

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**

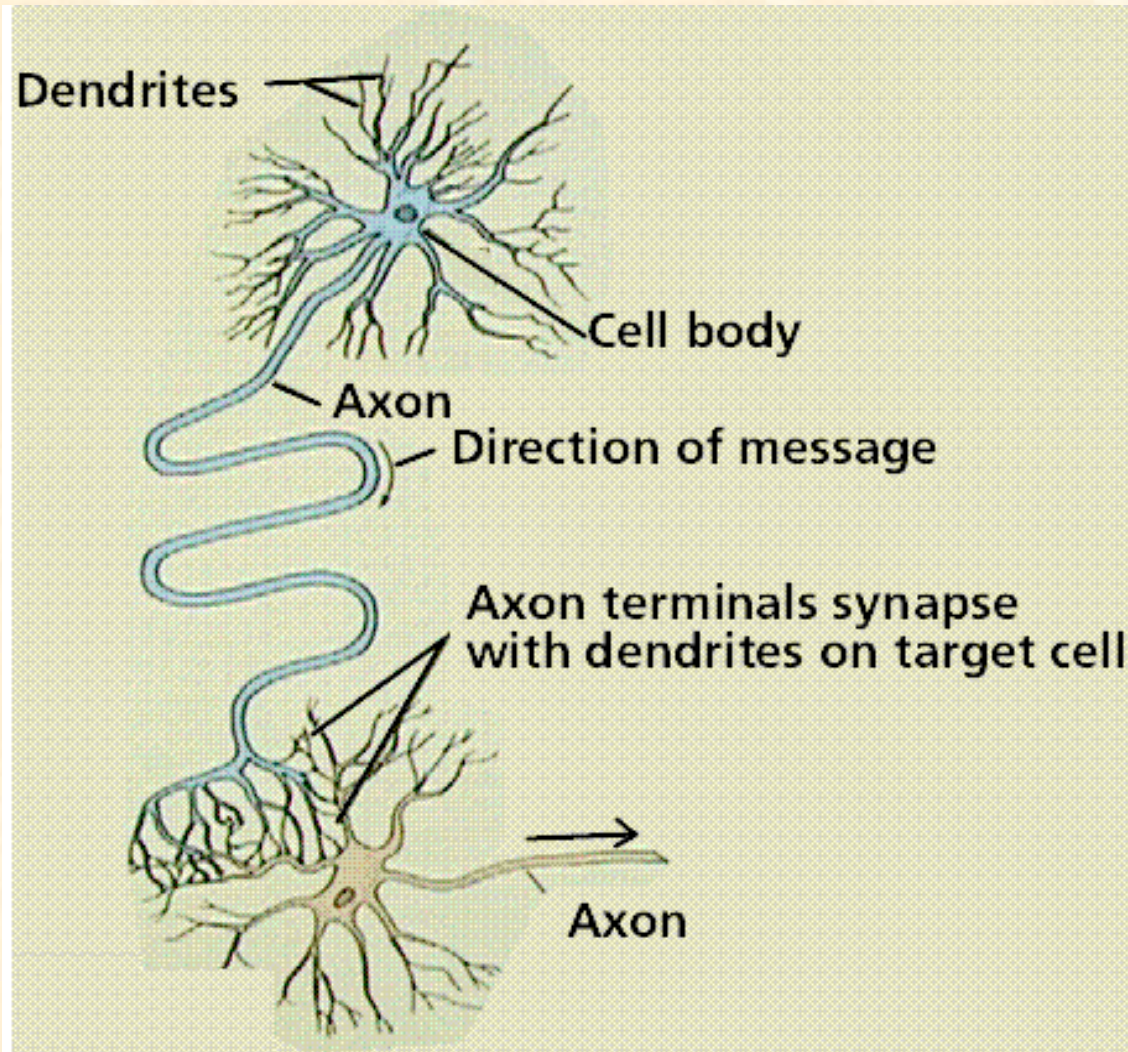
Medical Therapy

