

Huntington's Disease: Movement Disorders and Treatment

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HDSA Convention

June 6 , 2009



Huntington's Disease Society of America

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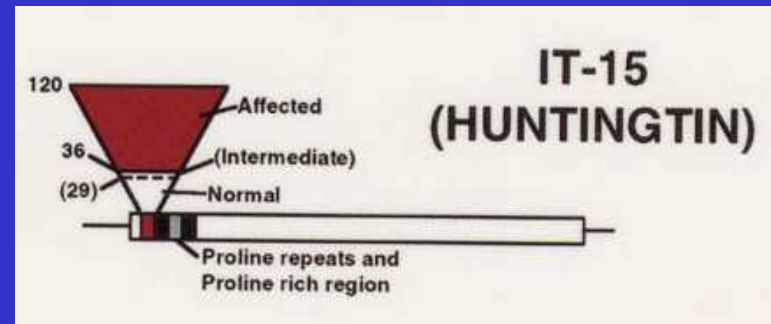
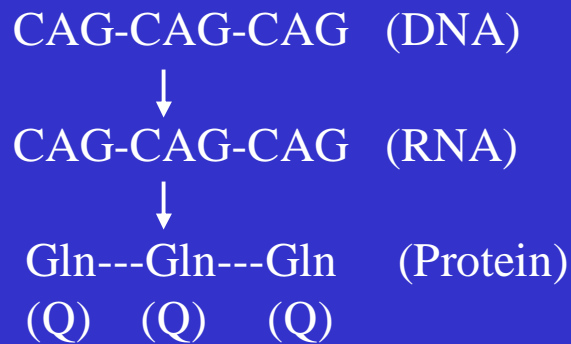
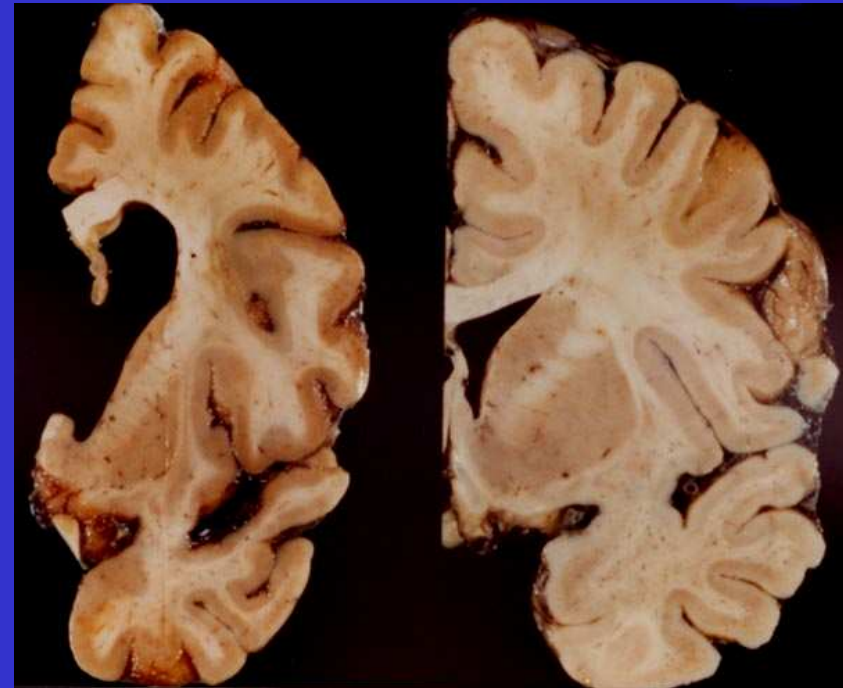
HDSA encourages all attendees to consult with their primary care provider, neurologist or other healthcare provider about any advice, exercise, medication, treatment, nutritional supplement or regimen that may have been mentioned as part of any presentation.

