Movement and HD: Medical Management of Motor Symptoms

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HDSA Convention 2012
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Presenter Disclosures

Victor Sung, MD

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

Served as a Consultant for Lundbeck, and the use of their product(s) will be discussed in this talk.
Medical Management of Motor Symptoms of HD

• Summary of Motor Symptoms
• Current Treatments
  – FDA-approved
  – Non FDA-approved
  – Summary of Scientific Data
• Multi-drug therapy
• Drug Interactions
• Real World Scenarios
• Summary
Introduction

- Though we don’t have a cure, there IS HOPE!
- Contrary to the impressions of many physicians, the motor symptoms of HD CAN be adequately managed!
Motor Symptoms of HD
Motor Symptoms of HD

• Importance
  – Prior to genetic testing (CAG repeat) availability, HD diagnosed by *motor* symptoms
  – Even now, onset of disease is defined by onset of *motor* symptoms

• Categorization
  – By stage of disease (early, middle, late)
  – By type of movement (chorea, dystonia, tics, myoclonus, rigidity, etc)
Types of Motor Symptoms

• Abnormal Involuntary Movements
  – Chorea
  – Dystonia
  – Tics / myoclonus

• Parkinsonism (Rigidity / bradykinesia)

• Speech / Swallowing Problems

• Balance/Walking Problems & Falls

• Eye Movement Abnormalities
Stages of Motor Symptoms

• Early Stage HD
  – Changes in coordination
    • Less control of handwriting
    • More difficulty with tasks like driving
  – Mild beginning of chorea
    • Fidgeting
    • Restlessness
  – Myoclonus / Tics
    • Irregular, sudden jerks
    • Facial twitch
Stages of Motor Symptoms

• **Middle Stage HD**
  – Chorea
    • Arms – dropping items
    • Legs – affecting gait
    • Trunk – writhing movements
  – Balance / walking problems
    • Stumbling, near falls
  – Speech / swallowing problems
    • Slurring of speech, coughing with food
  – Slow reaction time
Stages of Motor Symptoms

- Late Stage HD
  - Parkinsonism
    - Rigidity (stiffness of muscles)
    - Bradykinesia (slowness of movement)
  - Dystonia
  - Severe speech / swallowing problems
    - Unintelligible speech
    - Choking
  - Loss of independence for ambulation
  - Inability to perform activities of daily living
Current Treatments for Motor Symptoms of HD
## Motor Symptoms of HD

<table>
<thead>
<tr>
<th>Specific Medical Treatments Available</th>
<th>NO Specific Medical Treatment Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorea</td>
<td>Speech problems</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Swallowing problems</td>
</tr>
<tr>
<td>Tics</td>
<td>Balance / Walking problems</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Falls</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>Eye Movement Abnormalities</td>
</tr>
</tbody>
</table>
Why Bother Treating These?

• Have you heard that argument?
  – The left column is less debilitating than the right column

• Because…
  – There is no ‘magic’ walking / swallowing / coordination improvement pill…and likely never will be!
  – These abnormal movements CAN be treated and DO contribute significantly to the other items on the right
  – Doing nothing is NOT an option – what do we have to lose??
Current Medical Treatments – Abnormal Involuntary Movements

• Chorea
  – Tetrabenazine (Xenazine)
    • FDA-approved in August 2008 for HD chorea
    • Data comes from Huntington’s Study Group trial called Tetra-HD
    • Not stocked in retail pharmacies
Tetrabenazine for HD

- **Tetra-HD**
  - 12-week randomized, double-blind, placebo-controlled multicenter trial
  - 16 Huntington's Study Group sites in the US
  - 84 Patients Enrolled
    - 54 randomized to tetrabenazine
    - 30 randomized to placebo
  - **Results**: Mean 23.5% reduction in chorea that returned to baseline during washout
  - Avg. dose in trial was 75mg/day
Tetrabenazine for HD

• What about the “black box” warning for depression / suicide?
  – In Tetra-HD, 1 suicide, 4 with worsened depression
  – My clinical experience

• What about the cost?
  – Very expensive, but usually covered by insurance
  – My experience with Reach Program

• Does it really work?
  – My patient stories…
Current Medical Treatments – Abnormal Involuntary Movements

• Chorea
  – Typical antipsychotics
    • **High potency**: haloperidol, fluphenazine, prochlorperazine
    • **Medium potency**: perphenazine, thiothixene, loxapine, trifluoperazine
    • **Low potency**: chlorpromazine, thioridazine
Current Medical Treatments – Abnormal Involuntary Movements

• Chorea
  – Typical antipsychotics
    • The higher the potency, the greater the effect on motor symptoms and less side effects
    • **Use of benztropine (Cogentin) is counter-productive in HD as it blocks the motor effects of the antipsychotic!**
Current Medical Treatments – Abnormal Involuntary Movements

• Chorea
  – Atypical antipsychotics
    • Risperidone, olanzapine, ziprasidone, aripiprazole
    • Quetiapine, clozapine (do NOT help chorea)
    • Black box warning for early death in elderly
  – Amantadine
    • Safe but mixed results
Typicals vs. Atypicals