- **Motor manifestations**

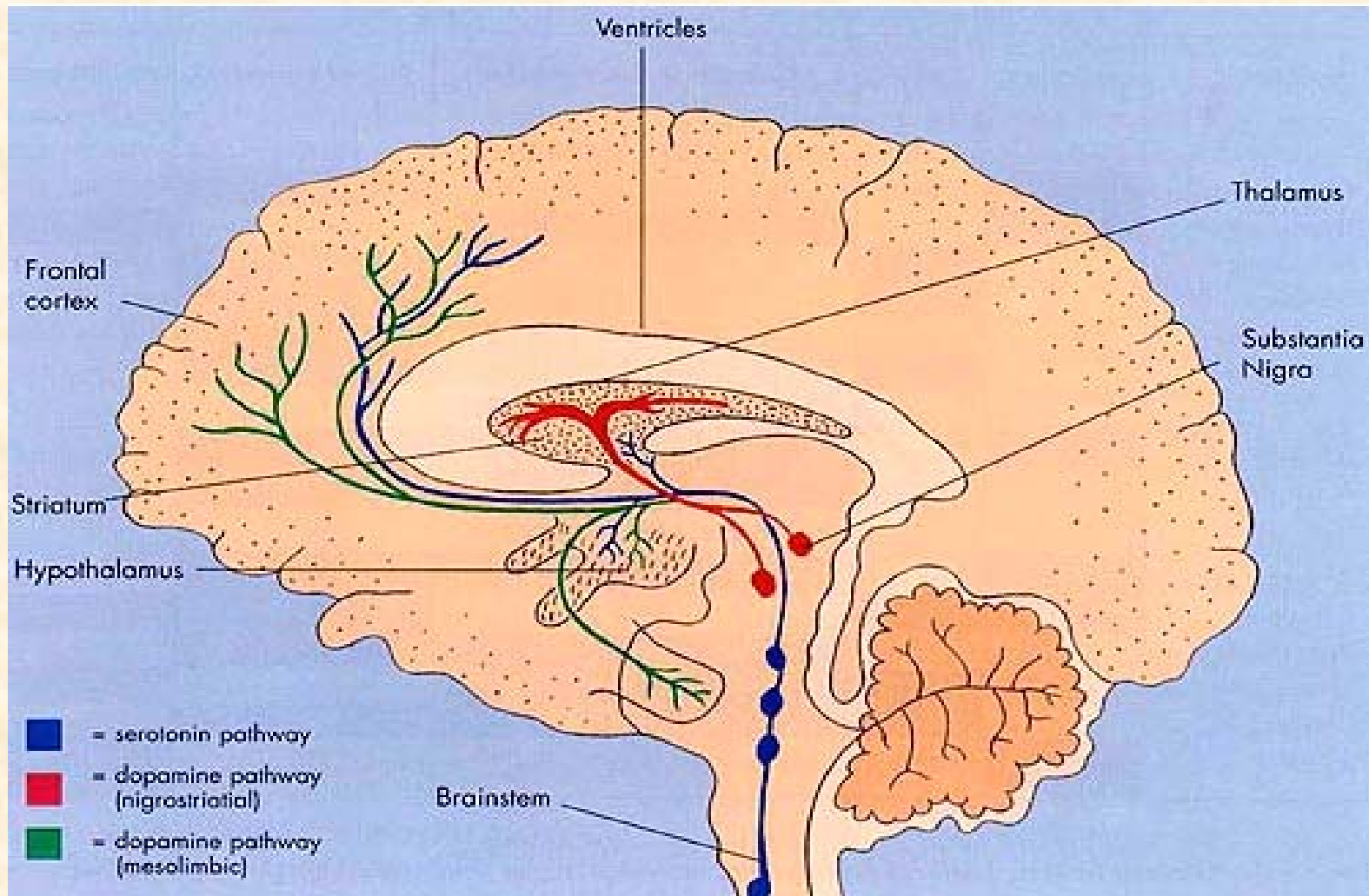
Chorea (jerking, involuntary movements)

