How to Effectively Manage the Motor Symptoms of HD

Yvette Bordelon, MD, PhD
Associate Clinical Professor of Neurology
David Geffen School of Medicine at UCLA
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Presenter Disclosures

Yvette Bordelon, MD, PhD

The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:

Speakers Bureau: Teva Pharmaceuticals
Motor Symptom Management

- **The WHY**: HD Anatomy, Pathology and Circuitry
- **The WHAT**: Types of Movement Problems
- **The WHEN**: Timing of Initiation and Adjustments
- **The HOW do we manage**: Medications and Other Interventions
HD Basics: The WHY

- Adult-onset progressive disease caused by the huntingtin mutation that affects the brain
- Impairs communication between basal ganglia and cortex
- Results in impaired movement, thinking and behavior.
First described in families in East Hampton, Long Island by George Huntington in 1872 at Meigs and Mason Academy of Medicine

- adult-onset
- progression
- inheritance pattern.
- ‘Hereditary Chorea’
Venezuela Collaborative HD Project

- 1972- Centennial celebration of Huntington’s paper- Description of HD families around Lake Maracaibo in Venezuela
- 1979- First American expedition to Maracaibo led by Dr. Nancy Wexler
- 1981- First of annual trips to the region
- 1983- Discovery of the HD gene marker on chromosome 4
- 1993- Identification of the gene- huntingtin (htt)
HD Basics: The WHY

• Genetic disorder. Expanded CAG repeat length in huntingtin gene
  – Higher CAG repeat length correlates roughly with earlier age of onset of disease
  – But CAG repeat length accounts for only 50-60% of onset age variability.

• Htt protein expressed in all cells in the body

• Function not completely known: involved in many important pathways

<table>
<thead>
<tr>
<th></th>
<th>CAG repeat length</th>
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<tbody>
<tr>
<td><strong>Definite HD</strong></td>
<td><strong>40 and higher</strong></td>
</tr>
<tr>
<td><strong>Probable HD</strong></td>
<td>36-39</td>
</tr>
<tr>
<td><strong>Grey Zone</strong></td>
<td>26-35</td>
</tr>
<tr>
<td><strong>No HD</strong></td>
<td><strong>Less than 26</strong></td>
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HD Basics: The **WHY**

- Cleaved to generate fragments which aggregate into clumps
- Aggregates cause dysfunction of neurons
- Aggregates of different proteins are also found in other neurologic disorders: Alzheimer disease, Parkinson disease and many others
HD Basics: The **WHY**

**Huntington Disease Pathology**

- Loss of the striatum is the hallmark of disease
- But entire brain is affected

Photos courtesy of Jean-Paul Vonsattel
Cortex

Striatum

D2

D1

GPe

GPi

STN

Thal

Chorea

GPe

GPi

STN

Thal

Inhibitory

Excitatory

Early HD

Later HD
The **WHAT**: Types of Movement Problems

- **Chorea**: uncontrolled, flowing movements from one muscle group to another resulting from abnormal basal ganglia function; from Greek- ‘dance’
  - Walking and Balance Problems
  - Clumsiness, Incoordination
  - Eye Movement Abnormalities
- **Dystonia**: uncontrolled activation of muscle groups resulting in abnormal postures
  - Rigidity (stiffness) and Slowness
HD Symptoms: Not in Isolation!

**MOTOR**
- Chorea
- Dystonia
- Eye movement abnl
- Gait, balance problems
- Rigidity, bradykinesia

**COGNITIVE**
- Executive Dysfunction
- Concentration
- Attention
- Multi-tasking
- Visuospatial Dysfunction
- Memory Problems

**FUNCTION**
- Employment
- Family Obligations
- Social Activities
- ADLs

**BEHAVIORAL**
- Depression
- Anxiety
- Obsessions, Compulsions
- Delusions, Hallucinations
- Apathy
- Impulsivity
The **WHEN**: Timing of Onset and Progression

- **Motor**
- **Cognitive**
- **Behavioral**
- **Functional**
The **WHEN**: Timing of Onset and Progression

- Cannot predict who will develop WHAT symptoms and WHEN
- While certain features may be similar within families
  - **EVERY PERSON is DIFFERENT**
- Thus, treatment is different for every person with HD
The **WHEN**: Timing of Initiation

- When *function* is impaired
- Very different meaning and different threshold for every person
- Work, social, family, self-care, safety
The **HOW** do we manage

- Medications
- Exercise
The HOW: Treatment

- **Chorea**
  - **Dopamine receptor blockers**/ Neuroleptics/ Antipsychotics
    - Olanzapine, Risperidone, Quetiapine, Aripiprazole, Haloperidol and others
      - Possible Side effects: restlessness, sleepiness, weight gain, parkinsonism
  - **Dopamine depleters**
    - Tetrabenazine (Xenazine) and deutetetabenazine (Austedo) deplete dopamine: the only FDA approved treatments for HD
      - Possible Side effects: depression, restlessness, parkinsonism
    - Good chorea control
Tetrabenazine
TETRA-HD Study Results

[Graph showing changes in chorea score over weeks for Placebo and Tetrabenazine groups, with adjusted means indicated.]

