



# 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

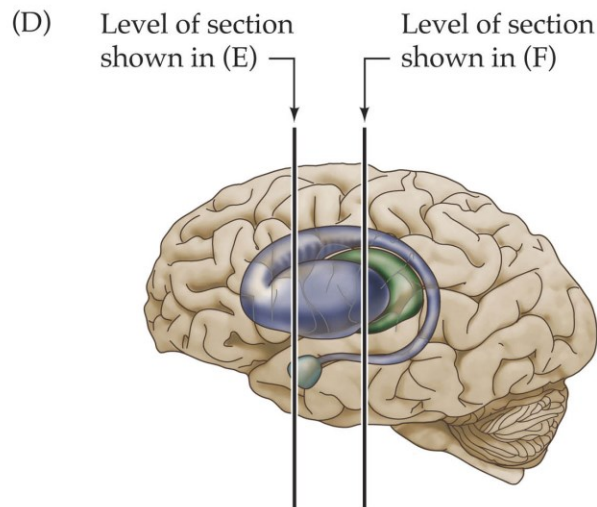
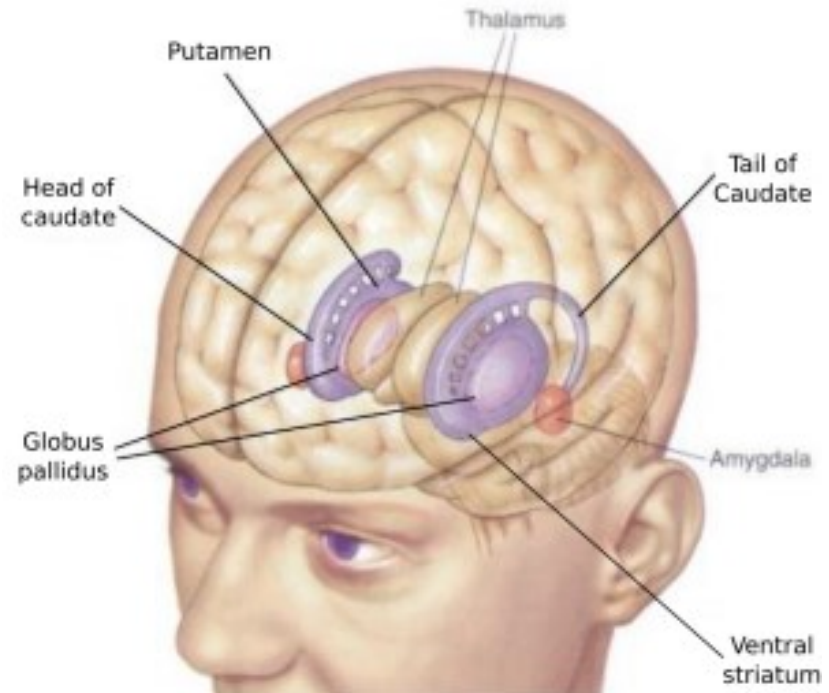


