

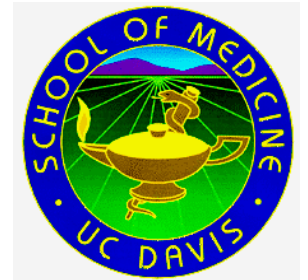
# Medications for Huntington's Disease



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Updated September 2017



# Outline

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- Introduction and disclaimers
- Medications for cognitive symptoms
- Medications for psychiatric symptoms
- Medications for sleep difficulties
- Medications for juvenile HD
- Medications for chorea and dystonia
- Conclusions

# Introduction

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- HD symptoms include cognitive impairment, chorea and movement difficulties, and psychiatric challenges. This presentation 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, counseling, speech, occupational and physical therapies and adaptive equipment are the primary forms of treatment for many HD symptoms.

# There are now TWO medications that are FDA-approved for HD

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- The **first** was tetrabenazine (Xenazine), in 2008
- The **second** is deutetabenazine (Austdeco), in 2017
- *Both drugs are approved to treat chorea in HD.*
- 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 continuing need for additional drugs and more studies.

# The relationship between HD symptoms and age

In adult-onset HD, most patients have chorea.

In juvenile-onset HD, chorea is rare, and rigidity and slowness predominate

## Presenting motor findings

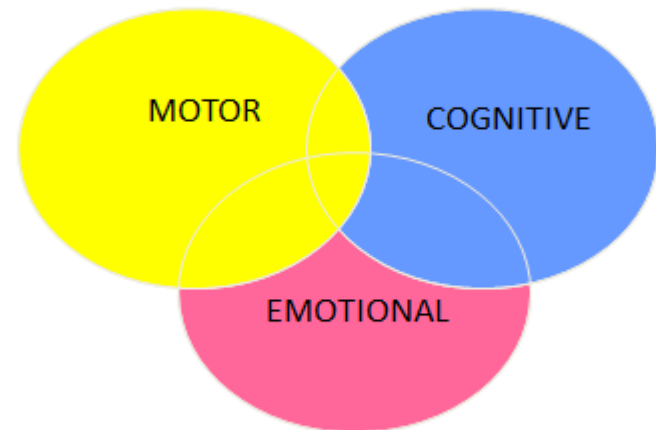


Juvenile HD

0 | 10 | 20 | 30 | 40 | 50 | 60 | 70

Age in years at HD onset

## Symptoms in HD



# Cognitive Impairments in HD

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- 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

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- We sometimes prescribe drugs developed for Alzheimer's disease.
- Those 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.

1. *Neurology* 2006;67:1268–1271

2. *Parkinsonism and Rel Disord* 13 (2007) 453–454

3. *Arch Neurol.* 2010;67(2):154-160

# Medications for Cognitive Difficulties

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



## Psychiatric symptoms in HD

Symptom	Prevalence	Description
Depression	33-69%	Similar to major depression
Suicidal thinking	25-70%	Peaks prior to HD diagnosis but can appear at any stage
Irritability	38-73%	Highly treatable
Aggression	70%	Mild verbal to severe physical
Perseveration	10-52%	Repetitive action or thought
Anxiety	34-61%	Any stage of disease
Sleep disorder	62%	Multiple sleep symptoms
Apathy	34-76%	Causes functional worsening
Psychosis	3-11%	Paranoid thinking
Mania/Bipolar Disorder	rare	Often misdiagnosis for irritability

# Medications for Depression

Class	Trade Name®	Generic Name
<b>Selective Serotonin Reuptake Inhibitors (SSRIs)</b>		
	<b>Zoloft</b>	<b>Sertraline</b>
	<b>Celexa</b>	<b>Citalopram</b>
	<b>Lexapro</b>	<b>Escitalopram</b>
	<b>Paxil</b>	<b>Paroxetine</b>
	<b>Prozac</b>	<b>Fluoxetine</b>
<b>Non-selective Serotonin Reuptake Inhibitors (NSRIs)</b>		
	<b>Wellbutrin</b>	<b>Bupropion</b>
	<b>Effexor</b>	<b>Venlafaxine</b>
<b>Other</b>	<b>Remeron</b>	<b>Mirtazapine</b>

**Side effects:** Usually well-tolerated. Occasional stomach upset, dizziness, sleepiness, sexual dysfunction; discontinuation syndrome for paroxetine.