Huntington Study Group, Neurology 2006;66:366-372
The HOW: Treatment

• Chorea
  • Benzodiazepines: clonazepam, lorazepam, diazepam
    – Side effects: sedation
  • Amantadine- mild chorea control
  • Valproic acid- very mild chorea control
Dystonia
- Benzodiazepines, baclofen, trihexyphenidyl, botulinum toxin

Gait and Balance Problems
- Exercise/Physical Therapy

Dysarthria, Dysphagia
- Speech and swallowing therapy

Rigidity
- Benzodiazepines and rarely used- levodopa, ropinirole, pramipexole
Medical Marijuana: Cannabidiols

**PROS**
- May help appetite
- May help chorea but there are no trials with convincing proof
- Cannabinoid receptors are in the basal ganglia

**CONS**
- Cognitive side effects
- Impairs balance
- Worsens delusions or hallucinations
- Worsens depression
- No data to guide what formulation or dose
- Trial of Sativex failed
The HOW: Treatment

• Medication that helps with multiple symptoms offers advantages in simplifying regimens

• 2 or more for 1 meds:
  – **Antipsychotics**
    • Chorea AND delusions, anxiety, irritability, outbursts, sleep, weight
  – **Benzodiazepines**
    • Chorea AND dystonia, anxiety, irritability, outbursts, sleep

• 2 for 1 meds
  – **Valproic acid**
    • Chorea AND mood stabilization
  – **Amantadine**
    • (maybe mild benefit) chorea AND walking
The HOW: Treatment

- **EXERCISE, EXERCISE, EXERCISE, EXERCISE, EXERCISE.....**
  - Critical component of HD symptom management
    - No specific recommendation for type or quantity of exercise
    - Physical Therapy can guide plan
    - Best treatment for walking and balance and maintaining overall mobility to prevent complications of immobility
    - Supervision when necessary
  - Safety
  - Best evidence for disease modifying benefit
  - PACE-HD: study to determine best recommendations
HD TREATMENT: Not Easily Standardized

- Treatment must be individualized
- Data are lacking to support best treatments
  - Most symptomatic HD treatments in use have not been studied in well-designed, randomized, placebo-controlled trials
- Discuss options with your physicians

Algorithm for the treatment of chorea in Huntington's disease

- **Antipsychotic (APD)**
  - First choice if co-morbid:
    - psychos
    - active depression
    - aggressive behavior
    - non-compliance
  - **Step 1. Start with low dose**
    - clozapine (2.5-10 mg)
    - risperidone (0.5-2 mg)
    - haloperidol (0.5-2 mg)
    - quetiapine (25-200 mg)
    - aripiprazole (2-15 mg)
    - sulpiride* (100-600 mg)
    - *sulpiride: available only in Europe
  - Advise twice daily dosing to minimize side effects and at least a 2-week interval prior dose increase
  - **Step 2. Dose optimization**
    - Go slow and gentle: goal is to decrease, not eliminate, chorea
    - Reassess response and side effects at each dose increment
    - Side effects are dose related; higher incidence when added to TBZ, SSRI, AED
  - Side effects:
    - sedation
    - Parkinsonism
    - akathisia
    - cognitive impairment
    - akathisia (motor and psychic restlessness)
    - metobolic syndrome
    - tardive dyskinesia
    - tardive dystonias
    - neuroleptic syndrome (can occur with rapid dose escalation or lowering)
  - Frequency of specific side effects varies by drug (see text)

- **Step 3. Combination therapy**
  - Add BZD if anxiety-related
  - Add TBZ with attention to increased side effects

- **Tetrazenzine (TBZ)**
  - Avoid if co-morbid:
    - psychosis
    - active depression
    - aggressive behavior
    - non-compliance
  - **Step 1. Start with 12.5 mg/day**
    - Elimination half-life varies greatly among individuals from 2-6 hours, and will ultimately require 4-5 doses per day.
    - Because chorea affects sleep, bedtime dosing is usually not helpful unless chorea interferes with sleep.
  - If used with SSRI avoid fluoxetine, paroxetine which can prolong half-life (see text)
  - Goal is to decrease chorea severity, not to eliminate it
  - **Step 2. Dose optimization**
    - Go slow by 12.5 mg/day increments.
    - Though the manufacturer suggests 1-week dosing intervals, most experts use 2 or more weeks before increasing dose.
    - Reassess for response and side effects at each dose increment.
    - Therapeutic dosage range (12.5-75 mg/day). Refer to specialist advised for higher dosing.
  - Side effects are dose related, with higher incidence of side effects when used with SSRI, AED, or APD.
    - sedation
    - depression
    - suicidal behaviors
    - Parkinsonism
    - akathisia
    - swallowing impairment
    - akathisia
    - neuroleptic syndrome
  - Stop the drug if suicidal behavior.
  - Decrease dosage for control of other side effects.

**Abbreviations**

- AED: most stimulating antipsychotic drug
- APD: antipsychotic
- BZD: benzodiazepine
- SSRI: serotonin reuptake inhibitor
- TBZ: tetrazenzine

Burgunder et al., 2011 PLoS Currents PMID: 21975581
HD Symptom Management: Not in Isolation!

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**PSYCHIATRIC**
- Depression
- Anxiety
- Obsessions, Compulsions
- Hallucinations, Delusions
- Apathy
- Impulsivity
- Suicidality
THANK YOU

• Everyone that has participated in a research study has contributed enormously to the advancements made in HD research.

• Everyone that **will** participate in a research study keeps the momentum going and gets us closer to more effective treatments!