Jean and Paul Amos
Parkinson’s Disease and
Movement Disorders
Program

www.neurology.emory.edu/movement
VIRTUAL SYMPOSIUM
Parkinson's Disease for the Clinician
SATURDAY, SEPTEMBER 26, 2020 • 8:30 AM–12:10 PM

Hyperkinetic Movement Disorders for the Clinician
SATURDAY, OCTOBER 3, 2020 • 8:30 AM–12:10 PM
EMORY UNIVERSITY | Jean and Paul Amos Parkinson's Disease and Movement Disorders Program

Parkinson's Disease for the Clinician
Hyperkinetic Movement Disorders
for the Clinician

JOIN US FOR A VIRTUAL SYMPOSIUM
September 26 & October 3

This virtual symposium, 2020, has been reviewed and is acceptable for Prescribed credit(s) by the American Academy of Family Physicians. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Residents, fellows and medical students are strongly encouraged to attend.
Learning Objectives:
Part I: Parkinson’s Disease
Upon completion of this course, participants should be able to:
• Diagnose and treat Parkinson’s disease
• Identify the cognitive, psychiatric and autonomic features of Parkinson’s disease
• Determine appropriate candidates for deep brain stimulation and examine outcomes and possible adverse events
• Recognize and diagnosis atypical parkinsonism.

Learning Objectives:
Part II: Hyperkinetic disorders
Upon completion of this course, participants should be able to:
• Recognize and diagnose different hyperkinetic disorders: including Dystonia, chorea and Huntington’s disease, tics and Tourette syndrome and tremor
• Recognize and diagnose ataxia disorders
• Recognize tardive dyskinesia and determine appropriate treatment
• Recognize the distinguishing features of the different botulinum toxins and their appropriate use.

REGISTRATION
www.neurology.emory.edu/movement
Call Cornelya Dorbin for more information at 404-796-4382.
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- Recognize the distinguishing features of the different botulinum toxins and their appropriate use.

REGISTRATION FEES AND DEADLINE INFO
Online registration
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Call Cornelya Dorbin for more information at 404-796-4382.
The Dystonias:
Evolving definition, clinical features, & diagnostic clues

Laura M. Scorr, MD MSc
Assistant Professor of Neurology
Emory University School of Medicine
Objectives

- A brief history of dystonia
- Evolving definition of dystonia
- Key clinical features of dystonia
## Problem of Diagnosis

<table>
<thead>
<tr>
<th>Publication</th>
<th>Country</th>
<th>Type of Dystonia</th>
<th>Time to Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powel et al, 1995</td>
<td>Australia</td>
<td>Adult onset focal dystonia</td>
<td>3.8 years</td>
</tr>
<tr>
<td>Jog et al, 2011</td>
<td>Canada</td>
<td>Adult onset focal dystonia</td>
<td>6.4 years</td>
</tr>
<tr>
<td>Creighton et al, 2013</td>
<td>USA</td>
<td>Laryngeal dystonia</td>
<td>4.4 years</td>
</tr>
<tr>
<td>Tiderington et al, 2014</td>
<td>USA</td>
<td>Cervical dystonia</td>
<td>3.7 years</td>
</tr>
<tr>
<td>Macerollo et al, 2015</td>
<td>Italy</td>
<td>Blepharospasm</td>
<td>4.8 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cervical dystonia</td>
<td>7.1 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hand dystonia</td>
<td>10.1 years</td>
</tr>
</tbody>
</table>
A Brief History

The term “dystonia” was coined by Oppenheim in 1911

“About a peculiar cramping sickness in children and adolescents”

He described four unrelated children previously diagnosed with hysteria
A Brief History

- Variation in muscle tone
- Twisting postures
- Worsening with activity
- Worsening over time
Evolving definition

- The term dystonia has since been used to describe:
  - The movement disorder itself
  - Disorders in which dystonia is the only sign
  - Disorders in which dystonia is part of a syndrome
Dystonia is characterized by sustained or intermittent muscle contractions causing abnormal movements, postures, or both.

Typically patterned, twisting, and may be tremulous.

Often initiated or worsened by voluntary action and associated with overflow muscle activation.
Who is affected by dystonia?

- Dystonia is the third most common movement disorder.
- About 500,000 people in North America have dystonia.
- Men, women, and children of all ages and backgrounds are affected.
- Dystonia may be genetic, secondary to other health conditions, a side effect of medications, or idiopathic.
Types of dystonia

- **Spasmodic Dysphonia/Laryngeal Dystonia**: Affects muscles of the vocal cords, making it difficult to speak.

- **Oromandibular Dystonia**: Affects the face, jaw, and/or tongue. Causes grimacing, tongue protrusion, jaw closure, or jaw opening.

- **Hand Dystonia/Writer’s Cramp**: Causes the fingers to curl and the hand and forearm to cramp. Occurs when a person attempts to use the hand for writing, playing a musical instrument, or other activities.

- **Blepharospasm**: Affects the eyelids, causing them to blink uncontrollably or remain closed.

- **Cervical Dystonia/Spasmodic Torticollis**: Affects neck and shoulder muscles, turning the head to the side or forcing the head back or forward. A tremor may be present.

- **Generalized Dystonia**: Affects many parts of the body simultaneously. Causes cramping and twisting in the feet, limbs, and torso.
Common patient experience

- Patients are often misdiagnosed or told their symptoms are due to psychiatric illness.

- Studies show mean time from onset of symptoms to diagnosis to be 4-6 years.

- Depression, anxiety, and social withdraw.
Dystonia: Key Clinical Features

- Characteristics of muscle contractions
  - Slow and sustained
  - Rapid and intermittent
  - Patterned

- Other helpful features
  - Overflow to nearby muscles
  - Triggered or worsened by voluntary action
  - Geste antagoniste (sensoric trick)
Cervical Dystonia

- Sustained contractions
- Abnormal postures
- Patterned
Blepharospasm

- Intermittent
- Repetitive
- Patterned
Dystonic tremor

- Intermittent
- Arrhythmic and positional
- Patterned
Writer’s cramp

- Triggered by action
- Overflow
- Sustained
- Patterned
Task specific dystonia

- Triggered by action
- Patterned
Overflow dystonia
Geste Antagonist
Dystonia is a movement disorder characterized by abnormal movements and postures.

The movements may be sustained, intermittent, or tremulous but are consistently patterned.

Overflow, task specificity, and sensory tricks are common.

Dystonia is the third most common movement disorder and timely recognition is key to advancing clinical care for dystonia.
Management of Dystonia:
Classification, Testing, and Treatment

Laura M. Scorr, MD MSc
Assistant Professor of Neurology
Emory University School of Medicine
Overview

- Introduction
- Clinical assessment
- Treatments
- Ongoing research
Definition of dystonia

- Movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures or both.
Classification

- **Axis 1: Clinical features**
  - Body distribution, age at onset, temporal aspects, and associated features

- **Axis 2: Etiology**
  - Inheritance pattern, neuropathology
Clinical features: Distribution
Clinical features: Distribution
Clinical features: Distribution
Clinical features: Age at onset
Clinical features: Temporal
Clinical features: Associated findings
Axis 1 & 2

Axis I: Clinical
- body area
- associated features
- temporal aspects
- age at onset

Axis II: Etiology

Syndromic Pattern
Classification to guide diagnosis

Is it dystonia?

- isolated dystonia
  - movement signs
    - parkinsonism
    - myoclonus
    - ataxia
    - etc...
  - neurologic signs
    - dementia
    - neuropathy
    - epilepsy
    - etc...
  - systemic signs
    - hematologic
    - endocrine
    - solid organ
    - etc...
- combined dystonia

Is it dystonia?
~200 different dystonic disorders

18 tables according to associated features
Clinical features guide evaluation

- For most common focal dystonias that emerge after 40 years of age, laboratory investigations are usually not needed.

- For any dystonia that emerges in a child or young adult, laboratory investigations are guided by history and exam.

- Labwork and genetic testing can help to guide treatment strategies.
Targeted treatment strategies

- For patients less than 40 or symptoms of diurnal fluctuation, levodopa trial is warranted.

- For patients with inherited disorders, i.e. Wilson’s disease, treatment of the underlying disorder can alleviate symptoms.

- For patients exposed to dopamine blocking agent who may have tardive dystonia, trial of VMAT2 inhibitor may alleviate symptoms.
Symptomatic Treatments

- Oral medications
- Botulinum toxin
- Surgical treatment
Treatment: oral medications

- There are no FDA approved oral medications for dystonia, and there is limited evidence of efficacy.

- Some commonly used groups of medications are:
  - Anticholinergics
  - Dopamine related drugs
  - GABA related drugs
  - Muscle relaxers
Botulinum toxin injections are the gold standard treatment.