# Medications for Anxiety

Class	Trade Name®	Generic Name
<b>Selective Serotonin Reuptake Inhibitors (SSRIs)</b>		
	<b>Zoloft</b>	<b>Sertraline</b>
	<b>Celexa</b>	<b>Citalopram</b>
	<b>Lexapro</b>	<b>Escitalopram</b>
	<b>Paxil</b>	<b>Paroxetine</b>
	<b>Prozac</b>	<b>Fluoxetine</b>
<b>Benzodiazepines</b>	<b>Klonopin</b>	<b>Clonazepam</b>
<b>Non-benzodiazepine anxiolytic</b>	<b>Buspar</b>	<b>Buspirone</b>

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

# Medications for Psychosis

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

# Medications for Mania

Class	Trade Name®	Generic Name	Side Effects
<b>Anti-epileptic drugs</b>			
	<b>Depakote</b>	<b>Divalproex sodium</b>	<b>Weight gain, liver toxicity</b>
	<b>Lamictal</b>	<b>Lamotrigine</b>	<b>Skin rash, possibly fatal</b>
	<b>Topamax</b>	<b>Topiramate</b>	<b>Memory impairment, kidney stones</b>
	<b>Tegretol</b>	<b>Carbamazepine</b>	<b>Bone marrow suppression, skin rash</b>
<b>Neuroleptic drugs</b>			
	<b>Many; depends on severity of symptoms. May need injectable medication.</b>		<b>Major sedation, parkinsonism</b>

# Medications for Obsessive-Compulsive Disorder

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- SSRI antidepressants (see slide 9)
- For severe cases, neuroleptics may be necessary (see slide 11)

# Medications for Irritability

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- Behavioral strategies are always first-line
- Medications can be considered if behavioral strategies are not adequate
  - SSRI drugs such as sertraline, fluoxetine, paroxetine
  - Benzodiazepines (clonazepam)
  - Anti-epileptic drugs such as valproic acid
  - Sometimes, neuroleptics

# Insomnia in HD

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- First, try “sleep hygiene”
  - Avoid sleep cycle problems: go to bed at night, get up in the morning on a regular schedule
  - Limit caffeine to no more than 1-2 cups before noontime
  - Limit or eliminate alcohol
  - Regular exercise, early in the day
  - Quiet night-time activities before bed
  - No computer, tablet or smart-phone screens before lights out
    - The brightness will signal “daytime” to your brain’s sleep center and make it more difficult to fall asleep



# Insomnia in HD

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- If sleep hygiene alone fails,
  - Avoid over-the-counter medications for sleep that contain diphenhydramine (“Benadryl”) as this medication may cause daytime sleepiness and impair memory/concentration
  - Avoid sedatives like zolpidem or benzodiazepines which may worsen cognition or mood
  - Melatonin may help people get to sleep and is safe at low doses (i.e. 0.5 – 1 mg at night).
    - Higher doses of melatonin may cause daytime sleepiness
  - Prescribed medications that your physician may consider
    - Antidepressants: trazodone, mirtazapine
    - Occasional use of neuroleptic quetiapine

# Treating Juvenile HD

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- Medications for cognition and school performance – none recommended
- Medications for psychiatric symptoms may 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
  - For treatment of dystonia, see slides 35-36
- Seizures may occur in JHD

# Juvenile Onset HD: Rigidity

Class	Trade Name®	Generic Name	Side Effects
<b>Benzodiazepines</b>			
	<b>Valium</b>	<b>Diazepam</b>	<b>Sedation</b>
	<b>Klonopin</b>	<b>Clonazepam</b>	<b>Sedation</b>
<b>Anti-spasticity</b>			
	<b>Lioresal</b>	<b>Baclofen</b>	<b>Sedation</b>
	<b>Zanaflex</b>	<b>Tizanidine</b>	<b>Sedation</b>
<b>Anti-parkinson agents</b>			
	<b>Symmetrel</b>	<b>Amantadine</b>	<b>Hallucinations</b>
	<b>Sinemet</b>	<b>Carbidopa-levodopa</b>	<b>Hallucinations</b>

# Juvenile Onset HD: Anti-seizure Medications

Trade Name®	Generic Name	Side Effects
Keppra	Levetiracetam	Sedation
Depakote	Divalproex sodium	Stomach upset, liver toxicity
Tegretol	Carbamazepine	Bone marrow depression, skin rash
Dilantin	Phenytoin	Sedation, gum disease
Klonopin	Clonazepam	Sedation
Many others ... will depend on seizure type		

# Adult-onset HD: Chorea is a difficult symptom

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- 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

