



# Mid-Stage Medications

Vicki Wheelock MD

Director, HDSA Center of Excellence at UC Davis

June 25, 2011



The information provided by speakers in workshops, forums, sharing/networking sessions and any other educational presentation made as part of the 2011 HDSA convention program is for informational use only.

HDSA encourages all attendees to consult with their primary care provider, neurologist or other healthcare provider about any advice, exercise, medication, treatment, nutritional supplement or regimen that may have been mentioned as part of any presentation.

# Presenter Disclosures

**Dr. Vicki Wheelock**

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

**No relationships to disclose or list**

I will discuss off-label use of medications for some HD symptoms.

Mid-stage HD challenges include increasing cognitive impairment, chorea and movement difficulties, and possibly psychiatric challenges. This session will review the indications, benefits and side effects of medications which are commonly used to manage these symptoms.

It is extremely important to recognize that behavioral techniques, speech, occupational and physical therapies and adaptive equipment are the primary forms of treatment for many HD symptoms.

## There is only one medication that is FDA approved for HD.

- That drug is tetrabenazine (Xenazine).
- Many other drugs approved for other indications (depression, psychosis, Parkinson's disease, Alzheimer's disease) have been tried and may be used for HD. This is called off-label prescribing.
  - In some cases, there are research studies that support use of these medications in HD.
  - As with all medications, HD patients must be monitored for side effects.
  - There is a great need for additional drugs and more studies.

Please refer to A Physician's Guide to the Management of HD, 3<sup>rd</sup> edition for guidance.

# Huntington Disease Stages

Mid-stage HD

Stage 0: Presymptomatic

Stage 1: Slightly lower performance at work; independent at home

Stage 2: Can still work (lower level), still mostly independent at home

Stage 3: Difficult to work, starts to need help with financial, home activities

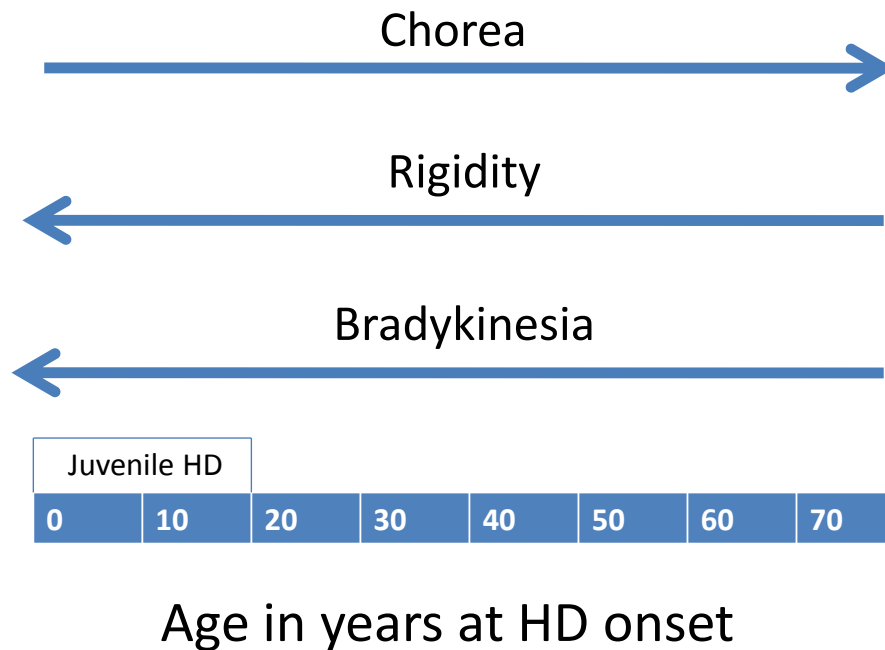
Stage 4: Unable to work. Needs major assistance with care