Credits and Conflict of Interest Statement

- Some of the slides and Tetrabenazine (“Xenazine”) info adapted from HSG, FDA, GAHEC, and Creighton University web sites
- No conflicts of interest to declare

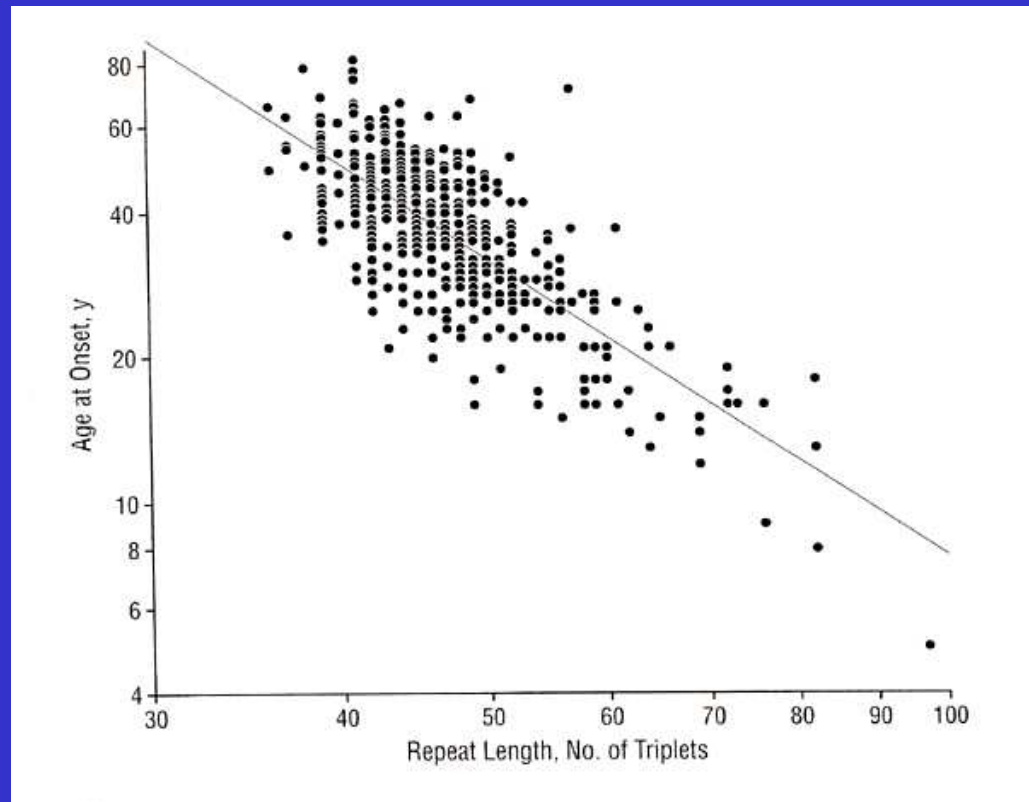
Huntington's Disease

- Selective neuronal degeneration in Basal Ganglia--Caudate and putamen, but also cerebral cortex and other regions
- CAG expansion mutation: longer CAG repeats have earlier onset and more widespread degeneration