Derived from a protein made by Clostridium botulinum.

There are several different types available:
- Type A: Botox, Xeomin, Dysport
- Type B: Myobloc
Treatment:
Choosing a type of toxin

- Clinical research supports efficacy of all toxins.
- If a patient has incomplete benefit, toxin injection pattern can be adjusted or toxin type can be changed.
- Co-pay varies per toxin type.
Treatment: Surgical

- Neuromodulation:
  - Deep brain stimulation

- Ablative:
  - Making a focal lesion in the brain

- Peripheral surgeries:
  - Selective peripheral denervation
  - Myectomy
Dystonia DBS Outcomes
Emerging therapies

- Physical therapy
- Transcranial magnetic stimulation
- Cannabinoid therapies
Ongoing research

- Clear need for ongoing research to understand the causes of dystonia, improve time to diagnosis, and develop better treatments.

- Categories of ongoing research:
  - Descriptive studies
  - Developing new measurements
  - Evaluating novel treatment strategies
Novel treatment strategies

- Industry sponsored study of a novel form of botulinum toxin.
- New oral medications for treatment.
- Novel deep brain stimulation techniques.
The dystonias represent a family of diseases which, untreated, are associated with pain and disability.

Classification can guide diagnostic evaluation and target management.

There are multiple treatment approaches.

Research is critically important to learn more about causes and develop better treatments for dystonia.
Acknowledgements

- The patients who kindly consented to video recording their movement disorders for the purposes of education.

- My clinical colleagues and research mentors including Dr. Buz Jinnah and Dr. Stewart Factor.

- Dystonia Medical Research Foundation, who provided me with funding support for fellowship training focused on dystonia.
Disclosures

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• Royalties: Demos, Blackwell Futura, Springer for textbooks, Uptodate

• Other Bracket Global LLC, CNS Ratings LLC
Tardive Syndrome - Definition

“... involuntary... movements (lasting at least several weeks) generally of the tongue, lower face, jaw, extremities - but sometimes involving pharyngeal, diaphragmatic or trunk muscles – developing in association with use of neuroleptic for at least several months. In older adults symptoms may develop after shorter period of medication use. Movements may occur after discontinuation or dose change/reduction (in which case term withdrawal-emergent dyskinesia is used). Withdrawal-emergent dyskinesia is usually time-limited so dyskinesia lasting > 4-8 weeks is considered TD.

DSM V
Types of Tardive Syndromes

- Classical Tardive dyskinesia (50%)
  - Tardive stereotypy
  - Oro-bucco-lingual dyskinesia
  - Bucco-lingual-masticatory dyskinesia
- Tardive dystonia (25%)
- Tardive akathisia
- Tardive tics
- Tardive myoclonus

- Tardive tremor
- Tardive Gait
- Tardive Pain & Sensory
- Tardive vocalizations
- Tardive ocular deviation
- Tardive complex (or mixed)

Cummings 1990
Savitt & Jankovic 2018
Lurasidone HCl

From Tripathi et al 2019
# Meta analyses:

**Prevalence Study:** Carbon et al J Clin Psychiatry 2017  
**Incidence Study:** Carbon et al World Psychiatry 2018

<table>
<thead>
<tr>
<th></th>
<th>Studies (N)</th>
<th>SGA</th>
<th>FGA</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Prevalence</strong></td>
<td>41 studies N= 11,493</td>
<td>21%</td>
<td>30%</td>
<td>P=.002</td>
</tr>
<tr>
<td><strong>Directly compared</strong></td>
<td>20 studies</td>
<td>25%</td>
<td>30%</td>
<td>P=.01</td>
</tr>
<tr>
<td><strong>Never previously exposed to FGA</strong></td>
<td>4 studies</td>
<td>7.2%</td>
<td>23.4% with FGA exposure but on SCA</td>
<td>P=.001</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>57 trials N=18,855</td>
<td>2.6% (95% CI 2.0–3.1%)</td>
<td>6.5% (95% CI 5.3–7.8%)</td>
<td>P=.0001</td>
</tr>
</tbody>
</table>
Antipsychotic Prescribing Data

• US: 1997 - 2011, 3-fold increase in antipsychotic prescriptions
• US: ~20% of nursing home residents are on antipsychotics
• Canada: 2005 - 2012, 300% increase in primary care physicians dispensing prescriptions for quetiapine, primarily for sleep problems and anxiety
54 million scripts (2011 data)

Conservative estimate (monthly scripts): 4.5 million pts prescribed

Incidence: 0.02-0.07/yr
Prevalence: 13-32%
Resolution 13%

90,000 - 315,000/year
509,000 - 1,253,000 with TS

Cloud et al 2014
Zutshi et al 2014
Factor et al 2019
AIMS Severity scale

1. Muscles of facial expression
   • Forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing

2. Lips and perioral area
   • Puckering, pouting, smacking

3. Jaw
   • Biting, clenching, chewing, jaw opening, lateral movement

4. Tongue

5. Upper (arms, wrists, hands, fingers)
   • Chorea, athetosis, dystonia, Stereotypy

6. Lower (legs, knees, ankles, toes)
   • Chorea, athetosis, dystonia, Stereotypy

7. Neck, shoulders, hips
   • Chorea, athetosis, dystonia, Stereotypy

Do not include tremor
All scored: 0=none; 1=minimal, may be extreme normal; 2=mild; 3=moderate; 4=severe
Evidence-based guideline: Treatment of tardive syndromes

Review Article

Updating the recommendations for treatment of tardive syndromes: A systematic review of new evidence and practical treatment algorithm
Roongroj Bhidayasiri, Onanong Jitkirtsadakul, Joseph H. Friedman, Stanley Fahn
Treatment

• Discontinue antipsychotics if able
  • Data are insufficient to support or refute TS treatment by DRBA withdrawal (Level U).

Clinical Context:
  • The APA Task Force recommends antipsychotic withdrawal only in patients who can tolerate it.
  • Dyskinesia may worsen
  • Psychotic relapse predictors include younger age, higher baseline antipsychotic dosage, and shorter hospitalization.

• Switch to atypical agents
  • Clozapine       Level U
  • Olanzapine      Level C
  • Quetiapine      Level U
  • Risperidone     Level B

Bhidayasiri et al Neurol 2013, JNS 2018
Meta-Analysis

Clozapine Monotherapy as a Treatment for Antipsychotic-Induced Tardive Dyskinesia:
A Meta-Analysis

J Clin Psychiatry 2018;79(6):17r11852

Thierry Q. Mentzel, MSc\textsuperscript{a,b,*}; René van der Snoek, BSc\textsuperscript{c}; Ritsaert Lieverse, PhD, MD\textsuperscript{a}; Margreet Oorschot, PhD\textsuperscript{c}; Wolfgang Viechtbauer, PhD\textsuperscript{a}; Oswald Bloemen, PhD, MD\textsuperscript{a,b}; and Peter N. van Harten, PhD, MD\textsuperscript{a,b}

- 4 studies investigated the severity of TD as a primary outcome
- Open label studies
- 48 patients total
- Up to 500 mg per day
Figure 2. Effect of Switching to Clozapine Treatment on Tardive Dyskinesia

A. Clinical tardive dyskinesia

<table>
<thead>
<tr>
<th>Study and Year</th>
<th>Standardized Mean Change [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Louzã and Bassitt, 2005</td>
<td>-5.36 [-8.32 to -2.40]</td>
</tr>
<tr>
<td>Spivak et al, 1997</td>
<td>-0.86 [-1.48 to -0.25]</td>
</tr>
<tr>
<td>Littrell and Magill, 1993</td>
<td>-4.46 [-6.38 to -2.53]</td>
</tr>
<tr>
<td>Moore et al, 1992</td>
<td>-0.70 [-1.59 to 0.19]</td>
</tr>
</tbody>
</table>

Random-effects model for clinical tardive dyskinesia group

-2.56 [-4.85 to -0.28]
# 1<sup>st</sup> Tier Agents

<table>
<thead>
<tr>
<th></th>
<th>Initial dose</th>
<th>Max Daily Dose</th>
<th>Dosing Frequency</th>
<th>CMax</th>
<th>Half life (hours)</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valbenazine</td>
<td>40 mg</td>
<td>80 mg</td>
<td>Daily</td>
<td>4-8 hours</td>
<td>15-22</td>
<td>Fatigue, Headache, Somnolence, Akathisia</td>
</tr>
<tr>
<td>Deutetrabenazine</td>
<td>12 mg</td>
<td>48 mg</td>
<td>BID</td>
<td>3-4 hours</td>
<td>9-10</td>
<td>Headache, Somnolence, Parkinsonism</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>12.5 mg</td>
<td>150 mg</td>
<td>TID</td>
<td>1-2 hours</td>
<td>5-7</td>
<td>Drowsiness, Parkinsonism, Depression, Akathisia</td>
</tr>
</tbody>
</table>
VMAT2 Inhibitors