Stage 5: Full-time nursing care required

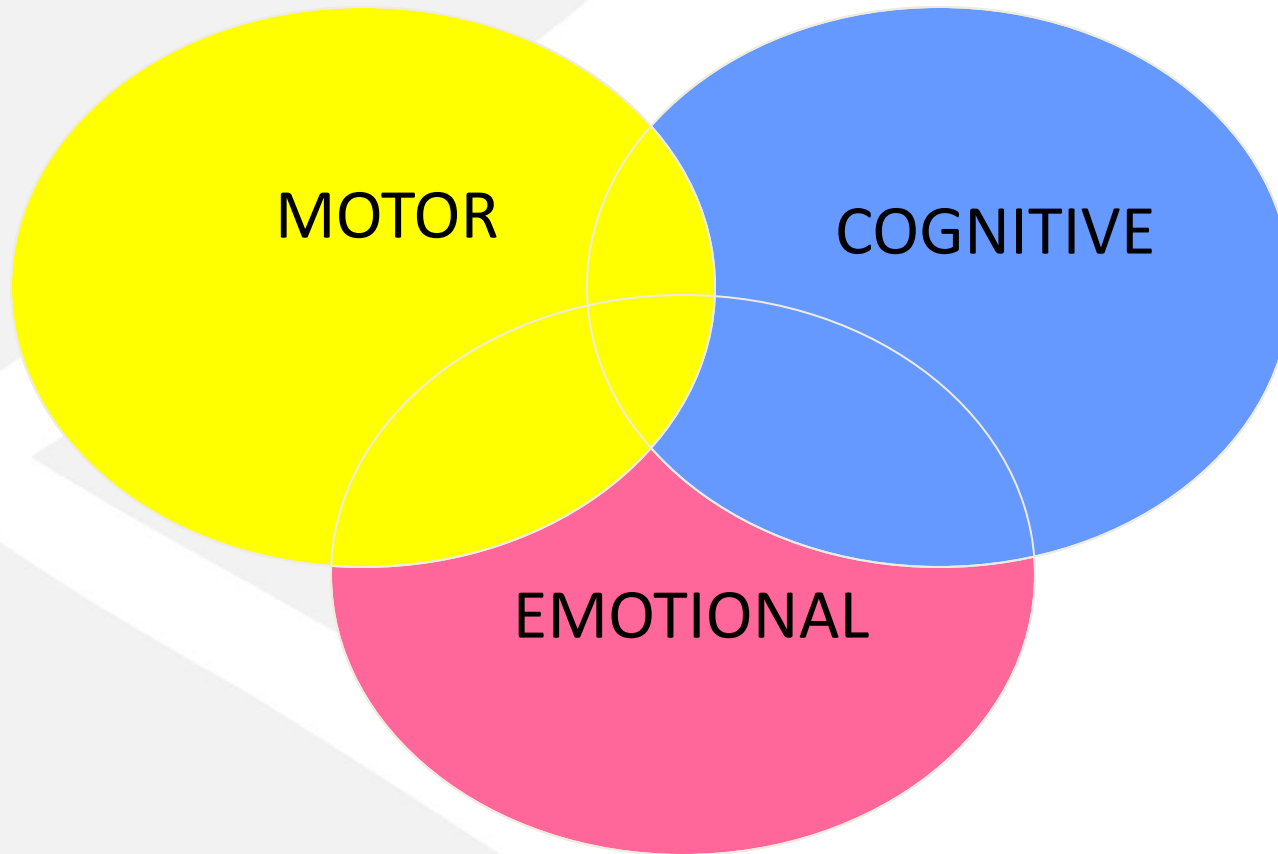
# The relationship between HD symptoms and age

from: Harper, PS. Huntington's disease

## Presenting motor findings



# Symptoms in HD





# Cognitive impairments in HD

- Learning and memory
  - Perceptual skills
  - Unawareness
  - Language difficulties
- Executive dysfunction
    - Speed of processing
    - Attention and concentration
    - Planning and organization
    - Lack of initiation
    - Perseveration: getting stuck
    - Impulsivity

## Medications for cognitive difficulties

- We sometimes prescribe drugs for from Alzheimer's disease .
- They which are best for memory and perhaps perceptual skills.
  - No benefit for executive dysfunction
- Donepezil, 5-10 mg daily may be tried – not effective in one randomized trial
- Rivastigmine 6 mg per day studied in open-label trial in Europe; showed possible benefit. Needs additional study
- Memantine: Pilot trial in 2009 showed no benefit for cognition.
- Latrepirdine (Dimebon) looked promising in Phase 2 trial, but failed in Phase 3 trial to improve cognition.