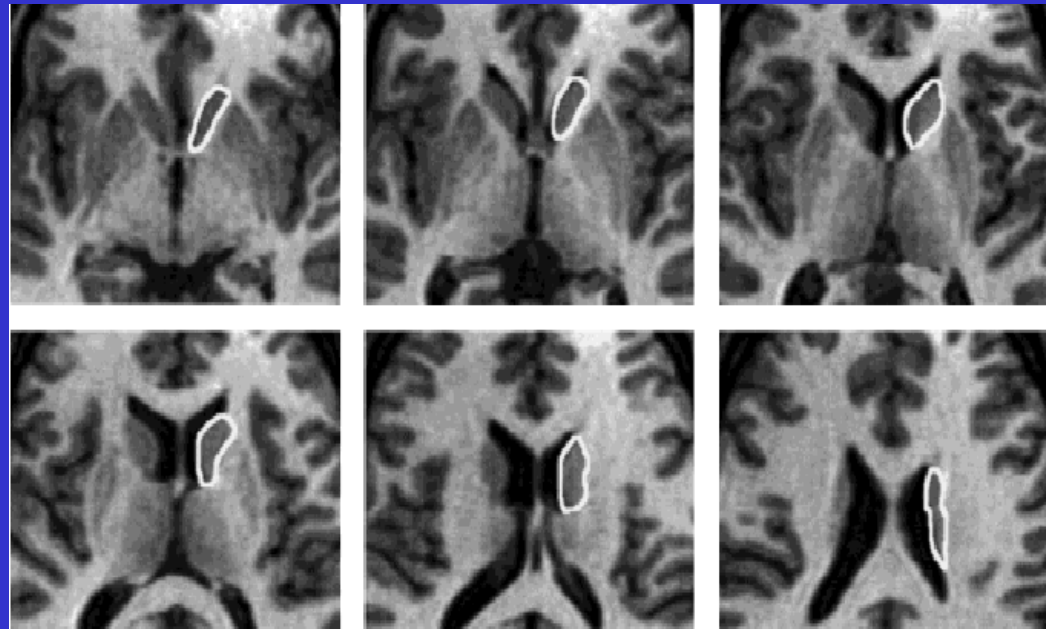
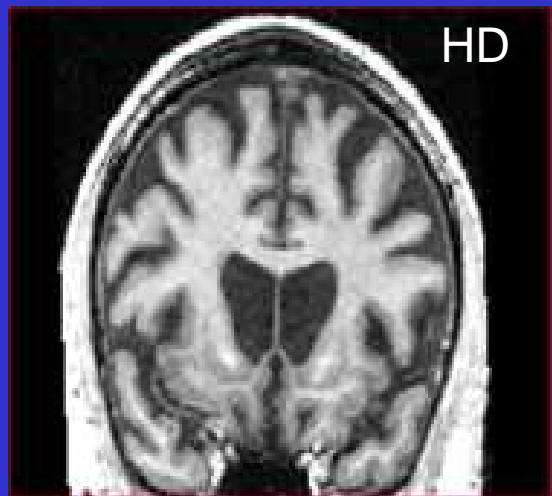
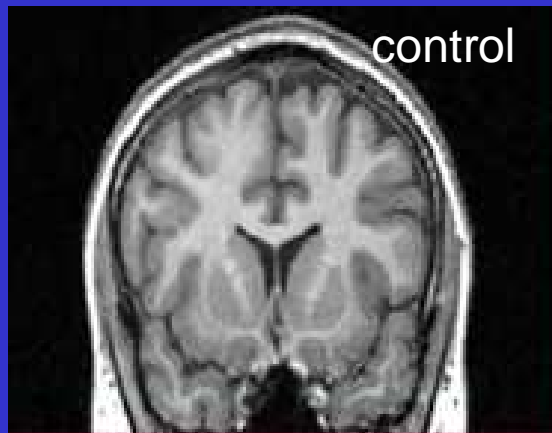
CAG Repeat length and Age of Onset of HD

- CAG repeats of 35 or less do not cause HD
- Incomplete penetrance (delayed onset) for CAG 36 to 40
- Longer expansions result in earlier onset ages—**thus can roughly predict onset age**
- Determinants of the rate of progression are still unknown



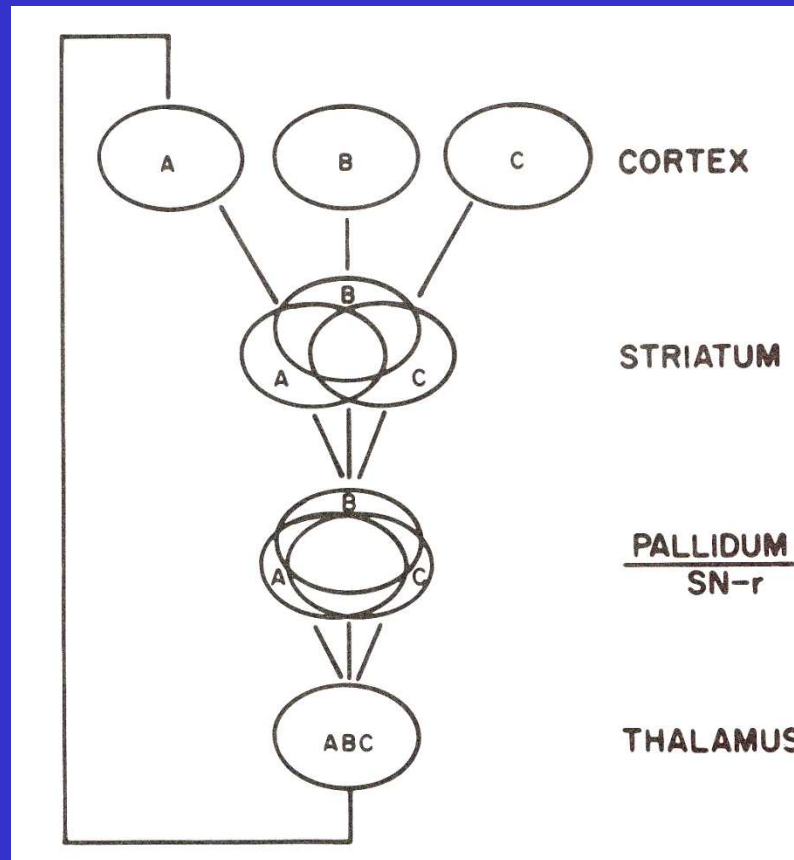
--Ranen et al Am. J. Hum. Genet. 1995, and
Margolis et al Arch. Gen. Psychiat. 1999