# Motor Symptom Management

- 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

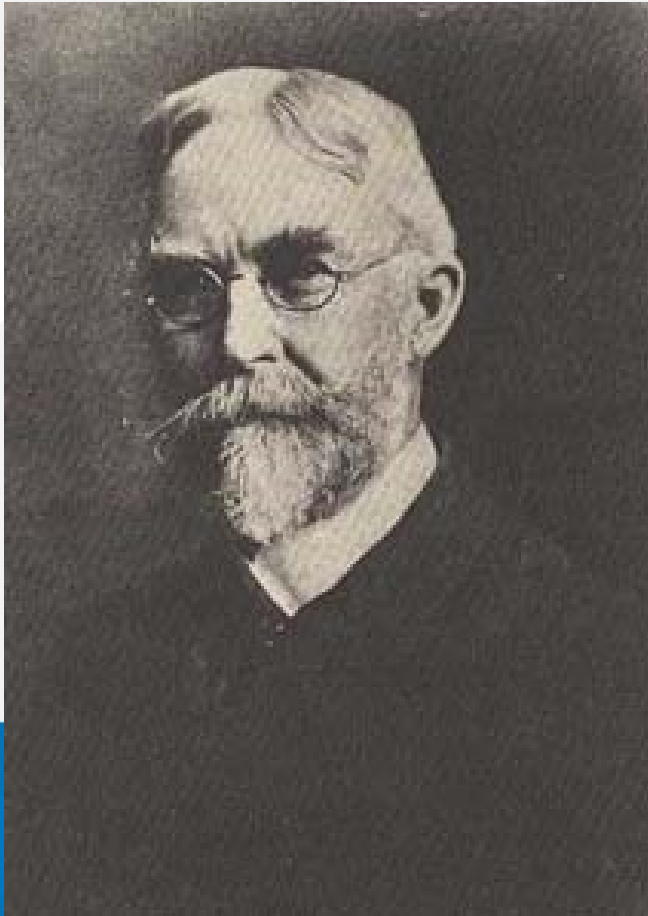
# HD Basics: The WHY

- 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.



# HD: The Beginning

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’

George  
Huntington

# 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)

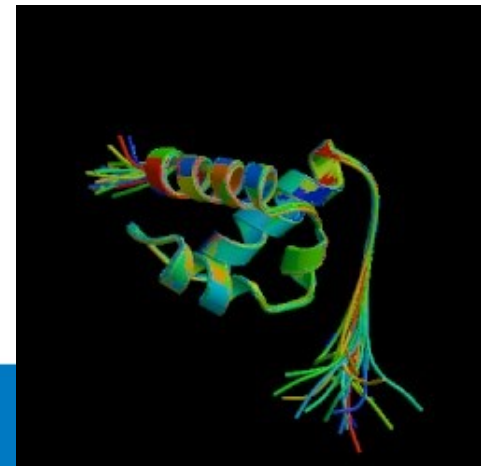


# HD Basics: The **WHY**

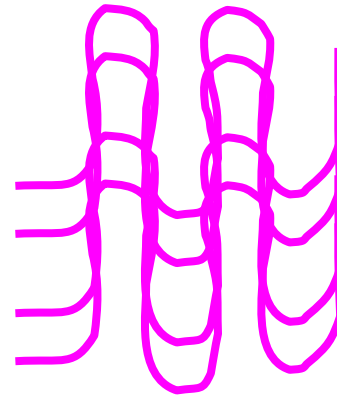
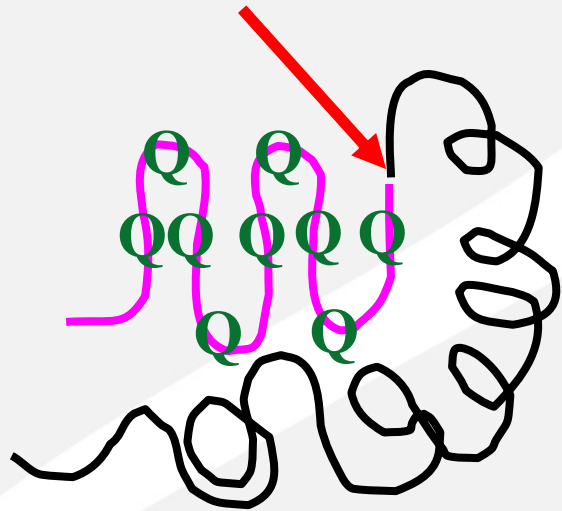
- Genetic disorder. Expanded CAG repeat length in huntingtin gene
  - Higher CAG repeat length correlates roughly with earlier age of onset of disease
  - But CAG repeat length accounts for only **50-60%** of onset age variability.
- Htt protein expressed in all cells in the body
- Function not completely known: involved in many important pathways



	CAG repeat length
Definite HD	40 and higher
Probable HD	36-39
Grey Zone	26-35
No HD	Less than 26



