement</th>
<th>Stereo-typed</th>
<th>Rhythmic</th>
<th>Premonitory sensations</th>
<th>Suppressible</th>
<th>Continuous</th>
<th>Persist in Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tic</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Dystonia</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Chorea</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Sterotypy</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Tremor</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Psychogenic</td>
<td>+/-</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
</tbody>
</table>

A. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently.

B. The tics occur many times a day (usually in bouts) nearly every day or intermittently throughout a period of more than 1 year
   • (deleted language: “during this period there was never a tic-free period of more than 3 consecutive months.”)

C. The onset is before age 18 years.

D. The disturbance is not due to the direct physiological effects of a substance (e.g., stimulants) or a general medical condition (e.g., Huntington’s disease or postviral encephalitis).
Primary Tic Disorders

- Transient tic
- Chronic Motor Tic
- Chronic Phonic Tic
- Tourette syndrome
Primary Tic Disorders: Prevalence

- Tourette: 1% of boys, 0.25% of girls
- Chronic tic disorder 1.6%
- Transient tic disorder 3%
- Higher overall rates among children requiring special education classes
When to anticipate a tic?

- Individuals with ADHD, OCD
- Family history of tics, ADHD or OCD
- Special education populations
  - Down syndrome/chromosomal disorders
  - Autistic spectrum/“PDD”
- Unexplained
  - Eye Problems
  - Nose/Throat problems
  - Neck or limb movements due to discomfort
- Pain due to repetitive limb or neck movements
Comorbidities

- Any psychiatric: 86% (57% 2 or more)
- Obsessive-compulsive disorder 66%
- Attention-deficit/hyperactivity 54%
- Mood 30%
- Anxiety 36%
- Disruptive behavior 29%

Tics: What to Expect?

- Cleveland Clinic, Yale:  
  - 50% “nearly tic free;” 25% same or worse.\(^1\)
- Rush University: 90% “tic free” still have tics\(^2\)
- Utah data (study of ‘tic remission’):\(^3\)  
  - 8/10 persistent; 2/10 improved (none tic-free)
- Females outcomes may differ\(^4\)  
  - 4.5:1 Juvenile M:F ratio → 2:1 in adult clinics

\(^3\)Shprecher et al, Tremor and other hyperkinetic disorders 2014.  
\(^4\)Lichter and Finnegan, Eur Psychiatry 2015.
### Management of Tics

<table>
<thead>
<tr>
<th>Class</th>
<th>Preferred agents</th>
<th>Special Indications</th>
<th>Common side-effects</th>
<th>Rare or serious AE’s</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIRST LINE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>Clinician</td>
<td>Always use</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nonmedical</td>
<td>CBIT</td>
<td>Motivated</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>α-2-agonists</td>
<td>Guanfacine, clonidine</td>
<td>ADHD</td>
<td>Sedation</td>
<td>irritability</td>
</tr>
<tr>
<td>Anti-epileptics</td>
<td>Topamax</td>
<td>HA, obesity</td>
<td>hypohydrosis</td>
<td>Kidney stone</td>
</tr>
<tr>
<td><strong>SECOND LINE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine depletors</td>
<td>tetrabenazine</td>
<td>Tx mood disorder first</td>
<td>Fatigue, depression</td>
<td>Suicide, NMS</td>
</tr>
<tr>
<td>Atypical APS</td>
<td>Risperdal, Abilify</td>
<td>Refractory OCD</td>
<td>metabolic</td>
<td>TD, NMS</td>
</tr>
<tr>
<td>Typical APS</td>
<td>fluphenazine</td>
<td>Self-injurious tics</td>
<td>EPS</td>
<td>TD, NMS</td>
</tr>
<tr>
<td><strong>THIRD LINE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical-DBS</td>
<td>Thalamic or GPi</td>
<td>Refractory, severe</td>
<td>Infection</td>
<td>Stroke, bleed, psychosis</td>
</tr>
</tbody>
</table>

Comprehensive Behavioral Intervention for Tics (CBIT)

- Education, Removal of reinforcing factors
- Tic (premonitory urge) awareness
- Competing response
- Similar efficacy to medication
  - Pediatric: 31% (vs 14.22% placebo response)
  - Adult: 26% (vs 11%)