Quantification of Caudate Volumes: Regions of Interest



--Aylward et al Neurology 2004

Simplified Basal Ganglia Circuit



Movement Disorder

- Involuntary movements- eg chorea
 - Often begins with hands or feet
 - May also include noises (“vocal tics”)
- Impaired voluntary movements
 - Clumsiness, swallowing, dysarthria, stiffness, slow movements
 - Eventually eclipses the chorea
 - Also “apraxia” difficulty organizing movements in space

Involuntary Movement Disorders

- Terms—”Hyperkinetic,” “Dyskinetic,” “Bradykinetic”
- Chorea (not really “dance-like”....)
- (Athetosis)
- Tics
- “dance-like” gait
- Dystonia
- Bradykinesia and rigidity

- Course: chorea early, but bradykinesia and rigidity late

Cognitive Disorders

- Disorders of “Executive Function”
 - Losses in speed, attention, and flexibility
 - Orientation, memory, language relatively preserved
- Impaired judgment can be a problem
- Mild early; more pronounced problems later

Types of Psychiatric Disturbances

- Mood disorders
 - Depression and mania
- Obsessive-Compulsive symptoms
- “Personality change”
 - Irritability, apathy, disinhibition

Depression

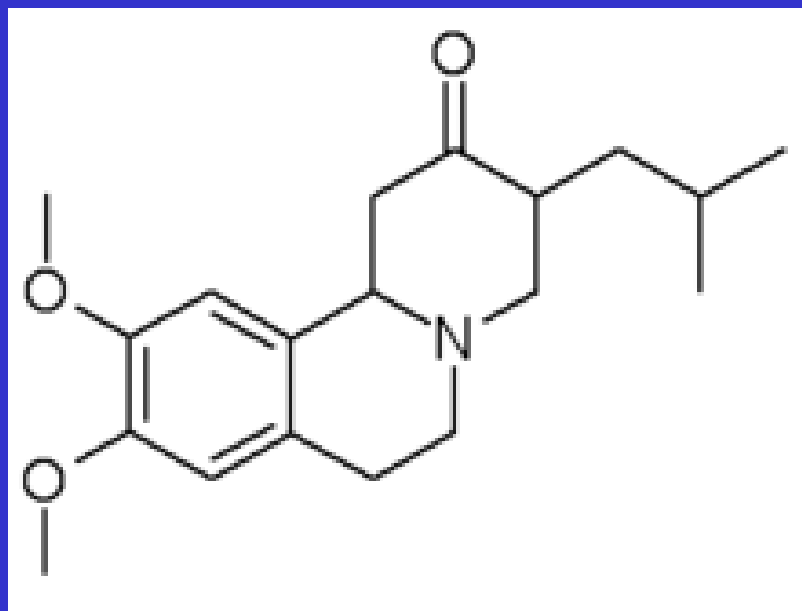
- Sad mood, diminished self-attitude (feeling “helpless and hopeless”), loss of interest in usual activities, poor sleep and appetite etc—suicide is potential complication....
- High prevalence of depression
 - ~40% in HD by some estimates
 - **Suicide rate 4-6x higher than normal**
- May still be underdiagnosed
- Distinguished from apathy