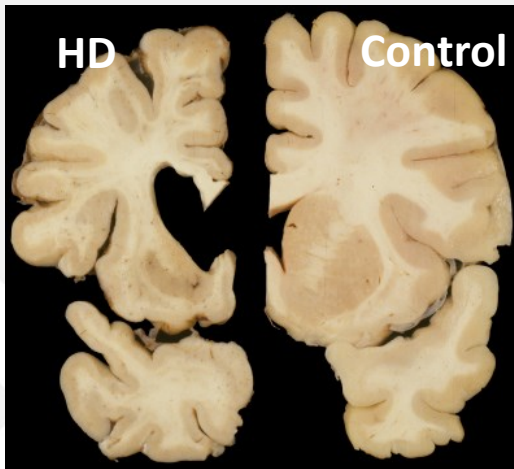
# HD Basics: The WHY



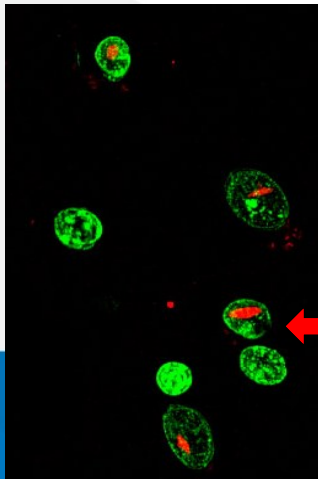
- Cleaved to generate fragments which aggregate into clumps
- Aggregates cause dysfunction of neurons
- Aggregates of different proteins are also found in other neurologic disorders: Alzheimer disease, Parkinson disease and many others

# HD Basics: The **WHY**

## Huntington Disease Pathology



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



Striatal huntingtin inclusions

# Cortex

## Striatum

~~D2~~ D1

### Chorea

GPe

GPI

Thal

STN

# Cortex

## Striatum

~~D2~~ ~~D1~~

### Less Movement

GPe

GPI

Thal

STN

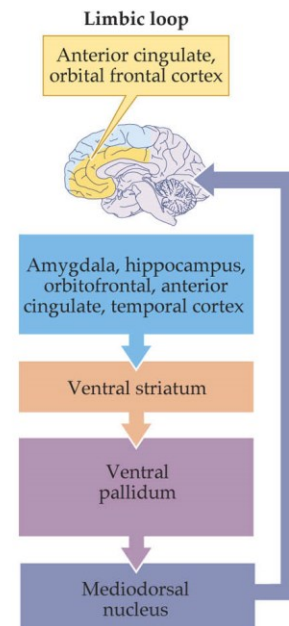
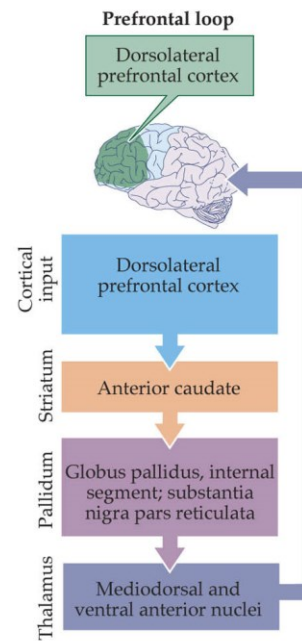
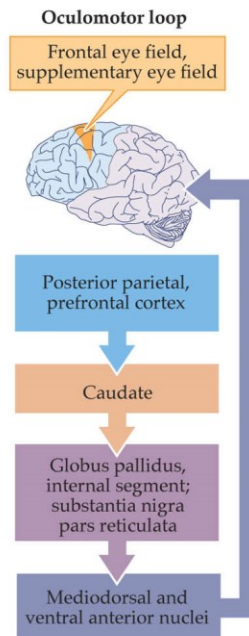
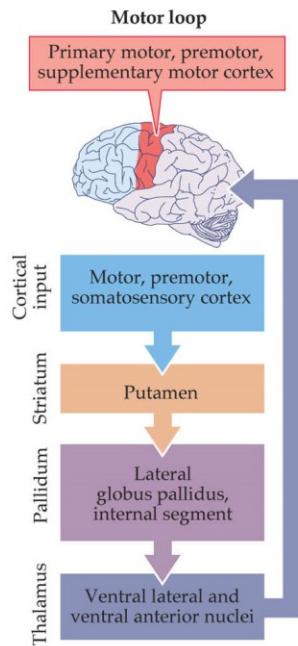
Inhibitory