- **Tetrabenazine**: Xenazine: Lundbeck
  - FDA Approved in 2008 for HD in U.S.
  - Level C recommendation
- **Valbenazine**, Ingrezza: Neurocrine
  - Prodrug of DTBZ
  - Approved 2017 for TD
  - Level A recommendation
- **Deutetrabenazine**, Austedo: Auspex & TEVA Pharmaceuticals
  - Deuterized TBZ
  - Approved 2017 for HD, TD
  - Level A recommendation
• 19 TD patients
• Treated for approximately 20 weeks in an open-label study with up to 150 mg of Tetrabenazine.
• Mean scores on the blinded videotaped AIMS assessment improved by 54% (p <0.001).
• Eleven patients rated themselves as markedly improved, 6 as moderately improved, and 2 as mildly improved.
<table>
<thead>
<tr>
<th></th>
<th>Tetrabenazine</th>
<th>Deutetetrabenazine</th>
<th>Valbenazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting Dose</td>
<td>12.5 mg daily</td>
<td>12 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Max total dose</td>
<td>150 mg</td>
<td>48 mg</td>
<td>80 mg</td>
</tr>
<tr>
<td>Dosing</td>
<td>TID</td>
<td>BID</td>
<td>Daily</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>1-2 hours</td>
<td>3-4 hours</td>
<td>4-8 hours</td>
</tr>
<tr>
<td>Half life</td>
<td>5-7 hours</td>
<td>9-10 hours</td>
<td>15-22 hours</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP2D6</td>
<td>CYP2D6</td>
<td>CYP2D6</td>
</tr>
</tbody>
</table>

From Scorr & Factor JNS 2018

Single, highly selective metabolite of TBZ
Randomized, double-blind, placebo-controlled, fixed-dose study

- 6-weeks of treatment with placebo, valbenazine 40 mg, or valbenazine 80 mg
  - Participants who completed were eligible to enter a 42 week extension period of double-blind valbenazine treatment (40 or 80 mg) and follow-up period (Weeks 48–52)
- **Primary Endpoint:** Change from baseline to Week 6 on the AIMS total dyskinesia score (items 1-7, scored by blinded central video raters)
- **Secondary Endpoint:** Clinical Global Impression of Change-TD (CGI-TD)

**KINECT 3: Study Design**

At the Week 6 visit, subjects initially randomized to placebo were re-randomized to VBZ 40 mg or 80 mg. Subjects initially randomized to VBZ 40 mg or 80 mg remained at their current dose. Subjects initially randomized or re-randomized to VBZ 80 mg received 40 mg for the first week.

AIMS, Abnormal Involuntary Movement Scale; VBZ, valbenazine.

Hauser et al Am J Psychiatry 2017
KINECT 3: AIMS Change from Baseline by Study Visit (ITT Population)

% of Participants Receiving Valbenazine or Placebo Who Had a ≥50% Improvement in AIMS Score (ITT Population)

Hauser et al. Am J Psychiatry 2017
Change in AIMS by Treatment Group

- 24 and 36 mg dose groups superior to placebo at Week 2 ($P<0.05$)
- 24 and 36 mg dose groups significantly different from placebo at all timepoints
Adverse Events

Valbenazine
- Dry Mouth
- Somnolence
- Akathisia
- Urinary Tract Infection
- Arthralgia
- Vomiting
- Dyskinesia

Deutetrabenazine
- Headache
- Diarrhea
- Nausea
- Nasopharyngitis
- Anxiety
- Fatigue
- Somnolence
- Depression
- Dry Mouth
- Muscle spasms
- Hypertension
# 2nd Tier agents

<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-A receptors</td>
<td>1 randomized trial N=19</td>
<td>4.5 mg</td>
<td>Sedation, Ataxia</td>
<td>B</td>
</tr>
<tr>
<td>Ginkgo biloba 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</td>
<td>Common adverse effects</td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>---------------------------------------------------------------------------</td>
<td>----------------------------------</td>
<td>------------</td>
<td>---------------------------------------------</td>
<td></td>
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<tr>
<td>Levetiracetam</td>
<td>SV2A: inhibition of synaptic vesicle release, N-type calcium channel blockade</td>
<td>1 randomized trial N=50</td>
<td>Up to 3000 mg</td>
<td>Sedation, Nervousness, Headache, Nasal Congestion</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 mg</td>
<td>Drowsiness, Insomnia, Anxiety, weight gain</td>
<td></td>
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<tr>
<td>Vitamin B6</td>
<td>Antioxidant</td>
<td>2 randomized trials N=60</td>
<td>400 mg</td>
<td>None</td>
<td></td>
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<tr>
<td>Melatonin</td>
<td>Antioxidant</td>
<td>2 randomized trials N=35</td>
<td>10-20 mg</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Baclofen</td>
<td>GABAergic-GABA-B receptors</td>
<td>3 randomized trial N=71</td>
<td>Up to 90mg</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 mg</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 mg</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 mg</td>
<td>Loss of appetite, Weight loss, Dizziness, Headache</td>
<td></td>
</tr>
</tbody>
</table>
Botulinum Toxin

• For Classical Tardive Dyskinesia there is little evidence to support its use.
  • One small single blind study which showed benefit: injections in orbicularis oris

• For Tardive Dystonia:
  • Craniocervical distribution
  • Widely utilized based on the response of patients with idiopathic dystonia. Several open label retrospective reports support its use for blepharospasm, oromandibular, lingual and cervical tardive dystonia.
  • Response of tardive dystonia is similar to that of idiopathic dystonia.
Surgical Treatment

Long-term efficacy and tolerability of bilateral pallidal stimulation to treat tardive dyskinesia


Neurostimulation in tardive dystonia/dyskinesia: A delayed start, sham stimulation-controlled randomized trial

Gruber, et al Brain Stimulation 2018
19 patients with severe pharmaco-resistant TS

Posteroventrolateral GPi DBS
  • Settings: 133.42 +/- 12.4 Hz, 3.17 +/- 0.67 V, and 120.8 +/- 32.6 ms pulse width

Assessed at baseline, 3, 6 (main outcome measure), & 12 months, and in the long term (6–11 years) for 14 patients

Assessments:
  • Extrapyramidal Symptoms Rating Scale [ESRS]
  • Abnormal Involuntary Movement Scale [AIMS]
  • Cognitive scales and a psychiatric/behavioral assessments.
  • Lehman Quality of Life Interview

Primary outcome: At 6 months, a double-blind ESRS evaluation was performed in the stimulation “on” and stimulation “off” conditions.

Class II evidence

Pouclet-Courtemanche et al Neurology 2016
Figure e-1. Double-blind evaluation of the effects of continuous pallidal stimulation on the Extrapyramidal Symptoms Rating Scale (ESRS) score 6 months after surgery.

Data are means. Vertical bars represent SEM. Black bars: stimulator turned off; gray bars: stimulator turned on. *** $p < 0.0005$. 
Effects of Gpi stimulation on TD at 3, 6, & 12 months post- surgery and long term (6-11 years). Motor symptoms were assessed using the ESRS (maximum score, 257) (A) and the AIMS (maximum score, 42) (B).

***p < 0.0005, comparison with the preoperative score.
Other Results

Pouclet-Courtemanche et al Neurology 2016

• Improvement over days to weeks
• Pallidal DBS improved dystonic and choreic-like abnormal movements
• Improved to a similar extent oro-buccolinguual, axial, and limb movements
• At 1 year after surgery, 8 /16 patients receiving antidyskinetic drugs at inclusion had stopped or decreased these therapies
• No relationship between symptom characteristics or duration and the % improvement.
Diagnosis of Clinically significant Tardive syndrome

- Discontinue Dopamine Receptor Blocking Agent
  - Or
- Switch to a less potent antipsychotic – strong consideration for Clozapine monotherapy

  If further treatment is still needed

Initiate a First Tier Drug: Valbenazine, Deutetranze, Tetrabenazine
- Or
- For Tardive Dystonia initiate Botulinum Toxin

  If further treatment is still needed

Initiate Second Tier Drug: clonazepam, Gingko Biloba, Amantadine

  If further treatment is still needed

Initiate Third Tier Drug: Levetiracetam, Piracetam, Vitamin B6, Melatonin, Baclofen, Propranolol, Zolpidem, Zonisamid
- Or
  For classical Tardive Dyskinesia: Botulinum Toxin

  If further treatment is still needed

Surgical approach for Tardive Dystonia and Classical Tardive Dyskinesia: Deep Brain Stimulation of the Globus Pallidus interna
Chorea and Huntington’s Disease

Thomas Wichmann, MD
Neurology/Movement Disorders
Emory University
What is chorea?