Xenazine[®] - Tetrabenazine

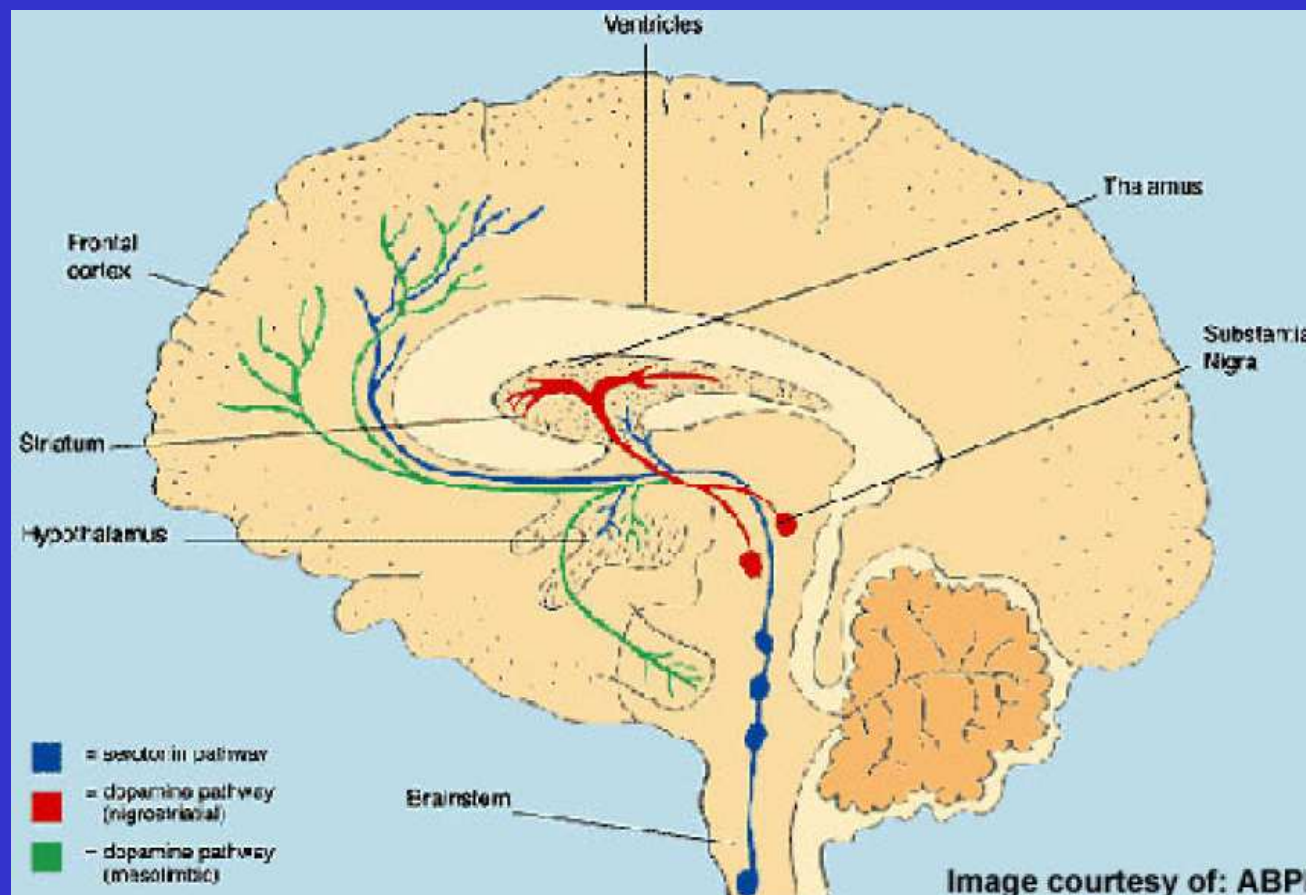
Summary

- Xenazine[®], tetrabenazine, is the first medication with a FDA-approved indication for Huntington's disease associated chorea. FDA Approval Date: 08/2008
- Patients must be thoroughly screened for depression and suicidality, as the FDA has issued a black box warning against using tetrabenazine in patients with depression.
- Also, tetrabenazine should not be used in patients taking reserpine, MAOIs, or drugs that prolong the EKG QTc interval.

Xenazine[®] - Tetrabenazine



Brain Monoamine Pathways



“Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial”

HSG, Neurology. 2006; 66(3): 366-72.