Excitatory

## Early HD

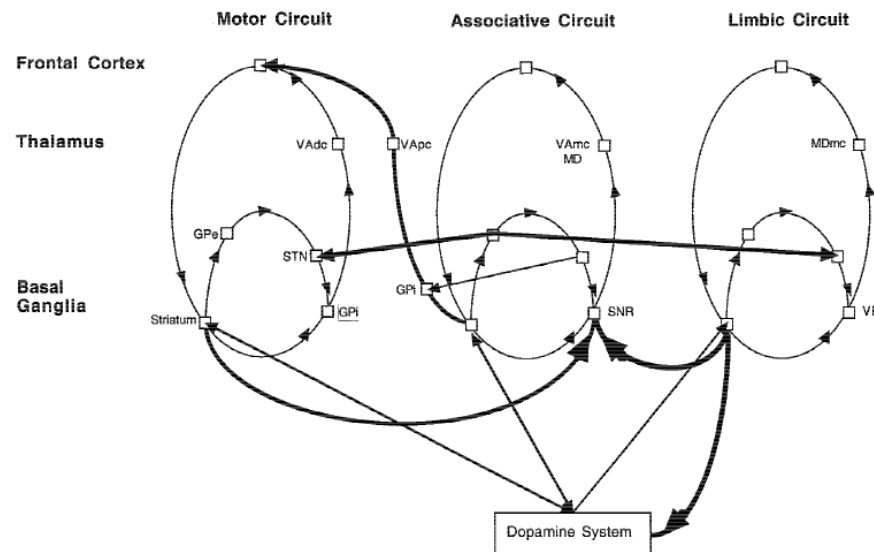


## Later HD



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# 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!

## COGNITIVE

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

## MOTOR

- Chorea
- Dystonia
- Eye movement abnl
- Gait, balance problems
- Postural instability