• Rapid, multi-focal, irregular movements
  • Usually non-stereotypic, involving various muscle groups in different body parts
  • Ranging from mild restlessness to flailing movements

• Many possible causes
Differential Diagnosis

- Examples of genetically caused choreas
  - Paroxysmal kinesigenic dyskinesia - PRRT2 mutations
  - Paroxysmal non-kinesigenic dyskinesia - PNKD mutations
  - Paroxysmal exertional dyskinesia - GLUT1 mutations, PARKIN, GCH1 mutations
  - ADCY5 dyskinesia
  - Huntington’s disease

- Examples of secondary choreas
  - Structural/vascular
  - Drug-induced (tardive, levodopa-induced, etc.)
  - Autoimmune, e.g. Sydenham’s, anti-LGI1, lupus, Sjoegren’s syndrome, paraneoplastic, anti-cardiolipin syndrome, celiac disease
  - Metabolic diseases, e.g. diabetic non-ketotic hyperglycemia, uremia
  - Polycythemia rubra vera
  - Many others
Huntington’s Disease
Genetics/Epidemiology

• Autosomal dominant disease, trinucleotide repeat disease, chromosome 4
  • 36 or more repeats results in HD
  • 36-40 repeats - incomplete penetrance
  • >40 repeats full penetrance

• Age of diagnosis depends on number of trinucleotide repeats
  • CAG repeat length accounts for roughly 70% of the variance
  • Anticipation: With paternal transmission, age of onset drops from one generation to the next

• Average age at diagnosis: 39 years
  • Extremely long repeat lengths (60 or more) lead to juvenile-onset HD

• Prevalence: 10.6–13.7/100,000 (1/7300!)
• Incidence: 4.7–6.9/million/year
Pathology

• Striatum most severely affected at all stages of the disease
  • Caudo-rostral gradient
  • Severe neuron loss, reactive astrogliosis

• Significant extra-striatal neuron loss (cortex, thalamus, cerebellum)
Genetic Testing

• Widely available, requires genetic counseling

• At-risk patients
  • Only 5-20% decide to undergo genetic testing
  • >50% of those requesting testing already have children
  • Receiving a positive test result does not alter reproductive decisions (much)
  • Useful for family planning purposes (IVF!)

• Manifest patients
  • May not need testing
  • Testing one family member can be sufficient

• Testing of minors is discouraged
Diagnosis = Clinical presentation + family history + genetic testing
Psychiatric Dysfunction

• Common, often early, very disabling
• Depression
  • Up to 50% of patients
  • Features/treatment similar to other cases of major depression
  • Suicide rates 5-10x general population
• Irritability
• Apathy
  • Often in late stages, progressive
• Obsessive-compulsive symptoms, stress, anxiety also very common
• Delusions, psychosis less common
Cognitive Dysfunction

• Progressive, may develop well before ‘motor’ diagnosis
• Usually executive dysfunction (similar to PD)
  • Reduced attention/easy distractibility, poor planning, cognitive slowing
  • Disinhibition, impulsivity, lack of insight
• Language often affected in later stages (impoverished -> mutism)
Motor Dysfunction

• Involuntary movements
  • Chorea (mostly in adult patients)
  • May decrease in late disease
• Incoordination, bradykinesia, rigidity, dystonia
• Often a relatively late phenomenon in the overall disease process
Other Findings

• Oculomotor findings
  • Slow saccades, slow optokinetic nystagmus
  • Square wave jerks, slow smooth pursuit
  • Vergence: Inability to converge

• Circadian rhythm dysfunction
  • Up to 90% suffer from early or late awakening, insomnia, excessive daytime somnolence

• Weight loss
  • Common and worrisome mid- to late-stage sign
  • Correlates with CAG repeat length
Huntington’s Disease

https://www.youtube.com/watch?v=OFl2Rs-wPa4
Juvenile Huntington’s Disease

• Disease starts before age 21 in 5-10% of patients
  • Childhood onset (Westphal variant; before age 10) is rare
• Progresses rapidly
• Diagnosis often delayed (“ADHD”, “anxiety”, “depression”, “psychosis”, “seizures”)
• Motor phenotype
  • Rigidity, dystonia, epilepsy (30% of patients!)
  • Bradykinesia, dysphagia, ataxia, speech changes, spasticity
• Cognitive and psychiatric symptoms similar to adult onset Huntington’s disease
Management of chorea

• Treat underlying cause (if possible)
• Ask whether treatment is needed
  • Do movements interfere with activities of daily living?
  • Secondary choreas may be self-limiting/may spontaneously resolve
• Ask which symptoms are most important
  • Cognitive, psychiatric, or behavioral symptoms
  • Other movement disorder symptoms present (e.g., dystonia, parkinsonism, myoclonus)
  • Speech and swallowing issues?
Management of chorea: Multidisciplinary Approach

• Movement disorder specialist
• Psychiatry
• Speech therapy (dysarthria, dysphagia)
• Nutrition assessment
• Physical therapy
• Occupational therapy
• Social work (family support)
Medical Treatment of Chorea

• Medication treatment
  • Dopamine depletion/receptor blockade
  • Other pharmacologic approaches
    • Enhancement of GABAergic neurotransmission
    • Inhibition of neurotransmitter release
    • NMDA-receptor antagonist treatment

• Surgical treatment: deep brain stimulation, pallidotomy
Drugs Blocking Dopamine D2-Like Receptors

- Atypical antipsychotics – quetiapine, olanzapine, aripiprazole, ziprasidone, lurasidone, (risperidone), etc.
- Clozapine – effective but requires monitoring of WBC count
- Haloperidol (low cost)
- Tiapride
Presynaptic Dopamine-Depleting Agents

• Tetrabenazine and derivatives

• Actions
  • Inhibit VMAT2, e.g., in dopamine-containing vesicles
  • Depletes dopamine, noradrenaline, serotonin, histamine

• Adverse effects:
  • Parkinsonism, hypotension, sedation, depression
  • Little risk of tardive dyskinesia

Tetrabenazine (Xenazine)

- Two enantiomers
  - $\alpha$ enantiomer reversibly inhibit VMAT2
  - $\beta$ enantiomer is weak dopamine D2 receptor antagonists

- Varying rates of metabolism (poor, intermediate, extended, ultra-rapid)
  - May depend on CYP2D6 metabolism

- Use
  - Start at 12.5 mg/day, increase weekly as tolerated/required
  - Eventually 3-4 doses/day
Deuterated Tetrabenazine (Austedo)

• Very similar to tetrabenazine, but slower metabolism (allows b.i.d. dosing)
• Approved for tardive dyskinesia and Huntington’s disease
• Use
  • Start at 6 mg/day; increase as needed to 24 mg b.i.d.
• One double-blind, placebo-controlled trial in 90 people with HD (Huntington Study Group, 2016)
  • Significant reduction in UHDRS scores compared with placebo
  • Improved dystonia
  • Fewer side effects
  • No significant effect upon QT interval
Valbenazine  
(Ingrezza)

- Valine ester of α-enantiomer tetrabenazine  
  - Metabolized to active α-enantiomer  
  - Further metabolism similar to tetrabenazine  
  - More specific to VMAT2

- Approved for tardive dyskinesia

- Use  
  - QD dosing  
  - Start at 40 mg/day, increase after 1 week to 80 mg/day if required

- Currently in trials for Huntington’s disease
Other Factors Important for Selection of Chorea Medication

• Psychiatric issues (psychosis, depression, disinhibition, irritability, OCD)
  • Atypical antipsychotics

• Other movement disorders
  • Dystonia – VMAT2 inhibitors
  • Myoclonus – benzodiazepines, levetiracetam

• Seizures (juvenile HD, chorea-acanthocytosis, McLeod syndrome)
  • Anticonvulsants

• Weight loss
  • Atypical antipsychotics, some anticonvulsants
Deep Brain Stimulation in Huntington’s Disease

• Poorly studied, mostly ‘anecdotal’ reporting with high degree of reporting bias, short follow-up
• Targets: usually GPi (also GPe, Vo thalamus, zona incerta)
• Stimulation parameters not well characterized
  • Frequencies 130 Hz vs 40 Hz
• Effects
  • Reduction in UHDRS scores of approximately 25% and in chorea of approximately 50%
  • Risk of intervention-induced bradykinesia
  • Limitations: disease progression, lead migration (b/o brain atrophy
Deep-Brain Stimulation in Non-HD Cases of Chorea