## Medications for cognitive difficulties

- Dysexecutive function: Trial of atomoxetine failed to help with attention and executive function in 2009 (J. Paulsen, 2009).
- Apathy and lack of initiation may respond to stimulant drugs such as methylphenidate, pemoline, or dextro-amphetamine (Rosenblatt, Physician's Guide to the Management of HD, 3<sup>rd</sup> edition).
  - Apathy may worsen with sedating drugs such as anti-psychotics or benzodiazepines

## Medications for psychiatric difficulties: Depression

Class	Trade name <sup>®</sup>	Generic name
Selective serotonin reuptake inhibitors (SSRIs)		
	Zoloft	Sertaline
	Celexa	Citalopram
	Lexapro	Escitalopram
	Paxil	Paroxetine
	Prozac	Fluoxetine
Non-selective serotonin reuptake inhibitors (NSRIs)		
	Welbutrin	Bupropion
	Venlafaxine	Effexor
Other	Remeron	Mirtazepine

Side effects: well-tolerated. Occasional stomach upset, dizziness, sleepiness, withdrawal syndrome for Paroxetine.

# Medications for psychiatric difficulties: Anxiety

Class	Trade name <sup>®</sup>	Generic name
Selective serotonin reuptake inhibitors (SSRIs)		
	Zoloft	Sertaline
	Celexa	Citalopram
	Lexapro	Escitalopram
	Paxil	Paroxetine
	Prozac	Fluoxetine
Benzodiazepines	Klonopin	Clonazepam
Non-benzodiazepine anxiolytic	Buspar	Buspirone

# Medications for psychiatric disorders: Psychosis

Class	Trade Name	Generic	Side effects
Atypical neuroleptics (newer agents)			
	Zyprexa	Olanzapine	Weight gain, sedation, metabolic syndrome, possible parkinsonism
	Seroquel	Quetiapine	
	Geodon	Ziprasidone	
	Abilify	Aripiprazole	
Typical neuroleptics (older agents)			
	Haldol	Haloperidol	Parkinsonism, tardive dyskinesia, sedation
	Prolixin	Fluphenzine	
	Risperdal	Risperidone	

## Medications for psychiatric disorders: Mania

Class	Trade name	Generic	Side Effects
Anti-epileptic drugs			
	Depakote	Divalproex sodium	Weight gain, liver
	Lamictal	Lamotrigine	Skin rash, possibly fatal
	Topamax	Topiramate	Memory impairment
	Tegretol	carbamazepine	Bone marrow suppression
Neuroleptic drugs			
	Many; depends on severity of symptoms. May need injectable medication.		Major sedation, parkinsonism

# Medications for psychiatric disorders: Obsessive Compulsive Disorder

- SSRI antidepressants
- For severe cases, neuroleptics may be necessary



## Medications for psychiatric disorders: Irritability

- SSRI drugs such as sertraline, fluoxetine, paroxetine
- Benzodiazepines (clonazepam)
- Anti-epileptic drugs such as Depakote
- Rarely, neuroleptics

# Insomnia in HD

- First, try “sleep hygiene”
  - Go to bed at night, get up in the morning
  - Limit caffeine to no more than 1-2 cups before noontime
  - Limit or eliminate alcohol
  - Regular exercise
  - Quiet night-time activities before bed – no computer
- If this fails,
  - Avoid sedatives like Ambien, Lunesta, benzodiazepines – or use only on occasion.
  - Melatonin may help people get to sleep and is safe
  - Antidepressants: trazodone ,mirtazepine
  - Occasional use of neuroleptic quetiapine

# Treating Juvenile HD

- Medications for cognition and school performance – not recommended
- Medications for psychiatric symptoms may occasionally be needed. Consult a Child Psychiatrist.
- Movement-related problems are usually different than in adults: slowness, rigidity and dystonia are most common
  - Some may have chorea
- Seizures may occur.