- Objective

- To examine the safety, efficacy, and dose tolerability of tetrabenazine for treating chorea in Huntington disease (HD)

- Study Design

- Multicenter, prospective, randomized, double-blind, placebo-controlled dose-finding study
- 84 randomized → 54 treatment arm; 30 placebo arm
- Treatment group: Dose was increased by 12.5mg /day per week up to 100mg or until desired antichoreic effect or intolerable SEs occurred
- Duration: 12 weeks

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- Inclusion Criteria

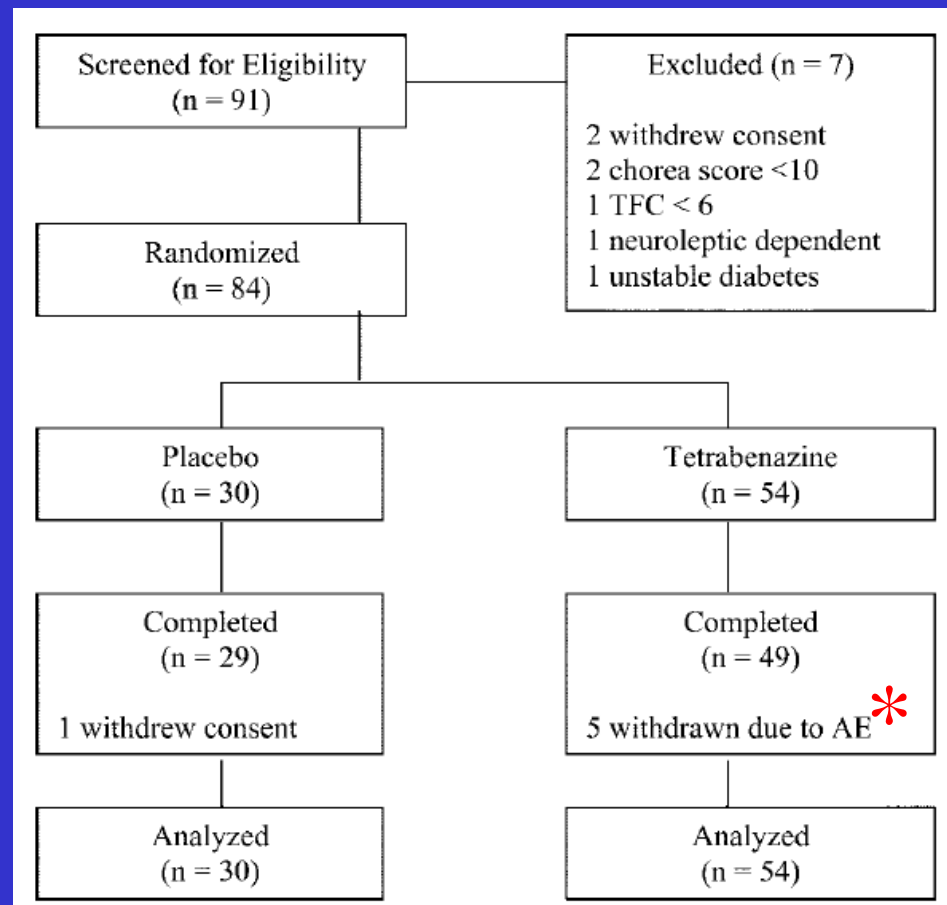
- HD as confirmed by the presence of a characteristic movement disorder (chorea), a family history, and an expanded CAG repeat ($N > 37$)
- Ambulatory with total functional capacity > 5
- Total maximum chorea ≥ 10

- Exclusion Criteria

- Disabling depression, dysphagia, or dysarthria
- Currently taking dopamine-depleting medications, D_2 blockers, dopamine agonists, MAOIs, levodopa, amantadine, or memantine

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*Note—one “completed” suicide.....