Pouclet-Courtemanche et al. (2016) Neurology 86:651

Waak et al. (2018) J Neurol Neurosurg Psychiatry 89:221

Nakano et al. (2015) 84:1177 e1-7

Nakano et al. (2005) J Neurosurg 102:1137

van Coller et al. (2014) Stereotact Funct Neurosurg 92:388

van Coller et al. (2013) Stereotact Funct Neurosurg 92:388

Hasegawa et al. (2009) Mov Disord 24:1697

Burbaud et al. (2002) Mov Disord 17:204

Miquel et al. (2013) PLOS One 8:e79241

Nakano et al. (2015) 84:1177 e1-7

Successful combination of pallidal and thalamic stimulation for intractable involuntary movements in patients with neuroacanthocytosis

Nakano et al., Masakazu Miyashita, Akiye Nakahara, Kazunori Saigusa, Yoshioji Ito, and Amami Kato

Successful long-term deep brain stimulation for hemichorea–hemiballism in a patient with diabetes

Case report

Efficacy of Deep Brain Stimulation in a Patient with Genetically Confirmed Chorea-Acanthocytosis

Alby Richard, Joey Hsu, Patricia Baum, Ron Alterman, and David K. Simon

*Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; †Division of Neurosurgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Mary O’Regan, Richard Selway, Joseph Symonds, Padraic Grattan-Smith, Jean Pierre Pierre, Russell C Dale, and Stephen Malone

Waak et al. (2018) J Neurol Neurosurg Psychiatry 89:221

Improvement of Severe Trunk Spasms by Bilateral High-Frequency Stimulation of the Motor Thalamus in a Patient With Chorea-Acanthocytosis

Pierre Burbaud, MD, PhD,1 Alain Rougier, MD,2 Xavier Ferrer, MD,3 Dominique Guelfi, MD, PhD,1 E. Cuny, MD,2 Pierre Arne, MD,1 Ch. Gross, PhD,3 and B. Biousac, MD, PhD

van Coller et al. (2000) Mov Disord 15:204

Long-term efficacy and tolerability of Deep-Brain Stimulation in Chorea-Acanthocytosis

Marie Miquel1,2, Umberto Spampinato3,4, Christelle Latxague1, Icier Aviles-Olmos5, Benedikt Bader2, Kelly Berthoud2, Kailash Bhada5, Pierre Burbaud2, Lelut Bourgeois5, Jin Whan Choi5, Emmanuel Cuny3, Adrian Danek2, Thomas Foltynie1, Pedro J. Garcia Ruiz2, Santiago Gilenez-Roldan4, Dominique Guelfi2, Jorge Gueir3, Marwan Harti5, Paul Jarman2, Zinovia Maria Katsiopoulou1, Patricia Limousin2, Hir Lipsman5, Andrea M. Loozno5, Elena Motzo5,6, Oriha Ng4,6, Maria Cruz Rodriguez-Orce5, Huitang Shang2, Hyewon Shin5, Ruth H. Walker3,6, Yusaku Yokochi2, Ludovic Zris2, Francois Tison5,6

Successful Treatment of Disabling Paroxysmal Nonkinesigenic Dyskinesia with Deep Brain Stimulation of the Globus Pallidus Internus

Riaan van Coller1,2, Pieter Slabbert1, Janardan Vaidyanathan3, Clara Schutte3

van Coller et al. (2014) Stereotact Funct Neurosurg 92:388
Pallidotomy

• Can be an option if DBS cannot be done
  • Non-progressive disorders
  • Post-stroke hemichorea
  • Post-hyperglycemic hemichorea

De Vloog (2019) Parkinsonism Relat Disord 61:228
Break
Tremor

Alan Freeman MD
Movement Disorders Clinic
Emory University School of Medicine
Tremor
Definition

- Rhythmic mechanical oscillation of at least one functional body region
- Most common movement disorder in adults
Tremor Definitions

- Rest tremors: tremor that occurs in repose (while resting the limb)
- Postural tremors: tremor which occurs while the body part is maintaining posture against gravity
- Kinetic tremor: tremor occurring during goal directed movements
- Mixed tremor: a combination of these
Tremor
Definitions

• Action tremor: some consider postural and kinetic as action type tremors
• Intention tremor: used interchangeably with action and kinetic tremor. This term is not used much presently
• Task specific tremors: tremor occurring with specific tasks; writing, musical instrument playing
Tremor Classification

- Rest tremors
  - Parkinson’s Disease
  - Secondary Parkinsonism
  - Severe essential tremor
  - Drug-induced tremor - neuroleptics
Tremor
Classification

• Postural tremors
  • Essential tremor
  • Physiological tremor
  • Neuropathic tremor
  • Dystonic tremors
  • Parkinsonism
• Drug induced - lithium, depakote, neuroleptics, caffeine, theophylline, tricyclics, amphetamines, cyclosporine
Tremor Classification

- Kinetic tremors
  - Classical Cerebellar tremor
  - Essential tremor
  - Primary writing tremor

- Mixed tremors
  - Wilson’s Disease
  - Rubral (Holmes) tremor
  - Psychogenic
# Major Tremor Syndromes

<table>
<thead>
<tr>
<th>Tremor Syndrome</th>
<th>Rest</th>
<th>Posture Action</th>
<th>Tremor Frequency, Hz</th>
<th>Relative Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential tremor</td>
<td>x</td>
<td>x</td>
<td>5-8</td>
<td>Common</td>
</tr>
<tr>
<td>Parkinsonian tremor</td>
<td>x</td>
<td></td>
<td>4-6</td>
<td>Common</td>
</tr>
<tr>
<td>Enhanced physiologic tremor</td>
<td></td>
<td>x</td>
<td>8-13</td>
<td>Common</td>
</tr>
<tr>
<td>Psychogenic tremor</td>
<td>x</td>
<td>x</td>
<td>Variable</td>
<td>Less common</td>
</tr>
<tr>
<td>Cerebellar tremor</td>
<td></td>
<td>x</td>
<td>2-4</td>
<td>Less common</td>
</tr>
<tr>
<td>Drug-induced tremor</td>
<td>x</td>
<td>x</td>
<td>4-8</td>
<td>Less common</td>
</tr>
<tr>
<td>Dystonic tremor</td>
<td></td>
<td>x</td>
<td>4-8</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Holmes tremor</td>
<td></td>
<td></td>
<td>2-3</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Orthostatic tremor</td>
<td></td>
<td></td>
<td>13-18</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Task-specific tremor</td>
<td>x</td>
<td></td>
<td>4-8</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

Frucht, S. Practical Neurology, 2018
Tremor Frequencies

Figure 2. Frequencies of the major forms of tremor. Amplitude appears on the y axis, and frequency (typical frequency) and range of frequencies seen appear on the x axis.

Frucht, S. Practical Neurology, 2018
Tremor

Physiologic Tremor

• Frequency between 6-12 Hz
• Barely visible
• Enhanced physiologic tremor – visible under physiologically stressful or other discernible causes (stress, hunger).
Tremor
PD Tremor

- Rest tremor, typically 4-6 Hz
- May have a postural component with the same frequency.
- Treatment:
  - PD medications, such as carbidopa/levodopa
  - DBS
Tremor
Cerebellar Tremor

- Pure or dominant intention tremor often unilateral
- Tremor frequency mostly below 4 Hz
- Possibly postural, but no rest tremor
- Does not respond well to medication
Essential Tremor
Clinical Features

- Tremor is primarily postural but there can be a kinetic component and on rare occasions after long term disease a rest tremor
- Frequency range is 4 to 12 Hz
- Response to alcohol noted in 74% of patients who drink
Essential Tremor
Clinical Features

• Hands and arms are involved in almost all patients (95%), usually bilateral, occasionally unilateral
• Head tremor in 34%; vertical or horizontal nodding
• Voice tremor in 12-25%
• Leg tremor in 30%
• Jaw, tongue, trunk less frequent up to 15%
Essential Tremor
Clinical Features

• Slowly progressive disorder - takes one or two decades to reach a severe enough level to seek medical attention
• Aggravated by fatigue, anxiety, temperature changes, pain, drugs.
• 20% have their job performance impaired
Differentiating Essential Tremor from Parkinson’s Disease

<table>
<thead>
<tr>
<th></th>
<th>Essential tremor</th>
<th>Parkinson’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body parts</strong></td>
<td>Arms&gt;Head&gt;Voice&gt;Lips</td>
<td>Arms&gt;Jaw&gt;Lips</td>
</tr>
<tr>
<td><strong>Rest tremor</strong></td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Postural tremor</strong></td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Kinetic tremor</strong></td>
<td>+++</td>
<td>±</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>7-12Hz</td>
<td>4-6Hz</td>
</tr>
<tr>
<td><strong>Bradykinesia</strong></td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td><strong>Rigidity</strong></td>
<td>±</td>
<td>++</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td>++</td>
<td>±</td>
</tr>
<tr>
<td><strong>Response to beta blockers</strong></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Response to levodopa</strong></td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td><strong>Postural instability</strong></td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
Therapeutic Options for Essential Tremor