<table>
<thead>
<tr>
<th>Agent</th>
<th>Phase</th>
<th>Sponsor</th>
<th>Mechanism</th>
<th>Main AE’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acamprosate</td>
<td>II a</td>
<td>Synchroneuron</td>
<td>Glutamate</td>
<td>?</td>
</tr>
<tr>
<td>AZD5213</td>
<td>II</td>
<td>Astrazeneca</td>
<td>H3 inv agonist</td>
<td>?</td>
</tr>
<tr>
<td>ecopipam</td>
<td>III</td>
<td>Psyadon</td>
<td>D1-R-i</td>
<td>sedation</td>
</tr>
<tr>
<td>Sativex</td>
<td>II (?)</td>
<td>GW Pharma</td>
<td>THC/CBD</td>
<td>?</td>
</tr>
<tr>
<td>Deutetetrabenazine</td>
<td>II</td>
<td>Teva</td>
<td>VMAT-2-i</td>
<td>-</td>
</tr>
<tr>
<td>Valbenazine</td>
<td>II</td>
<td>Neurocrine</td>
<td>VMAT-2-i</td>
<td>-</td>
</tr>
</tbody>
</table>
# Secondary tic disorders

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune</td>
<td>Demyelinating disease</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>Stimulants, lamotrigine, neuroleptics</td>
</tr>
<tr>
<td>Chromosomal disorders</td>
<td>Beckwith Weidemann, Down, or Klinefelter syndromes, Fragile-X</td>
</tr>
<tr>
<td>CAG repeat disorders</td>
<td>DRPLA, HD</td>
</tr>
<tr>
<td>Genetic mutations</td>
<td>Lesch-Nyhan, Neuroacanthocytosis, NBIA, Wilson, tuberous sclerosis</td>
</tr>
<tr>
<td>Infectious (encephalitis)</td>
<td>Mycoplasma, Lyme, syphilis, HSV</td>
</tr>
<tr>
<td>Post-infectious</td>
<td>Post-HSV, post-streptococcal</td>
</tr>
<tr>
<td>Trauma/vascular</td>
<td>TBI, stroke</td>
</tr>
<tr>
<td>Toxic</td>
<td>Carbon monoxide</td>
</tr>
</tbody>
</table>

Stimulant medication- generally considered a comorbidity treatment, not tic cause

- 4x4 Trial- Tourette syndrome study group
  - Methylphenidate, guanfacine
  - Active treatment showed tic improvement

- Methylphenidate (MPH) vs placebo
  - MPH suppressed ADHD, oppositional defiant disorder, and peer aggression behaviors
  - No tic or OCD worsening

Pediatric Autoimmune Disorder Associated with Streptococcal Infection

1. Presence of OCD and/or tics, particularly multiple, complex or unusual tics
2. Age Requirement (Symptoms of the disorder first become evident between 3 years of age and puberty)
3. Acute onset and episodic (relapsing-remitting) course
4. Association with Group A Streptococcal (GAS) infection
5. Association with Neurological Abnormalities, by SC

PANDAS with chorea = Sydenham’s?

- PANDAS-chorea and SC show similar biomarkers
  - Elevated anti-dopamine 1 receptor (D1R) and anti-dopamine 2 receptor (D2R) immunoglobulin (Ig)G levels
  - May cross react with Lysoganglioside-GM1 and tubulin
- PANDAS- chronic tics and OCD (no chorea)
  - Tic/OCD exacerbations did NOT correlate w Strep infection
  - Elevated calcium calmodulin kinase-II activity identified in all 3 groups (SC, PANDAS w/wo chorea)

Functional Movement Disorders

- Term preferred over “psychogenic”
- Psychiatric illness may not be comorbid
- If present, etiological life events may require in-depth, specialized interview to identify
- Specialized rehabilitation techniques have been shown beneficial over usual care
- Objective clues about etiology include
  - Loss of sensory attenuation
  - Neuroimaging data: Functional connectivity, fMRI

Factors suggesting a FMD

- Distractibility and/or entrainment (to frequency of repetitive movements)
- False weakness/sensory signs, astasia-abasia
- Inconsistent over time, abrupt onset
- Selective disability
- Co-contraction(tremor)/Bereitschafts(myoclonus)
- Atypical response to pharmacological agent
- Atypical stimulus sensitivity
- Paroxysmal, periods of spontaneous remission

Conclusions

• Psychiatric patients should be periodically monitored for movement disorders
• Two new therapies were FDA-approved April 2017 for tardive dyskinesia and chorea.
  – Valbenazine and Deutetrabenazine
  – Modest potential side effects (sedation or fatigue)
  – More research is needed to support on-label treatment of pediatric hyperkinetic movement disorders
• For complex cases, movement disorders neurology consultation is available- and can be considered