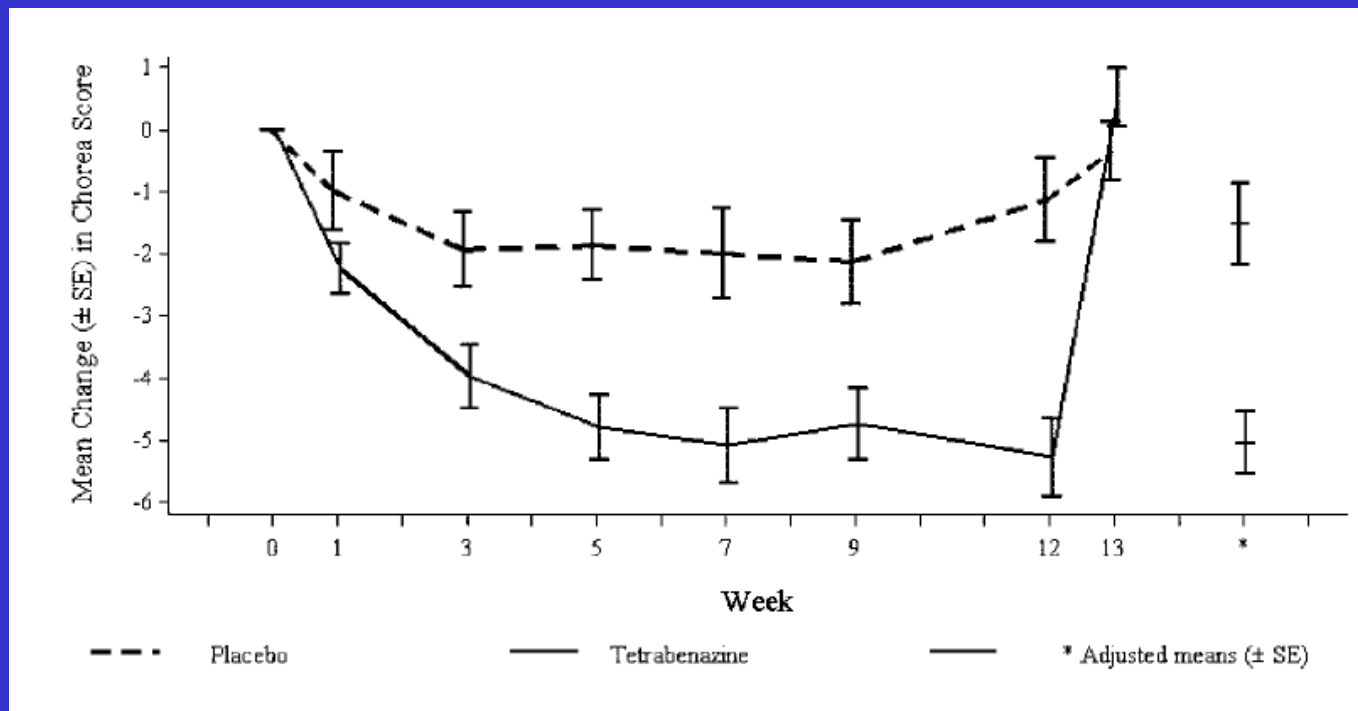
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	Direction of favorable change	Placebo, n = 30	TBZ, n = 54	p Value < 0.05
Primary outcome variable				
Δ UHDRS tot max. chorea	–	–1.5 ± 0.7	–5.0 ± 0.5	0.0001*
Secondary outcome variables				
CGI Global Improvement‡		3.7 ± 0.2	3.0 ± 0.2	0.007*
Δ UHDRS total motor	–	–3.5 ± 1.5	–6.8 ± 1.1	