• No Treatment
  – Mild non-troublesome tremor
  – Diet adjustment: avoid caffeine

• Pharmacologic Therapy
  – Many agents have some effect
  – Trial and error

• Botulinum toxin injection
  – For head tremor, voice tremor

• Surgical Treatment
Essential Tremor
Medical Treatment

• Propranolol - Standard & Long acting
  • decreases amplitude
  • 40-70% of patients improve by 50-60%
  • no correlation with plasma concentration
  • Dosage range 60-320 mg/day
  • Effect starts 2 to 6 hrs after a dose and effects last up to 8 hrs
  • Contraindicated in asthma, COPD, CHF
  • Side effects: bradycardia, syncopy, fatigue, depression, impotence
Essential Tremor
Medical Treatment

• Primidone
  • Dose 50 to 250 mg/day
  • Plasma levels do not correlate with response
  • Response similar to propranolol
  • Acute side effects (30%): vertigo, general ill feeling, unsteadiness, nausea, ataxia, confusion
  • works well in combination with propranolol
Primidone for Essential Tremor

Primidone vs Propranolol

• Similar efficacy
• Acute side effects – Primidone
• Chronic side effects – Propranolol
• Combined therapy by be better than either alone (no double-blind studies)
• Both maintain benefit at 1 yr in ~50%

Gorman et al JNNP 1986
Deitrichson et al Act Neurol Scand 1987
Koller et al Neurology 1986, 1989
## Medications

### Table 1  Recommended drugs for essential tremor

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean or median effective daily dosage</th>
<th>Estimated percentage improvement in tremor amplitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>40–240 (320) mg/d</td>
<td>32–75</td>
</tr>
<tr>
<td>Primidone</td>
<td>&lt;62.5 –750.0 mg/d</td>
<td>42–76</td>
</tr>
<tr>
<td>Topiramate</td>
<td>100–333 mg/d</td>
<td>30–41</td>
</tr>
</tbody>
</table>

Schneider, S, Deuschl, G. Neurotherapeutics, 2014.
## Medications

### Table 2: Drugs for essential tremor with probable or weak efficacy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean or median effective daily dosage</th>
<th>Estimated percentage improvement in tremor amplitude [ref.]</th>
<th>Percentage improvement by accelerometry [ref.]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>50–100 mg/d</td>
<td>24–38 [21, 22]</td>
<td>37 [23]</td>
</tr>
<tr>
<td>Sotalol</td>
<td>80–240 mg/d</td>
<td>29–51 [21, 22]</td>
<td>–</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1200–1800 mg/d</td>
<td>39 [24]</td>
<td>77</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0.75–1.5 mg/d</td>
<td>48–60 [25, 26]</td>
<td>–</td>
</tr>
</tbody>
</table>

### Medications

**Table 3** Drugs for essential tremor with uncertain efficacy (likely not efficacious)

<table>
<thead>
<tr>
<th>Level C possibly effective (daily dosage of the respective studies) [ref.]</th>
<th>Agents with recommendations against use</th>
<th>Inadequate evidence to confirm or exclude efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam (0.5–4.0 mg) [27]</td>
<td>Acetazolamide/methazolamide</td>
<td>Olanzapine</td>
</tr>
<tr>
<td>Clozapine (18–75 mg) [28]</td>
<td>Amantadine</td>
<td>Pregabalin</td>
</tr>
<tr>
<td>Flunarizine (10 mg) [29]</td>
<td>Carisbamate</td>
<td>Tiagabine</td>
</tr>
<tr>
<td>Nadolol (120–240 mg) [30]</td>
<td>Isoniazid</td>
<td>Sodium oxybate</td>
</tr>
<tr>
<td>Nimodipine (120 mg) [31]</td>
<td>Levetiracetam</td>
<td>Zonisamide</td>
</tr>
<tr>
<td>Botulinum toxin (depending on injected muscles)</td>
<td>Pindolol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trazodone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3,4-Diaminopyridine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mirtazapine</td>
<td></td>
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<tr>
<td></td>
<td>Nifedipine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td></td>
</tr>
</tbody>
</table>
Fig. 1 The estimated percent improvement of tremor amplitude of different interventions is shown. The values show the mean value of the studies reported here. Patients in the surgical studies usually have much higher tremor amplitudes. Tremor amplitude estimation is based on standard algorithms computed as change in tremor rating scale and change in tremor amplitude on accelerometry [9, 15].
Essential Tremor
Botulinum Toxin

- Hand/Arm tremor: Jankovic 1991;
  - Effectively treats tremor at doses up to 100 units/arm
  - 30-70% moderate weakness

- Head (40-400 units) & voice (.6-15 units) Pahwa et al 1995 DB, PC 10 subject trial
  - improved in 70% of patients
  - Side effects mild weakness
  - Side effects: voice weak & breathy (80%)
Tremor
Psychogenic/Functional

- Most common form of all functional movement disorders
- Distractible
- Sudden onset
- Variation in tremor frequency
- History of movement of tremor from body region to body region
Cala Trio for Essential Tremor

- Wrist-worn device that delivers neuromodulation therapy
- In a small clinical study, tremor improvement in 75% of patients after a 40 minute therapy session
- Subject rated improvement in ADLs were significantly greater with treatment than with sham

Future Treatments

• Efficacy and safety of CX-8998 in T-CALM, a randomized, double-blind, placebo-controlled, phase 2a trial in participants with essential tremor. Subgroup analysis by baseline tremor severity.

The Ataxias

Chip Wilmot, MD PhD

October 3, 2020
Disclosures

- Larimar Therapeutics – Safety Monitoring board
- Biohaven Pharmaceuticals - Advisory Board, Research support
- Reata Pharmaceuticals – Advisory Board, Research support
Ataxia

- Ataxia – incoordination -- abnormal integration of movement force, speed, and distance.
- “The Ataxias” – Diseases in which ataxia is the primary symptom.
Case

55yo RH male presents with several year history of gait imbalance

Exam shows imbalanced gait, inability to tandem

What’s the diagnosis?
Ataxia Manifestations

- Motor:
  - movement delay
  - prolonged deceleration
  - dysmetria
  - bradykinesia
  - dyssynergia
  - Dysdiadochokinesia
  - Hypotonia
  - dysarthria

- Eyes:
  - Nystagmus
  - impairment in smooth pursuit and saccades
  - Vestibuloocular reflex cancelation deficit
VOR Cancelation

- VOR – allows eyes to stay on a stationary target during head movements
  - tested with the head impulse test

- VOR cancelation – Allows the eyes to follow a moving target during head movements
  - Tested by having head and target move together

- VOR cancelation is frequently impaired in cerebellar disease, and can “rule in” the cerebellum in the disease process

- https://www.youtube.com/watch?v=ExOs7HSHv-c
Case

55yo RH male presents with several year history of gait imbalance

Exam shows gait instability, cerebellar eye findings, and limb ataxia

What’s the diagnosis?
Ataxia

Acquired
- Idiopathic Late-Onset Cerebellar Atrophy
- Multiple Systems Atrophy
- Autoimmune
  - Paraneoplastic cerebellar degeneration (anti-Purkinje cell Ab’s)
- Anti-GAD65
- Gluten ataxia
- Others (thyroid, etc)

Inherited
- Primary
- Secondary
  - Hypothyroidism
  - Stroke
  - Multiple sclerosis
  - Tumor
  - Wernicke’s
  - Vitamin E deficiency
  - Toxic

Late-Onset
Ataxia

Acquired

Inherited

Primary

X-linked

Autosomal Dominant
- SCA1
- SCA2
- SCA3
- SCA5
- SCA6
- SCA7
- SCA8
- SCA10
- SCA11
- SCA12
- SCA13
- SCA14
- SCA15/16
- SCA17

...and there’s more, of course

Mitochondrial
- SAA
- FXTAS
- NARP

Secondary
- Very syndromic

Autosomal Recessive
- FRDA
- AVED
- ARSACS
- AT, ATLD
- AOA1-4
- ARCA1/SCAR8/SYNE1
- ARCA2/SCAR9/ADCK3

...Up to SCA48...and more with genes still to be found
My diagnostic approach

• Consider the phenotype
• Every one gets scanned
• If imaging shows just atrophy or is normal
  • Screen for more common, treatable disorders
    • Check for EtOH history, medication history
    • Check TFTs, B12, vit E, anti-gliadin and anti-tissue transglutaminase, anti-GAD, ?rheum labs
    • If negative, then investigate for less common causes
  • If rapid progression:
    • check paraneoplastic panel, anti-TPO, and consider LP
    • DWI imaging if not initially performed
    • Don’t miss Wernicke’s!
Diagnostic workup

