



Movement and HD: Medical Management of Motor Symptoms

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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

Specific Medical Treatments Available	NO Specific Medical Treatment Available
Chorea	Speech problems
Dystonia	Swallowing problems
Tics	Balance / Walking problems
Myoclonus	Falls
Parkinsonism	Eye Movement Abnormalities

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**
 - Typicals: Haloperidol, fluphenazine, prochlorperazine, thioridazine, thiothixene all on \$4 List
 - Most atypicals branded

Typicals vs. Atypicals – Side Effects

Typicals	Atypicals
+ Weight Gain	++ Weight Gain / Metabolic Syndrome **
++ Tardive dyskinesia**	+/- Tardive Dyskinesia
+/- Sedation	++ Sedation
+ Dry mouth	Dry mouth
+ Orthostatic hypotension	Orthostatic hypotension
+ Parkinsonism	Parkinsonism
+ Dystonia	Dystonia

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

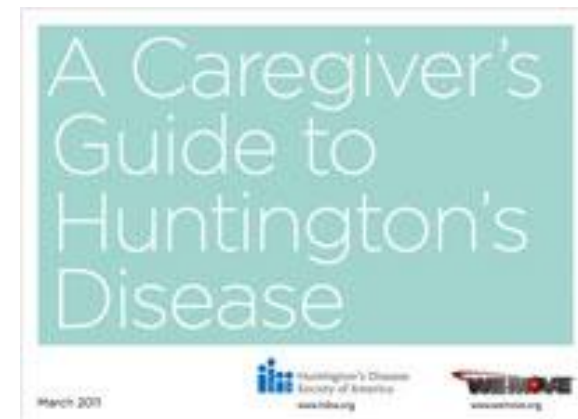
- There IS hope – there ARE treatments that can help
- So what do I really do?
 - Push towards early treatment – why?
 - Is the alternative of doing nothing really better?
 - Analogy of chemotherapy for cancer
 - If pure motor symptoms, TBZ first
 - If motor symptoms but some depression, add SSRI first to stabilize then add TBZ
 - If equally mixed motor/psychiatric, antipsychotic first
 - Weigh typicals vs. atypicals 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)
 - http://www.mdvu.org/downloads/HD_CGG_4.pdf



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