# Juvenile Onset HD: Rigidity

Class	Trade name	Generic	Side effects
Benzodiazepines			
	Valium	Diazepam	Sedation
	Klonopin	Clonazepam	Sedation
Anti-spasticity			
	Lioresal	Baclofen	Sedation
	Zanaflex	Tizanidine	Sedation
Anti-parkinson agent			
	Symmetrel	Amantadine	Hallucinations
	Sinemet	Carbidopa-levodopa	Hallucinations

# Juvenile Onset HD: Dystonia

Class	Trade name	Generic
Benzodiazepine		
	Klonopin	Clonazepam
Anti-spasticity		
	Lioresal	Baclofen
	Zanaflex	Tizanidine
Anticholinergics		
	Artane, others	Trihexyphenidyl
Chemodenervation		
	Botox, others	Botulinum toxin

## Juvenile onset HD: Anti-Seizure medications

Trade name	Generic	Side effects
Keppra	Levetiracetam	Sedation
Depakote	Divalproex sodium	Stomach upset, liver
Tegretol	carbamazepine	Bone marrow depression
Dilantin	phenytoin	Gum disease
Klonopin	clonazepam	Sedation
Many others....will depend on seizure type		

# Chorea is a difficult symptom

- Affects nearly all adult HD patients (progressively disabling)
- Reduces employability
- Contributes to social isolation and stigmatization
- Presents an increased safety risk (falling, worsened gait, need for supervision)
- Contributes to weight loss
- Can lead to injury and make caregiving difficult, especially in late-stage HD

## Historical treatment of chorea

- Anti-psychotic drugs have been extensively used off-label to treat chorea.
- The problem: no Level 1 studies of these drugs
- Side effects: worsening bradykinesia, sedation, dystonia , weight gain and metabolic syndromes
- Other drugs: sedatives like clonazepam may help with mild chorea, but can be ineffective and cause sedation.