• **Efficacy**
  – Generally, typicals more potent for motor symptoms
  – Equal efficacy for psychotic symptoms

• **Cost**
  – Typical: Haloperidol, fluphenazine, prochlorperazine, thioridiazine, thiothixene all on $4 List
  – Most atypicals branded
## Typical vs. Atypical – Side Effects

<table>
<thead>
<tr>
<th>Typical</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ Weight Gain</td>
<td>++ Weight Gain / Metabolic Syndrome **</td>
</tr>
<tr>
<td>++ Tardive dyskinesia**</td>
<td>+/- Tardive Dyskinesia</td>
</tr>
<tr>
<td>+/- Sedation</td>
<td>++ Sedation</td>
</tr>
<tr>
<td>+ Dry mouth</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>+ Orthostatic hypotension</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>+ Parkinsonism</td>
<td>Parkinsonism</td>
</tr>
<tr>
<td>+ Dystonia</td>
<td>Dystonia</td>
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</tbody>
</table>
Other Treatments

• Amantadine
  – One study using 400mg/day showed some reduction in chorea
  – One study using 300mg/day showed no benefit
  – Overall well tolerated

• Benzodiazepines
  – Not directly beneficial but decrease stress amplification component
Current Medical Treatments – Abnormal Involuntary Movements

- **Dystonia**
  - Botulinum toxin injections if focal
- **Parkinsonism (rigidity/bradykinesia)**
  - Can use small dose carbidopa/levodopa
- **Myoclonus / Tics**
  - Benzodiazepines
  - Anticonvulsants (topiramate, levetiracetam)
  - Clonidine
Other Therapies

• Healthy, balanced diet
  – High protein or supplements (creatine/CoQ10)
• Exercise
• Physical Therapy, Occupational Therapy, Speech Therapy
  – All shown to be beneficial
  • Cost can be a barrier for some
  – Importance of a multidisciplinary clinic if available
Surgical Treatments

• Deep Brain Stimulation Surgery
  – For medically refractory chorea (and possibly dystonia, tics)
  – A few case reports
Multi-Drug Therapy
Multi-Drug Therapy

- Often not done out of fear of side effects
- Possible combinations
  - TBZ + typical antipsychotic
  - TBZ + atypical antipsychotic
  - Multiple antipsychotics (typical + atypical)
  - Any of above + Amantadine
  - Any of above + Benzodiazepine
Drug Interactions
Drug Interactions

• Typical antipsychotic + Tetrabenazine
  – Some can increase levels of tetrabenazine
  – In general, additive effects can cause more side effects (sedation, cardiac arrhythmias)

• Paroxetine or Fluoxetine + Tetrabenazine
  – Both are on $4 List, commonly used
  – When taken in combination with tetrabenazine, should HALF the dose of tetrabenazine
Drug Interactions

- Multiple antipsychotics
  - Typical + Atypical can be used with caution
  - In general, not recommended to use multiple typicals or multiple atypicals

- Decongestants
  - Many will increase levels of tetrabenazine and antipsychotics

- Coumadin
  - Surprisingly, no major drug interactions
Real World Scenarios
Real World Scenarios

• Very mild chorea on exam
  – Chorea doesn’t bother patient
  – Prominent depression, cries during exam, follows with a psychiatrist

• Mild-moderate chorea on exam, tripping/falls
  – On no treatment
  – Reports depression
Real World Scenarios

• Patient is on tetrabenazine 25mg 3x/day
  – What if chorea is better but now developing depression?
    • Options?

  – What if chorea still not better on that dose?
    • Options?
Real World Scenarios

• Primarily psychiatric symptoms, controlled on a typical antipsychotic for many years
  – Now beginning to develop uncomfortable movements in abdomen

• Some mild chorea on exam, already on olanzapine 10mg daily
  – Olanzapine primarily for psychiatric purposes
Summary
Bottom Line

• There IS hope – there ARE treatments that can help
• So what do I really do?
  – Push towards early treatment – why?
    • Is the alternative of doing nothing really better?
    • Analogy of chemotherapy for cancer
  – If pure motor symptoms, TBZ first
  – If motor symptoms but some depression, add SSRI first to stabilize then add TBZ
  – If equally mixed motor/psychiatric, antipsychotic first
  – Weigh typicals vs. atypicalys based on side effects and cost
Horizon Treatments

- Not enough time in this lecture, but…
- Pridopidine (ACR-16/Huntexil)
  - Looks promising for chorea but less side effects
  - FDA wants another Phase III trial to prove efficacy
- ??Virtual Cures
  - Gene silencing technologies
    - Sirtuin-1 Inhibition (histones)
    - Small interfering RNA (siRNA)
    - Antisense oligonucleotides (ASO)
    - RNA interference (RNAi)
References / Resources

• Stanford University’s HOPES (Huntington’s Outreach Project for Education at Standford) site:
  – https://www.stanford.edu/group/hopes/cgi-bin/wordpress/

• Huntington’s Disease Drug Works Site:
  – http://hddrugworks.org

• HD Lighthouse
  – http://www.hdlf.org

• WEMOVE.org’s Free HD Caregiver Guide (PDF)
Acknowledgements

- HDSA / UAB Center of Excellence
- HD Patients and Families