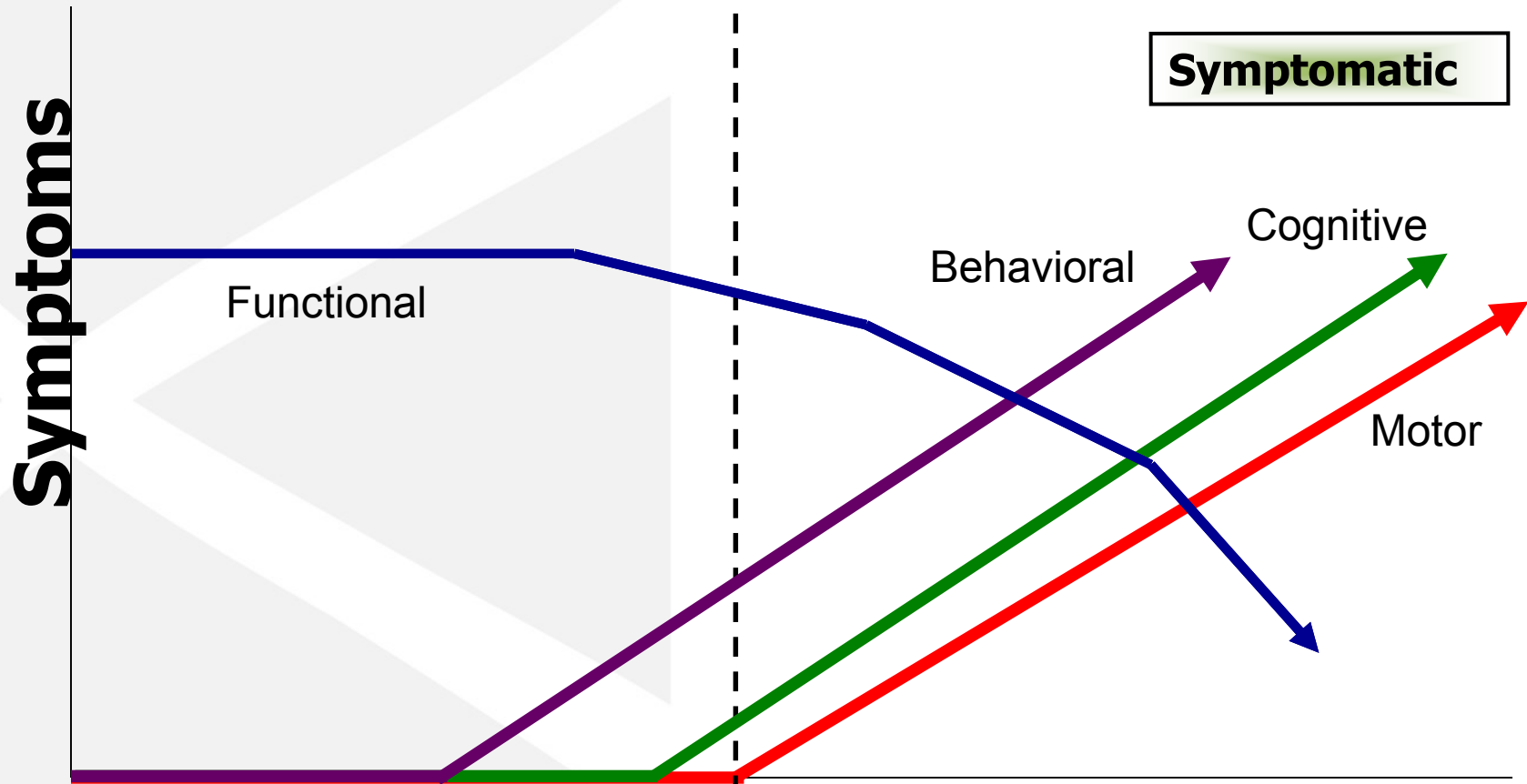
## FUNCTION

- Employment
- Family Obligations
- Social Activities
- ADLs

## BEHAVIORAL

- Depression
- Anxiety
- Obsessions, Compulsions
- Delusions, Hallucinations
- Apathy
- Impulsivity

# The **WHEN**: Timing of Onset and Progression



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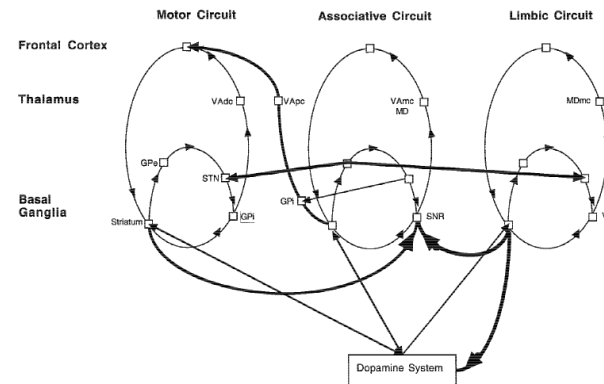
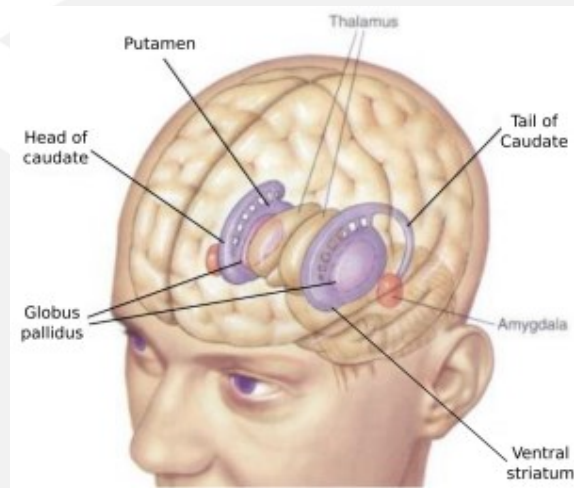
- Cannot predict who will develop WHAT symptoms and WHEN
- While certain features may be similar within families
  - **EVERY PERSON is DIFFERENT**
- Thus, treatment is different for every person with HD