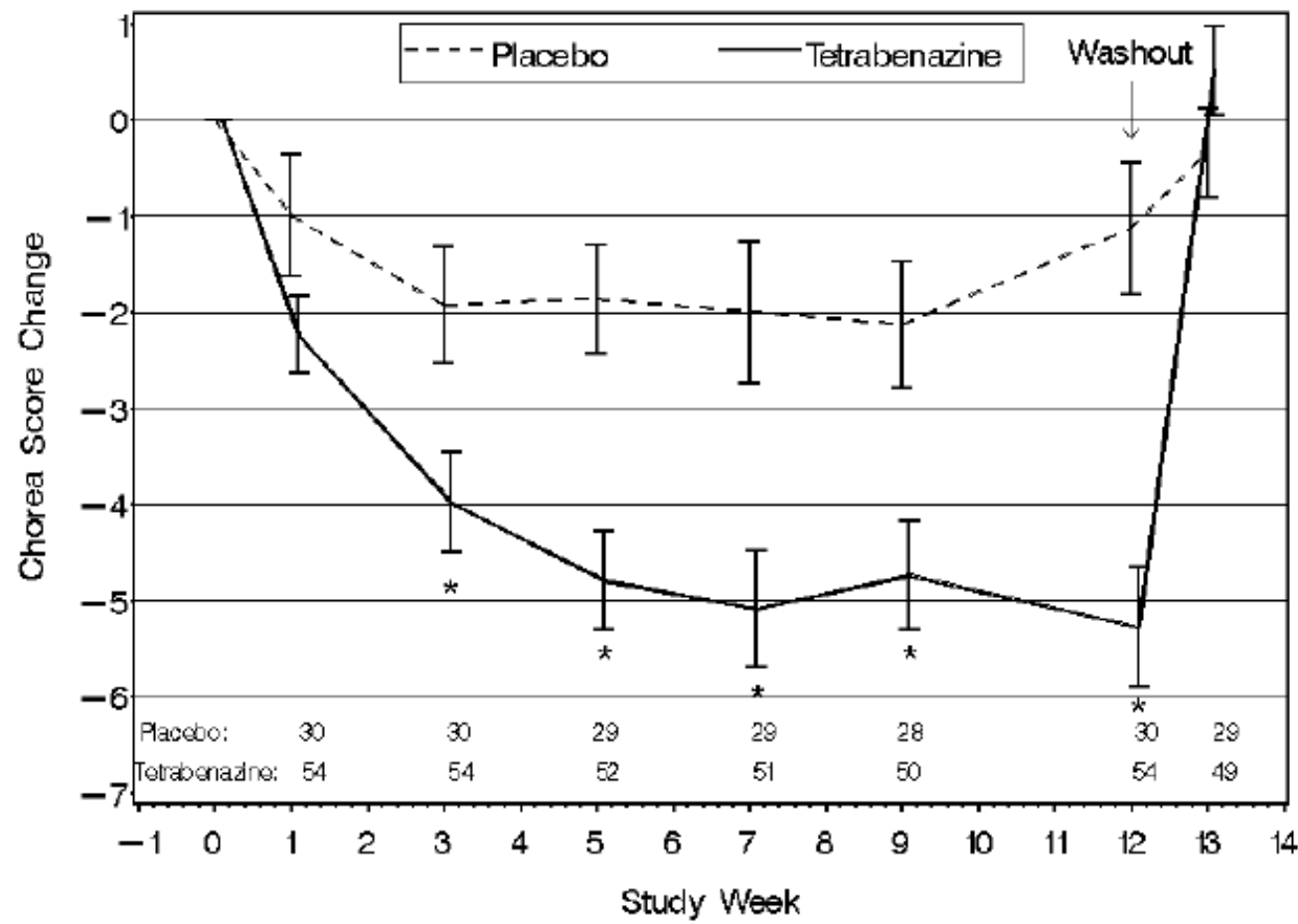


# Tetrabenazine: First drug for the treatment of Huntington's disease to receive FDA approval (TETRA study)

- Double-blind, placebo-controlled study of tetrabenazine in manifest HD
- 84 people with HD, randomized 2:1 to tetrabenazine or placebo for 12 weeks
- Primary endpoint: chorea score



# TETRA Study results



# Tetrabenazine



**Benefits:** reduces chorea

**Side effects:**

swallow dysfunction  
depression/suicide  
restlessness

**Interactions:**

Some anti-depressants  
Other anti-chorea drugs

**Dosing:**

Genetic test  
Monitor EKG

**Cost:** Special program

# Tetrabenazine and depression

- 20% of TETRA participants had new or worsening depression
- Patients, their caregivers, and families are informed of the risks of depression.
  - Monitor the patient for any new or worsening symptoms of depression
  - Seek help immediately if the patient develops thoughts of suicide
  - Sometimes dosage reduction will help
  - If depression or suicidal thoughts don't respond to dose reduction, then tetrabenazine must be discontinued.

## Medications for chorea

- First-line: Tetrabenazine (FDA-approved in 2008 as the first drug in US for HD)
- Second line: benzodiazepines
- Third line: antipsychotic drugs
  - “Typical” (older): haloperidol, fluphenazine
  - “Atypical” (newer): olanzapine, risperidone, others

## Anti-chorea medications

- In patients with significant psychiatric disturbances (severe depression, mania, anger outbursts or psychosis), neuroleptic drugs made be first-choice because they will treat both the psychiatric symptoms and reduce chorea.
- Atypical neuroleptics work well for both psychiatric symptoms and chorea, except for quetiapine, which doesn't help chorea.

## Further recommendations about treatment of chorea

Anti-chorea therapy should be re-evaluated at least annually.

Some patients will require increasing doses of anti-chorea medications over time. Some may even require the addition of two or more drugs to control chorea.

Many will eventually develop increasing dystonia and rigidity with HD progression, necessitating reduction or cessation of anti-chorea medications.

## Treating the rigid-dystonic form of HD: rigidity

Class	Trade name	Generic
Benzodiazepines		
	Valium	Diazepam
	Klonopin	Clonazepam
Anti-spasticity		
	Lioresol	Baclofen
	Zanaflex	Tizanidine
Anti-parkinson agents		
	Symmetrel	Amantadine
	Sinemet	Carbidopa/levodopa
	Requip, Mirapex	Ropinirole, pramipexole

**Tetrabenazine is not indicated for patients with rigid-dystonic HD.**



## Treating the rigid-dystonic form of HD: Dystonia

Class	Trade name	Generic
Benzodiazepine		
	Klonopin	Clonazepam
Anti-spasticity		
	Lioresal	Baclofen
	Zanaflex	Tizanidine
Anticholinergics		
	Artane, others	Trihexyphenidyl
Chemodenervation		
	Botox, others	Botulinum toxin
Anti-parkinson agents		
	Symmetrel	Amantadine
	Sinemet	Carbidopa/levodopa

**Tetrabenazine is not indicated for patients with rigid-dystonic HD.**

# Questions?

Thank you!

- Patients and families affected by HD
- Dr. Martha Nance, Dr. Jane Paulsen, Dr. Adam Rosenblatt
- Ms. Deb Lovecky, HDSA National
- Joseph P. Roberson Foundation
- Les and Margaret Pue Foundation

