Huntington’s Disease: Movement Disorders and Treatment

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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

\[
\begin{align*}
\text{CAG-CAG-CAG} & \quad \text{(DNA)} \\
\downarrow & \\
\text{CAG-CAG-CAG} & \quad \text{(RNA)} \\
\downarrow & \\
\text{Gln---Gln---Gln} & \quad \text{(Protein)} \\
(Q) & \quad (Q) \quad (Q)
\end{align*}
\]
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

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”

• **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 \( \rightarrow \) 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 int tolerable SEs occurred
  – Duration: 12 weeks
“Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial”

• 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, D₂ blockers, dopamine agonists, MAOIs, levodopa, amantadine, or memantine
“Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial”

Note—one “completed” suicide......
“Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial”

<table>
<thead>
<tr>
<th>Direction of favorable change</th>
<th>Placebo, n = 30</th>
<th>TBZ, n = 54</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome variable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ UHDRS tot max. chorea</td>
<td>−</td>
<td>−1.5 ± 0.7</td>
<td>−5.0 ± 0.5</td>
</tr>
<tr>
<td>Secondary outcome variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI Global Improvement‡</td>
<td>3.7 ± 0.2</td>
<td>3.0 ± 0.2</td>
<td>0.007*</td>
</tr>
<tr>
<td>Δ UHDRS total motor</td>
<td>−</td>
<td>−3.5 ± 1.5</td>
<td>−6.8 ± 1.1</td>
</tr>
</tbody>
</table>
“Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial”
“Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial”

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Tolerability analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo, n (%), n = 30</td>
</tr>
<tr>
<td>Subjects withdrawn (see text)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Subjects experiencing at least one serious adverse event (SAE) (see text)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>New AEs per subject, mean ± SD</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1.5 ± 1.8</td>
</tr>
<tr>
<td>Excluding mild</td>
<td>0.6 ± 0.9</td>
</tr>
<tr>
<td>Subjects reporting AEs</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>21 (70.0)</td>
</tr>
<tr>
<td>Excluding mild</td>
<td>10 (33.3)</td>
</tr>
<tr>
<td>Subjects with week 12 reduced dosage due to intolerability</td>
<td>1 (3.3)</td>
</tr>
</tbody>
</table>

TBZ = tetrabenazine; SAE = serious adverse event.
“Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial”

Figure 3. Distribution of Clinical Global Impression Global Improvement ratings at week 12 (end of active treatment phase) by treatment group. Scores are as follows: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse. There is a shift of the curve to the left (improvement) in the tetrabenazine group \( (p = 0.0001 \) for proportion achieving score of \( \leq 3; \chi^2 \) intention to treat).
More Common Adverse Effects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation/somnolence</td>
<td>(31%)</td>
<td>[3%]</td>
</tr>
<tr>
<td>Fatigue</td>
<td>(22%)</td>
<td>[13%]</td>
</tr>
<tr>
<td>Insomnia</td>
<td>(22%)</td>
<td>[0%]</td>
</tr>
<tr>
<td>Depression</td>
<td>(19%)</td>
<td>[0%]</td>
</tr>
<tr>
<td>Akathisia</td>
<td>(19%)</td>
<td>[0%]</td>
</tr>
<tr>
<td>Nausea</td>
<td>(13%)</td>
<td>[7%]</td>
</tr>
</tbody>
</table>
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….