• Brain imaging (MRI)
  • Rule out structural lesions (stroke, bleed, abscess, tumor, demyelinating lesion, etc)
  • Often see cerebellar atrophy
    • nonspecific
  • Certain ataxic disorders associated with classic MRI findings:
    • Hypoparathyroidism: cerebellar calcification
    • Fragile X tremor/ataxia syndrome: T2 signal in MCPs
    • Polymerase γ (POLG1) syndrome: T2 signal just dorsal to dentate
    • MSA: hot-cross buns sign, T2 bright just lateral to putamen
    • Superficial siderosis: blood around cerebellar foliae on GRE
    • CJD: High signal on FLAIR and/or DWI in pulvinar, caudate, putamen
Diagnostic workup

• If MRI doesn’t give answer, then what?
• Potentially lots of tests you can do...
• Blood tests:
  • TFTs, vitamin levels, tox screen, lipids, ANA and other rheum tests, paraneoplastic antibodies, GAD antibody, anti-thyroperoxidase antibodies, anti-gliadin antibodies, heavy metals, RPR, ceruloplasmin, Whipple’s PCR, lactate/pyruvate, blood smear for acanthocytes, VLCFA, AFP, Ig, phytanic acid, cholesterol, hexosaminidase A/B, etc
• CSF:
  • cell count, glucose, protein, tau/14-3-3, lactate/pyruvate, paraneoplastic antibodies
• Genetic testing
  • SCAs, Friedreich’s, DRPLA, FXTAS, etc
• Electrodiagnostic testing (NCS, EMG, EEG)
• Autonomic testing
• Ophthalmologic testing
  • Kayser-Fleischer rings, retinopathy, cataracts
Case

55yo RH male presents with several year history of gait imbalance

Exam shows gait instability, cerebellar eye findings, and limb ataxia

What’s the diagnosis?
Case

55yo RH male presents with several year history of gait imbalance

Exam shows gait instability, cerebellar eye findings, and limb ataxia

What’s the diagnosis?

- Autonomic or Parkinsonian/Lewy Body Findings – MSA-c
- Anti-GAD65 antibodies – Anti-GAD ataxia
- Tremor, Cognitive change – FXTAS
- +Family Hx – Genetic
- Work-up negative, Pure Cerebellar – ILOCA
Case

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- Tremor, Cognitive change – FXTAS
- +Family Hx – Genetic
- Work-up negative, Pure Cerebellar – ILOCA. - Continue to evaluate Dx
Yield of Genetic Testing

JAMA Neurol. 71:1237 (2014)

Neurology 89:1043 (2017)

Human Mutation
DOI:10.1002/humu.23946 (2019)
Exome sequencing identifies up to 50% of undiagnosed ataxias

- Higher in early onset vs. late onset
- Higher in familial cases
- Even in well-defined sporadic cases, genetic causes are present in small numbers
- Even in well-defined familial cases, genetic causes are NOT found in ~30% using WES (may need WGS)
- A small number of actionable diagnoses may be revealed
# SCA Phenotypes

![Table of SCA Syndromes: Diagnostic Testing](https://neuromuscular.wustl.edu/ataxia/domatax.html#scaddx)

<table>
<thead>
<tr>
<th>Clinical sign</th>
<th>1° Testing</th>
<th>2° Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellar ataxia, Pure</td>
<td>6, 5</td>
<td>11, 14, 15, 16, 22</td>
</tr>
<tr>
<td>Spasticity</td>
<td>3</td>
<td>1, 7</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>3, 4, 18, 25</td>
<td>1</td>
</tr>
<tr>
<td><strong>Cortical disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>17, DRPLA</td>
<td>2, 13, 19, 21</td>
</tr>
<tr>
<td>Psychosis</td>
<td>DRPLA, 17</td>
<td>3, 27 (Episodic)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>10, DRPLA</td>
<td>17</td>
</tr>
<tr>
<td><strong>Movement disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chorea</td>
<td>DRPLA, 17</td>
<td>1 (Late stage)</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>DRPLA</td>
<td>2, 19</td>
</tr>
<tr>
<td>Tremor</td>
<td>2, 8, 12</td>
<td>15, 21, 27</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>3, 9, 12, 17</td>
<td>2, 21</td>
</tr>
<tr>
<td>Dystonia</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td><strong>Ocular disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ophthalmoplegia</td>
<td>3, 2, 1, 9</td>
<td></td>
</tr>
<tr>
<td>Nystagmus</td>
<td>1, 3, 6</td>
<td></td>
</tr>
<tr>
<td>Slow saccades</td>
<td>2</td>
<td>1, 3, 7, 17</td>
</tr>
<tr>
<td>Pigmentary retinopathy</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>
Genetic testing of SCAs

- Athena Diagnostics labs ataxia panels largely Sanger sequencing and are expensive!
  - Cost tens of thousands of dollars and insurance may not cover the expense
- Next Gen Sequencing can do gene panels more cost effectively, but usually miss repeat expansions
- Whole Exome Sequencing is getting more commonplace. WGS on research basis
- How can you be smart about testing?
  - Go on phenotype when it is distinctive and predictive SCA7, SCA2, SCA3
  - Rule out repeat expansions SCA 1, 2, 3, 6, 8, 7, 17, and DRPLA (also others) –St Francis, Fulgent
  - For non-SCA tests, other (and cheaper) options available GeneDx)
Video
Treatment Strategies

• Non-cerebellar symptoms
  – depression, spasticity, fatigue, pain, bladder function ...

• Cerebellar symptoms
  – PT/OT/ST much more relevant than any medicines
    • Riluzole, varenicline, 4-aminopyridine, others

• Disease Altering/Neuroprotective hopefully coming
Tourette Disorder

JL Juncos, MD
Emory University
School of Medicine
TAA Center of Excellence
Brain Health &
Movement Disorders Program
What is Tourette Disorder?

• It is a developmental neurologic disorder defined by...
  – Persistent motor and phonic/vocal tics
• Frequently associated with...
  – Internal urges
  – Obsessions and compulsions
  – Anxiety
  – Mood problems & irritability
  – Disruptive behaviors
  – Attentional difficulties
• A hereditary disorder heavily influenced by environmental factors
• Tics affect 0.3 -1% of the population
Tics and tics disorders

- Co-Morbid Problems
  - Inattention / hyperactivity
  - Impulsiveness
  - Obsessive-compulsive symptoms
  - Anxiety
  - Disruptive behaviors
  - Mood problems / Irritability

- Functional impairment
  - (Storch et al. 2007)

- Quality of life (Evans et al. 2016)
Natural history of comorbid disorders

Leckman 2002
Etiology of Tourette Syndrome

• Not known.
  • *Genetics*: Developmental disorder of synaptic neurotransmission (e.g. dopamine, glutamate, GABA, histamine?)
  • From mutations to ‘susceptibility coding variants’. *De novo sequence and copy number variants (‘mutations’) each with small effect size*
  • *Genetic vulnerability* is dynamic and can be modified / interact with environmental factors (e.g. rearing, resiliency, trauma, others)
  • **Physiology: Disinhibition** of striatal-thalamic-cortical circuitry
  • **Autoimmune susceptibility** (PANS) in a subset of patients?
TOURETTE’S SYNDROME
Clinical Spectrum

Motor Signs
Abnormal linkage mediated by developmental factors with ‘failure of inhibition/gating’ mediated through basal ganglia & its circuits

Sensory Experiences
TICS
The external phenotype

- What you see
- Unwanted attention
- Drains resiliency, compromises attentional band width
  May foster co-dependency
  …a unique opportunity to
  look beyond the tic (‘under the hood’)
Phonic Tics

Simple phonic tics are inarticulate noises.

Sniffing, throat clearing, grunting, squeaking, screaming, coughing, barking, blowing, and making sucking sounds.

Complex vocal tics have linguistic meaning, consisting of partial words (syllables), words, or phrases. Include linguistically meaningful utterances and verbalization.

- coprolalia
  - Shouting of obscenities, profanities, or otherwise socially inappropriate words or phrases.

- echolalia
  - Repetition of someone else's words.

- palilalia
  - Repetition of one's own utterances, particularly the last syllable, word, or phrase in a sentence.

Courtesy M. Merello and S. Perez-Lloret
When severe, tics are seldom alone

- Tics + separation anxiety
- Tics + other anxiety disorders
- Tics + pervasive developmental disorder
- Tics + disruptive behavioral disorders
- Tics + major depression
- Tics + substance abuse
- Tics + personality disorder
What makes brains tic?