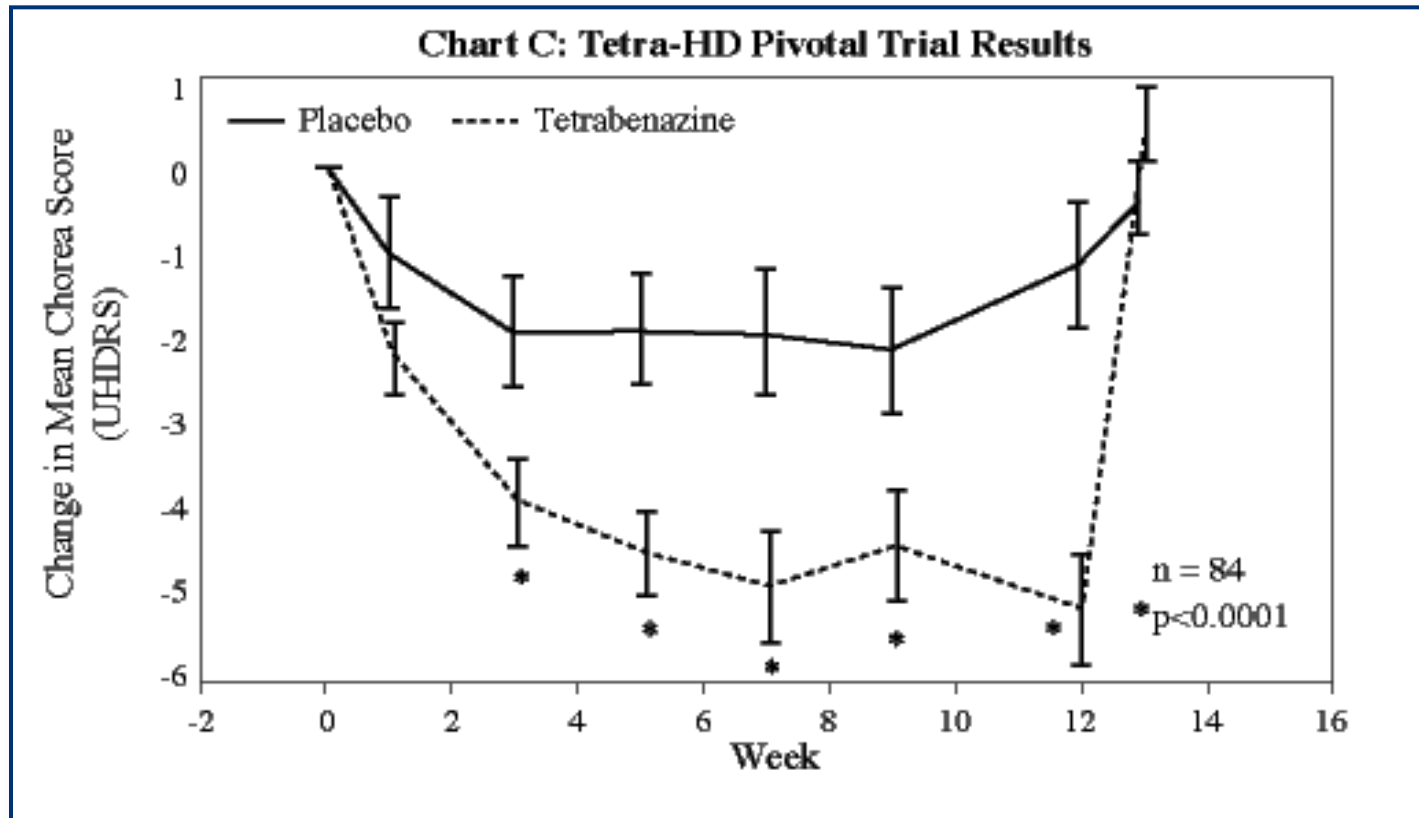
## **Tetrabenazine: First drug for the treatment of Huntington's disease to receive FDA approval (TETRA study)**

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- 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: Unified Huntington's disease Rating Scale 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 for higher doses

Monitor EKG

**Cost:** Special program 2008-15

**Generic form is now available (2015- )**



# Tetrabenazine and Depression

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- 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.