# 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

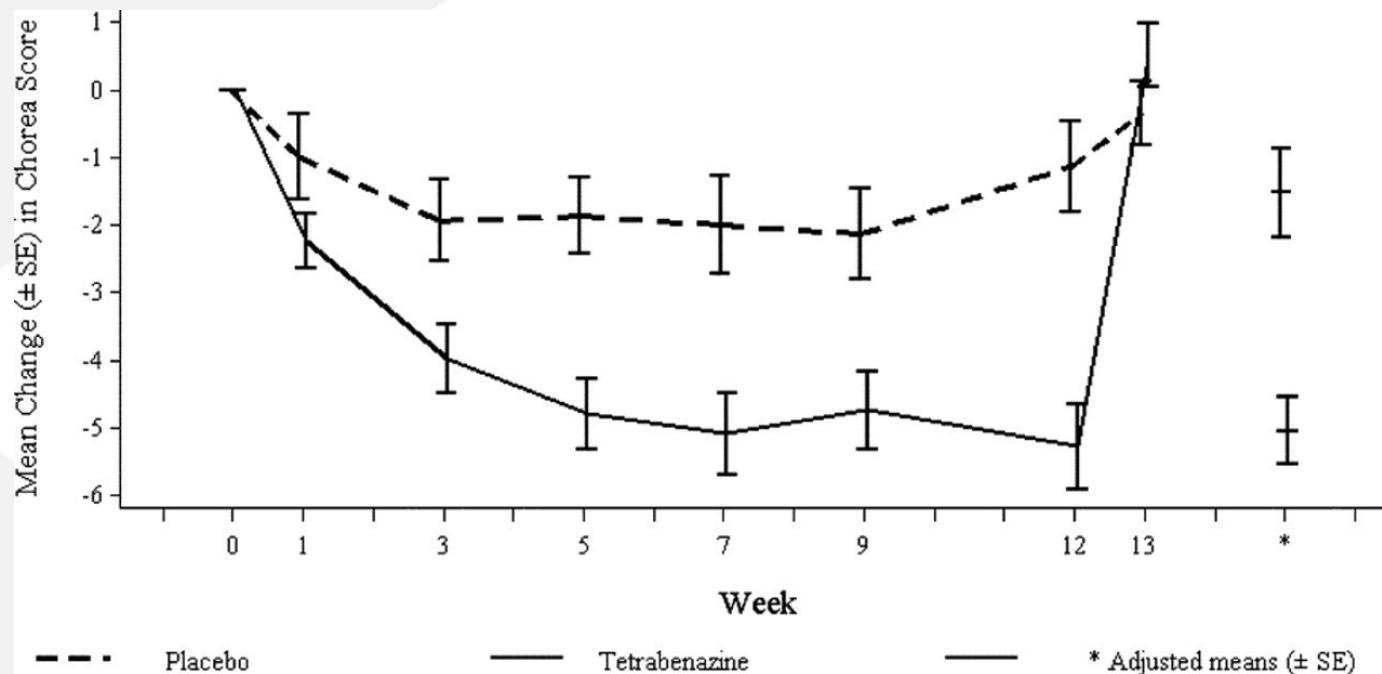


# The HOW: Treatment

- 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 deutetabenazine (Austedo) deplete dopamine: the only FDA approved treatments for HD
      - Possible Side effects: depression, restlessness, parkinsonism
  - Good chorea control

# Tetrabenazine

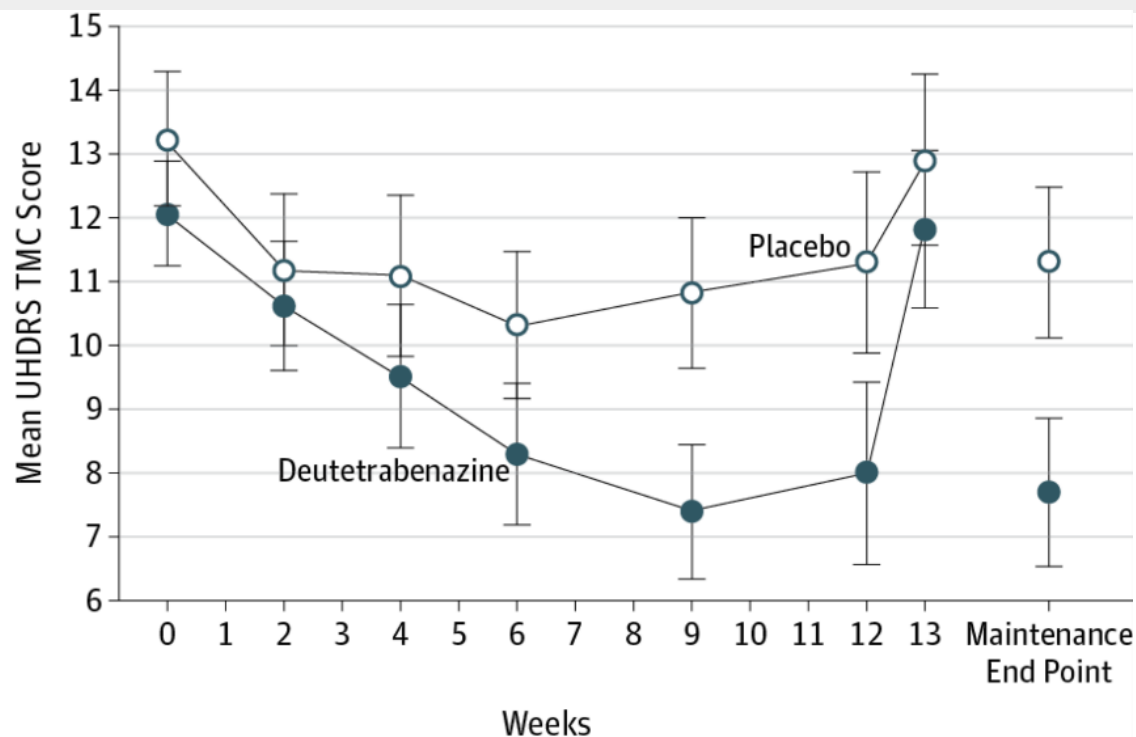
## TETRA-HD Study Results



Huntington Study Group, *Neurology* 2006;66:366-372

From: **Effect of Deutetrabenazine on Chorea Among Patients With Huntington Disease**A Randomized Clinical Trial

