Medications for Early/Mid Stage HD

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Disclosures

• Dr Moore has nothing to disclose
Levels of Treatment for HD

• Symptomatic treatment – direct treatments for the manifestations of HD caused by abnormal (mutant) gene expression

• Neuroprotective treatment – treatment to protect nerve cells from the effects of abnormal protein formation

• Preventive treatment – treatment to prevent mutant gene expression

• Curative treatment – treatment that reverses the effects of mutant gene expression
A Challenging Enigma in HD - Facts

• The genetic abnormality in HD is an expansion of a CAG repeat zone in the huntingtin gene on chromosome 4; the only difference is in the number of repeats but this is almost always between 40 and 50.

• Nevertheless, all HD patients are not alike
Phenotypic Expressions of the HD Gene – Types of HD

- Juvenile HD (prepubertal onset, ~7% of cases)
  - Rigidity
  - Slowness and stiffness
  - Awkwardness in walking
  - Clumsiness and frequent falls
  - Difficulty in speaking
  - Choking and drooling
  - Behavioural/personality changes
  - Slowness in responding
  - Variable/poor school performance
  - Seizures
- Summary: an akinetic-rigid syndrome with few movements, severe behavioral manifestations and seizures
Phenotypic Expressions of the HD Gene – Types of HD

• Adult Onset

1. Chorea and other motor signs predominate, behavioral manifestations less prominent

2. Behavioral signs predominate, motor signs less prominent

3. Motor and behavioral manifestations are both prominent, mixed form

4. Akinetic-rigid, motor signs predominate
The Clinical Course of HD

• Prodromal period – brain pathology has begun, intermittent movements, a bit clumsy, basic personality traits become more pronounced

• Early phase – clear motor and/or behavioral changes but able to function quite well

• Middle phase – signs and symptoms more pronounced, function is impaired, unable to live independently

• Late phase – motor and cognitive function severely impaired, requires total care
Medical Therapy

• Motor manifestations

1. Chorea (jerking, involuntary movements)
2. Ataxia (unsteadiness walking)
3. Dysarthria (unclear speech), difficulty swallowing
Medical Therapy

• Motor manifestations

Chorea (jerking, involuntary movements)
  - tetrabenazine
  - atypical anti-psychotics
    1. risperidone (Risperdal)
    2. quetiapine (Seroquel)
    3. ziprasidone (Geodon)
    4. clozapine (Clozaril)
Neurons - Information Processing Cells of the Brain

- Dendrites
- Cell body
- Axon
- Direction of message
- Axon terminals synapse with dendrites on target cell
Dopamine Neurotransmission
Chorea is thought to occur because of an abnormality in dopamine signalling in the putamen.
Dopamine Terminal

- Dopamine
- VMAT 2
- Synaptic Vesicle

In the diagram:
- Neuron releasing dopamine
- Tyrosine → L-dopa → Dopamine
- Dopamine is broken down by monoamine oxidase
- Autoreceptors
- Recaptured dopamine
- G protein
- Receptor
- Target neuron
Tetrabenazine
(Prestwick Pharmaceuticals)

side effects with TBZ, most report mild symptoms such as drowsiness, constipation, insomnia (already a common occurrence in HD), akathisia, drooling, weakness, and depression.
Action of Tetrabenazine

Normal synaptic vesicle containing dopamine

Tetrabenazine

Synaptic vesicle depleted of dopamine
Action of Tetrabenazine
Atypical Antipsychotics

Atypical anti-psychotics

1. risperidone (Risperdal)
2. quetiapine (Seroquel)
3. ziprasidone (Geodon)
4. clozapine (Clozaril)

Block dopamine receptors
Dopamine Receptors

DA 1, DA 2 – motor
DA 3 – DA 5 – other functions
Side Effects of Atypical Antipsychotics

- **Side effects**
- **Urgent Side Effects**
- Allergic reaction: hives; difficulty breathing; swelling of your face, lips, tongue, or throat.
- Worsening behavioral symptoms such as: mood or behavior changes, anxiety, panic attacks, trouble sleeping, or if you feel impulsive, irritable, agitated, hostile, aggressive, restless, hyperactive (mentally or physically), more depressed, or have thoughts about suicide or hurting yourself.

Other serious side effects include:
- fever, stiff muscles, confusion, sweating, fast or uneven heartbeats;
- jerky muscle movements you cannot control
- sudden numbness or weakness, especially on one side of the body;
- sudden headache, confusion, problems with vision, speech, or balance;
- increased thirst, frequent urination, excessive hunger, or weakness;
- feeling like you might pass out
- weight gain, diabetes

Less serious side effects may include:
- dizziness, drowsiness, or weakness;
- dry mouth, runny nose, sore throat;
- nausea, vomiting, stomach pain, constipation;
- blurred vision, headache, anxiety, agitation;