# Newest drug for HD: Deutetrabenazine (Austedo™)

*the*  
PHARMACEUTICAL JOURNAL  
*A Royal Pharmaceutical Society publication*

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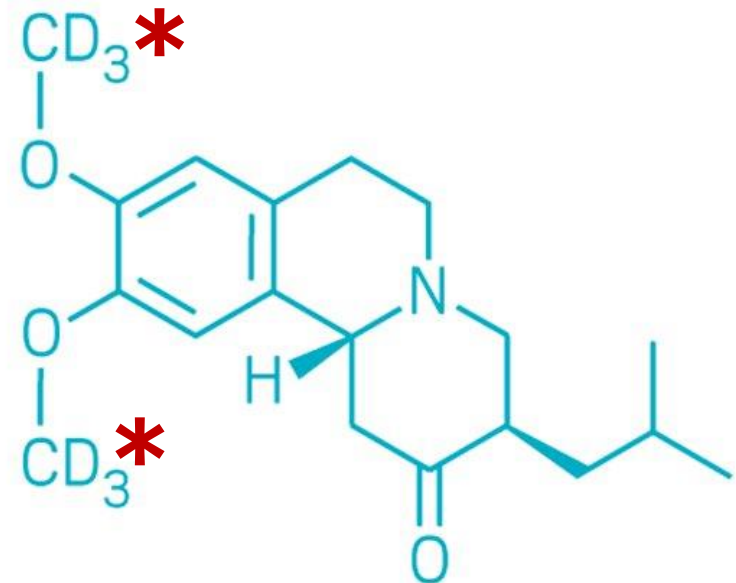
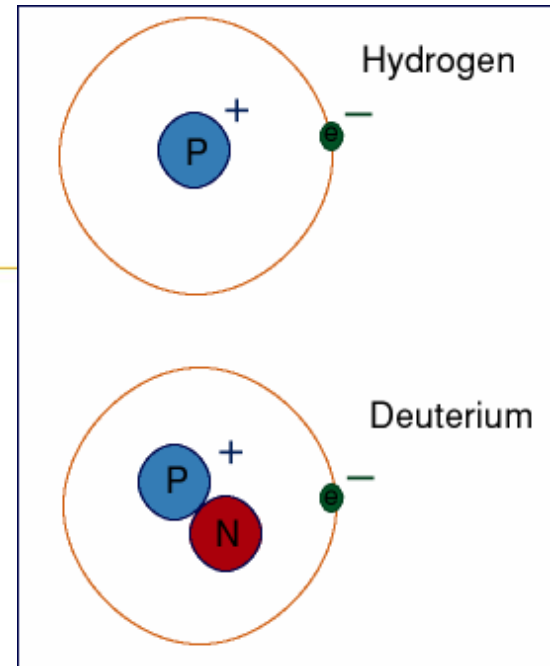
## FDA approves Austedo for Huntington's chorea

 **Austedo™**  
(deutetrabenazine)  
tablets

Approved April 2017

## Deutetrabenazine

- Deuterated form of tetrabenazine
- Deutetrabenazine was designed by substituting naturally occurring "heavy hydrogen" (deuterium) molecule at 2 locations
- This results in slower metabolism and less variability in blood levels.



## FIRST-HD trial



- **Design:** Double-blind, placebo-controlled study of tetrabenazine in HD patients with chorea
- **Subjects:** 90 patients with HD, randomized to receive deutetrabenazine or placebo for 12 weeks
- **Primary endpoint:** Unified Huntington's disease Rating Scale chorea score