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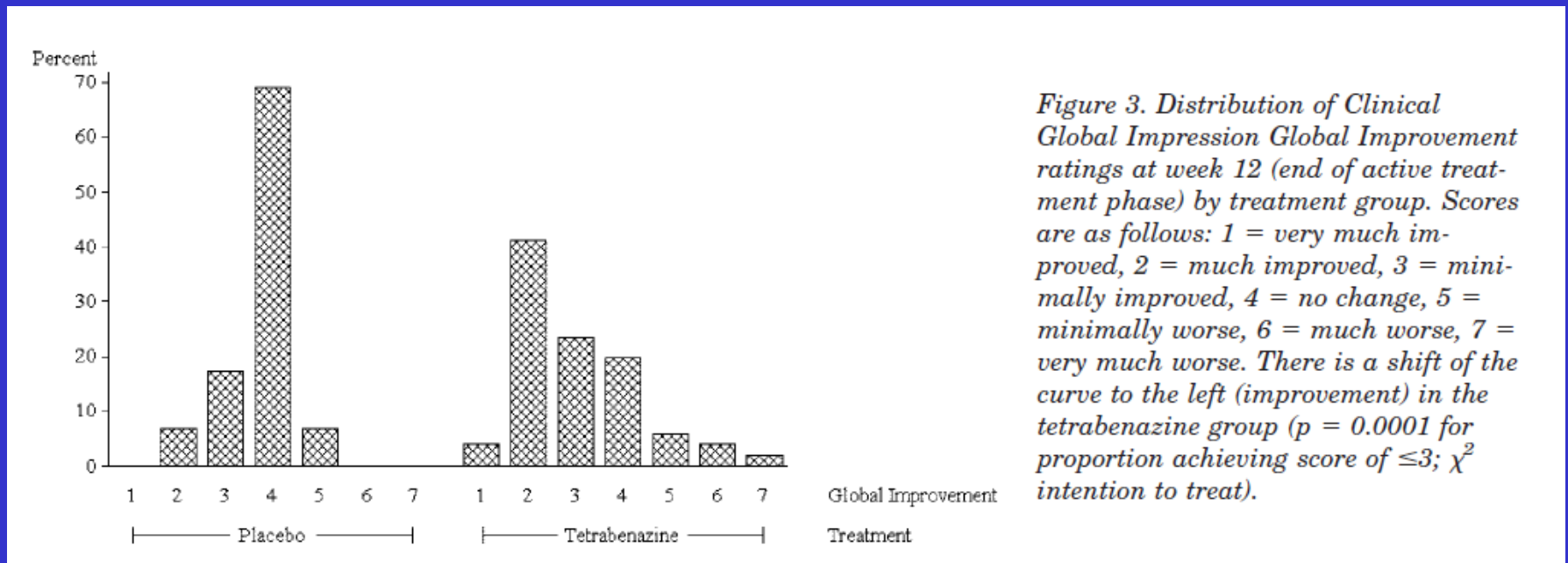
Table 2 Tolerability analyses

Variable	Placebo, n (%), n = 30	TBZ, n (%), n = 54	p Value
Subjects withdrawn (see text)	1 (3.3)	5 (9.3)	NS
Subjects experiencing at least one SAE (see text)	0 (0)	4 (7.4)	NS
New AEs per subject, mean \pm SD			
All	1.5 \pm 1.8	3.8 \pm 3.1	0.0005
Excluding mild	0.6 \pm 0.9	1.9 \pm 2.0	0.0007
Subjects reporting AEs			
All	21 (70.0)	49 (90.7)	0.01
Excluding mild	10 (33.3)	37 (68.5)	0.002
Subjects with week 12 reduced dosage due to intolerability	1 (3.3)	24 (44.4)	<0.0001

TBZ = tetrabenazine; SAE = serious adverse event.

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Xenazine[®] - Tetrabenazine

More Common Adverse Effects

Sedation/somnolence	(31%) [3%]
Fatigue	(22%) [13%]
Insomnia	(22%) [0%]
Depression	(19%) [0%]
Akathisia	(19%) [0%]
Nausea	(13%) [7%]

Xenazine[®] - Tetrabenazine

Contraindications

- “Black Box” warning:
 - Inadequately treated depression and patients who are actively suicidal
- Contraindications and warnings:
 - Hepatic function impairment
 - Concomitant use with MAOIs or reserpine
 - Akathisia
 - CNS depression
 - Esophageal dysmotility/aspiration
 - Neuroleptic Malignant Syndrome
 - Orthostatic Hypotension
 - QT prolongation

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Other Treatment for Chorea

- Dopamine receptor blocking agents
 - Eg haloperidol (“Haldol) and related drugs
- Effective for chorea
- Side effects include sedation, bradykinesia and rigidity (especially in excess)
- Does not cause depression
- Can be helpful for irritability, other emotional symptoms
- Has never been compared to tetrabenazine....

What Potential Benefits to Expect from these Drugs

- Decreased chorea
- MAY help with gait
- Little help for dystonia
- NO benefit for incoordination, slow or stiff movements

- Thus these drugs of most benefit early in the course of HD, less benefit later

- First (symptomatic) treatment for HD....we look for more to come in the future....