Failure of Inhibition
Pathophysiological Model

Genetics

Environment

Neurobiologic Substrate

TS Phenotypes
Environmental Factors that Maintain Tics

**Antecedents**
- Places/Situations
- Other People
- Activities
- Internal Experiences (e.g., premonitory urge)

**Consequences**
- Positive Reinforcement (e.g., others’ reactions to tics)
- Negative Reinforcement (e.g., escape from activities, relief from aversive unpleasant internal experiences)
**Key points**

- Imaging in TS suggests diffuse structural abn. beyond the CBGTC circuits
- Tics (eyes, face) preferentially affect part of a phylogenetically conserved, sexually dimorphic subcortical circuits (SBN)*
- SBN interdigitate with the CBGTC circuit to form a larger network, the SDMN**.
  - BG – evaluation of socially relevant stimuli and actions
  - SBN responsible performance of social acts
- TS – “Developmental dis of social decision-making network?”

**Social Behavioral Network***

**Figure 1** The Social Behaviour Network (SBN). Adapted from Newman (1999). This network mediates a large number of relatively stereotyped social behaviours. Is modulated by gonadal steroids, and has sex dimorphic components. The PAG is the main efferent node, driving lower circuits responsible for specific behaviours. AH = anterior hypothalamus; MA = medial amygdala; LS = lateral septum.

**Social Decision-Making Network**

**Figure 2** The Social Decision-making Network (SDM).
URGES
‘Internal’ Phenotype

Premonitory Urges
- Sensations that precede tics
- Unpleasant itch, tension, tingle, pressure
- Sometimes localized, sometimes generalized
- Awareness begins around age 9 -10
- Very common: up to 90% of TS individuals describe urges
- Urges more likely to precede complex tics than simple tics
Premonitory urges

Leckman et al, 2001
Possible link between exteroceptive / interoceptive awareness in the premonitory urge in TS
Genetic summary

- TS is a genetic disorder
- Individual genetic markers and genes responsible are rare and do not define the vast majority of cases.
- Pooled data from family studies indicate the risk of TS among relatives = 9.8 to 15%. Risk of other tics = 15 to 20% (Pauls 2003).
- Transmission is affected by
  - sex, variable expression, incomplete penetrance >80% in men, 50% in women. Higher if isolated OCD is included. (Pauls, Leckman, 1986).
- The above paradigm + a 25% frequency of bilinear transmission (Hanna 1999) suggest polygenic inheritance.
From the periphery to centre stage: de novo single nucleotide variants play a key role in human genetic disease

Chee-Seng Ku,¹ Eng King Tan,²,³ David N Cooper⁴

J Med Genetics 2013;50: 203-211
De Novo Sequence and Copy Number Variants Are Strongly Associated with Tourette Disorder and Implicate abnormalities in Cell Polarity in Copy Number Variants and the DeNovo Sequences and in the Pathogenesis of TS

Wang S, Mandell JD, Kumar Cell Reports 2018
Family-based Genetic Association Study of DLGAP3 in Tourette Syndrome

Jacquelyn Crane1,2, Jesen Fagerness1,2, Lisa Osiecki1,2, Boyd Gunnell1,2, S. Evelyn Stewart1,2, David L. Pauls1,2, and Jeremiah M. Scharf1,2,3,4 and the Tourette Syndrome International Consortium for Genetics (TSAICG)5

De Novo Coding Variants Are Strongly Associated with Tourette Disorder

A. Jeremy Willsey1,2,12, Thomas V. Fernandez3,12, Dongmei Yu4,5,13, Robert A. King3,13, Andrea Dietrich6,13, Jinchuan Xing7,13, Stephan J. Sanders1, Jeffrey D. Mandell1,2, Alden Y. Huang3,9, Petra Richer3,10, Louw Smith1, Shan Dong1, Kaitlin E. Samocha4,5, Tourette International Collaborative Genetics (TIC Genetics), Tourette Syndrome Association International Consortium for Genetics (TSAICG), Benjamin M. Neale4,5, Giovanni Coppola6,9, Carol A. Mathews11,14, Jay A. Tischfield7,14, Jeremiah M. Scharf4,5,14,15, Matthew W. State1,14,15,* and Gary A. Heiman7,14,*
Tourette is encompassed by a spectrum of disorders characterized by genetically-determined Glutamate transmission and/or GABA inhibition at yet unknown pathways/levels of the CBGT circuits.

2019 - A PARADIGM SHIFT FOR TS

Autism Spectrum disorders (ASD)

OCD

GAD / & its Multiple phenotypes

NOS other Behaviors

ADHD/LDs
The ‘language’ of ADHD & OCD in children

• ADHD
  - Hyperactive
  - Jiggly legs
  - Inattentive
  - Distractable
  - Impulsive
  - Sleepy dreamy subtype

• Executive dysf
  - Defects in task initiation, goal directed behaviors, planning, prioritizing, pacing
  - Execution, sequencing, organizing, set shifting, inhibiton

• OCD/Anxiety
  - Gets angry has to say something
  - Stuck
  - Dangerous, morbid thoughts
  - ANTS
  - Rigid, cannot be interrupted
  - Doubts so much it is hard to make decisions
  - Nail biting, skin picking
  - Collects things (dead phones), cannot get rid of things, hoarding
  - Special #s (e.g. 7,9)
  - FEARS and Phobias
  - Anxiety attacks (‘meltdowns’)

- Self-monitoring defects
Highest behavioral-social disability scores in TS were: hyperactive-impulsive ADHD > inattentive ADHD >> no ADHD

Functional impairment in TS correlates better with severity of ADHD than with tic severity.

Severity of obsessions and compulsions was independently correlated with the Thought Problems subscale of the CBCL scale.

Thus, in patients with TS, the severity of ADHD symptoms is the main predictor of behavioral/social problems.
Treatments
Comprehensive Behavioral Intervention for TS (CBIT)

- Relaxation techniques
  - Habit reversal
  - Tic suppression
- Family therapy
- Treatment of co-morbidities
Behavior Therapy for Children With Tourette Disorder: A Randomized Controlled Trial

John Placentini; Douglas W. Woods; Lawrence Scahill; et al.


http://jama.ama-assn.org/cgi/content/full/303/19/1929
# Pharmacologic treatments

<table>
<thead>
<tr>
<th>Agents</th>
<th>Dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha-2 agonists</strong></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.05-0.5</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>0.5-4</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
</tr>
<tr>
<td>Pimozide</td>
<td>0.5 - 10</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.5 - 16</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>0.5 - 8</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.5 - 8</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1 - 10</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.5 - 6</td>
</tr>
<tr>
<td>Baclofen</td>
<td>15 - 40</td>
</tr>
<tr>
<td>Topiramate</td>
<td></td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>12.5 to 100 QD to TID</td>
</tr>
<tr>
<td>Valbenazine</td>
<td>?</td>
</tr>
<tr>
<td>Deutetetabenazine</td>
<td>40 to ?</td>
</tr>
<tr>
<td>Canabinoid/TCH derivatives</td>
<td></td>
</tr>
<tr>
<td><strong>Glutamate antagonists (riluzole, D-serine, Ketamine, amantadine?)</strong></td>
<td>Negative studies so far</td>
</tr>
</tbody>
</table>
Surgical approaches
Deep Brain Stimulation in TS

- About 200 patients have received DBS for TS worldwide with good results on tic control, variable results in QOL.

- Surg. targets:
  a. Thalamus – PF/CM/VO
  b. Gpi
  c. Accumbens
  d. Ant. limb internal capsule

- Still experimental.

Summary and Conclusions
MANAGEMENT OF TS:
Take home recommendations

- Educate parents, teachers, child
- Avoid diagnostic confusion
- Not all symptoms are related to TS
- Tics are not an excuse for bad behavior
- If present, treat the sensory experience first
  anxiety/OCD – reassurance, behavioral Rx., pharmacotherapy
- For mild tics: behavior modification, CLON/GUAF, botulinum toxin, or short term benzodiazepines
- Severe tics: Typical vs. atypical agents, tetrabenazine, others
- If present, consider cautious treatment of ADHD symptoms once tics are under control
Treatment plan (the ‘layered cake’)

- **PTSD** and *outside the home* “camera effect with hyperfocus” drives the coprolalia. ADHD maintains the hyper focus and compounds the *fight or flight responses* to the outside environment from the PTSD.

- **For PTSD and ADHD** – Start the alpha 2 agonist CLONIDINE hs.

- **OC/anxiety** - Over the next few weeks, taper stop sertraline and aripiprazole (lack of efficacy, wgt gain). Gradually increase the dose of VILAZODONE from 10 to 40 mg/d

- **OC/anxiety if persistent and still contributing to coprolalia**, use alternate strategy to augment the vilazodone effect. AMANTADINE that can also help executive function with ADHD.

- **ADHD**: Ultimately we predict she will need more aggressive management of the ADHD with a RITALIN derivative (stimulant)
Thank you!!