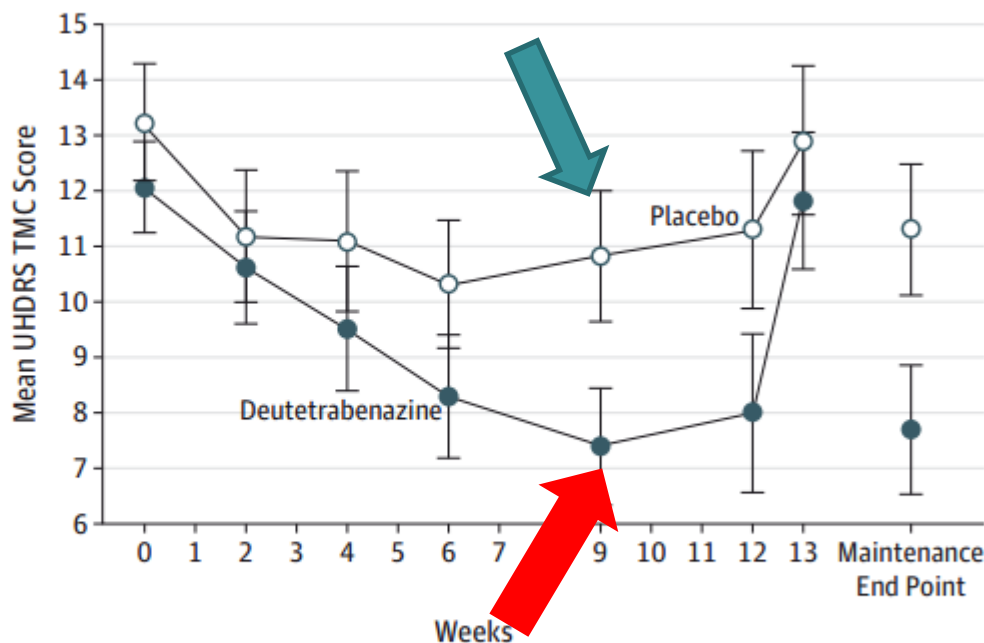
Original Investigation

# Effect of Deutetrabenazine on Chorea Among Patients With Huntington Disease

## A Randomized Clinical Trial

Figure 2. Total Maximal Chorea Score by Week

**Deutetrabenazine significantly reduced chorea scores compared to placebo in a 12 week randomized placebo-controlled study**



Patients	0	2	4	6	9	12	13	End Point
Deutetrabenazine	45	45	44	44	45	45	44	45
Placebo	45	45	45	44	42	43	43	45

# Side effects

- Most common: somnolence, diarrhea, dry mouth and fatigue
- **Black Box Warning: risk of depression and suicide**
- **Contraindications: patients with depression or liver disease**
- Use with care in patients taking anti-depressant drugs such as paroxetine, fluoxetine, quinidine, bupropion which can raise the levels of deutetrabenazine, or other drugs which can affect heart conduction
- Patients already taking tetrabenazine can be switched over to deutetrabenazine



- Teva's Shared Solutions program to support patients starting treatment
- Resources:
  - Nursing support
  - Education
  - Financial assistance program



# Medications for Chorea

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- First-line: Tetrabenazine or deutetabenazine
- Second line: benzodiazepines
- Third line: neuroleptic/antipsychotic drugs
  - “Typical” (older): haloperidol, fluphenazine
  - “Atypical” (newer): olanzapine, risperidone, others



# Off-label Anti-Chorea Medications

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- **In patients with significant psychiatric disturbances** (severe depression, mania, irritability and anger outbursts or psychosis), **neuroleptic drugs may 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.

(See slide 11 for details)

# Further Recommendations about Treatment of Chorea

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- 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.

## Medications for HD

# 10% of adults have the rigid-dystonic form of HD. Treating rigidity:

Class	Trade Name®	Generic Name
<b>Benzodiazepines</b>		
	Valium	Diazepam
	Klonopin	Clonazepam
	Ativan	Lorazepam
<b>Anti-spasticity</b>		
	Lioresal	Baclofen
	Zanaflex	Tizanidine
<b>Anti-parkinson medications</b>		
	Symmetrel	Amantadine
	Sinemet	Carbidopa/Levodopa
	Requip, Mirapex	Ropinirole, pramipexole

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

# Dystonia

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- **Definition:** repetitive, abnormal patterns of muscle contraction frequently associated with a twisting quality
- Often emerges in **mid- to late-stage HD**, but **common in juvenile HD** and rigid-dystonic variant
- **Examples:** Arm elevation while walking, twisting of trunk, grinding teeth or difficulty opening mouth, elevation and turning of foot while walking.
- **Rare:** Painful dystonic spasms can be severe in juvenile HD

# Treating Dystonia in HD

Class	Trade Name®	Generic Name
<b>Benzodiazepine</b>		
	Klonopin	Clonazepam
<b>Anti-spasticity</b>		
	Lioresal	Baclofen
	Zanaflex	Tizanidine
<b>Anticholinergics</b>		
	Artane, others	Trihexyphenidyl
<b>Chemodenerivation injections<sup>2</sup></b>		
	Botox, Myobloc, others	Botulinum toxin
<b>Anti-parkinson agents</b>		
	Symmetrel	Amantadine
	Sinemet	Carbidopa/Levodopa

## Notes:

1. Tetrabenazine and deutetrabenazine are not indicated for patients with rigid-dystonic HD.
2. We are seeing excellent results with botulinum toxin injections for dystonia in HD.

# Concluding Thoughts

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- Behavioral strategies, speech therapy, physical therapy, counseling lifestyle changes are important tools in helping to treat HD.
- The only medications for HD that are FDA-approved are tetrabenazine (Xenazine) and deutetabenazine (Austedo), but many others have been used successfully on an off-label basis.
- All medications have side effects, and selecting the right medication should be individualized for each HD patient.
- All medications should be re-evaluated periodically as HD symptoms change or progress.

# Resources

Go to <http://hdsa.org/shop/publications/>  
To download a pdf or order copies