JAMA. 2016;316(1):40-50. doi:10.1001/jama.2016.8655



Patients

Deutetrabenazine	45	45	44	44	45	45	44	45
Placebo	45	45	45	44	42	43	43	45



Huntington's Disease  
Society of America

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# The **HOW**: Treatment

- **Chorea**
  - **Benzodiazepines**: clonazepam, lorazepam, diazepam
    - Side effects: sedation
  - **Amantadine**- mild chorea control
  - **Valproic acid**- very mild chorea control

# The **HOW**: Treatment

- **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

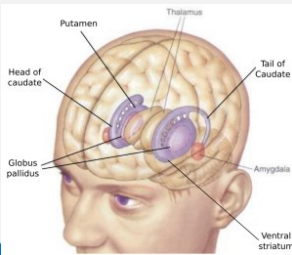
# Medical Marijuana: Cannabidiols

- **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 med:
  - **Antipsychotics**
    - Chorea AND delusions, anxiety, irritability, outbursts, sleep, weight
  - **Benzodiazepines**
    - Chorea AND dystonia, anxiety, irritability, outbursts, sleep
- 2 for 1 med
  - **Valproic acid**
    - Chorea AND mood stabilization
  - **Amantadine**
    - (maybe mild benefit) chorea AND walking

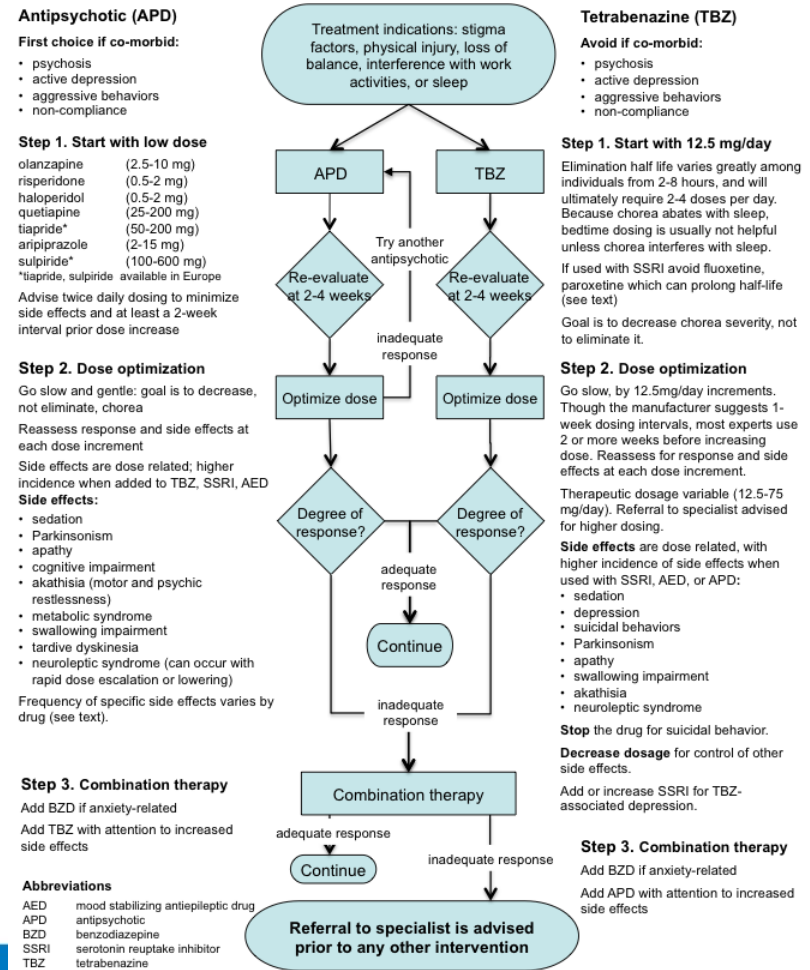
# The HOW: Treatment

- 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



# HD Symptom Management: Not in Isolation!

## COGNITIVE

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## FUNCTION

- Employment
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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!