- **tetrabenazine**
- **atypical anti-psychotics**
 1. **risperidone (Risperdal)**
 2. **quetiapine (Seroquel)**
 3. **ziprasidone (Geodon)**
 4. **clozapine (Clozaril)**

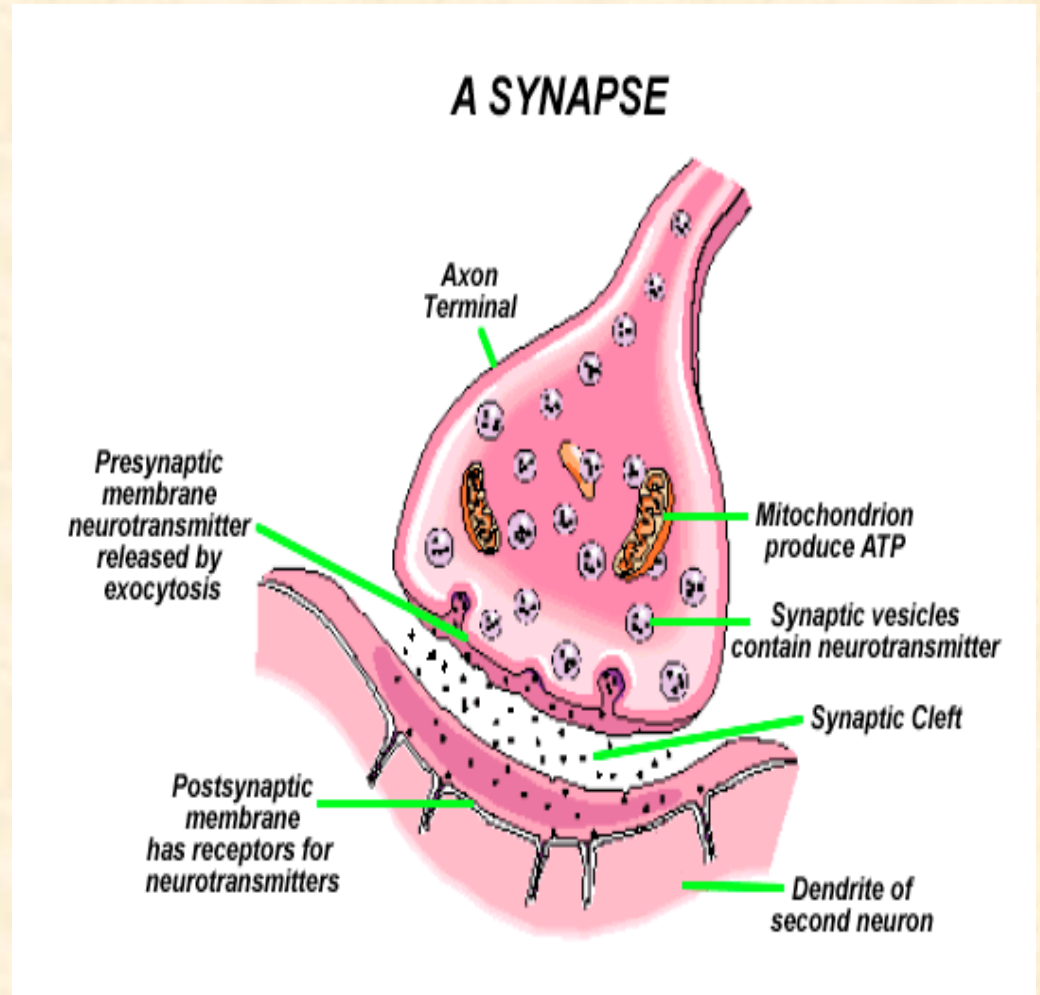
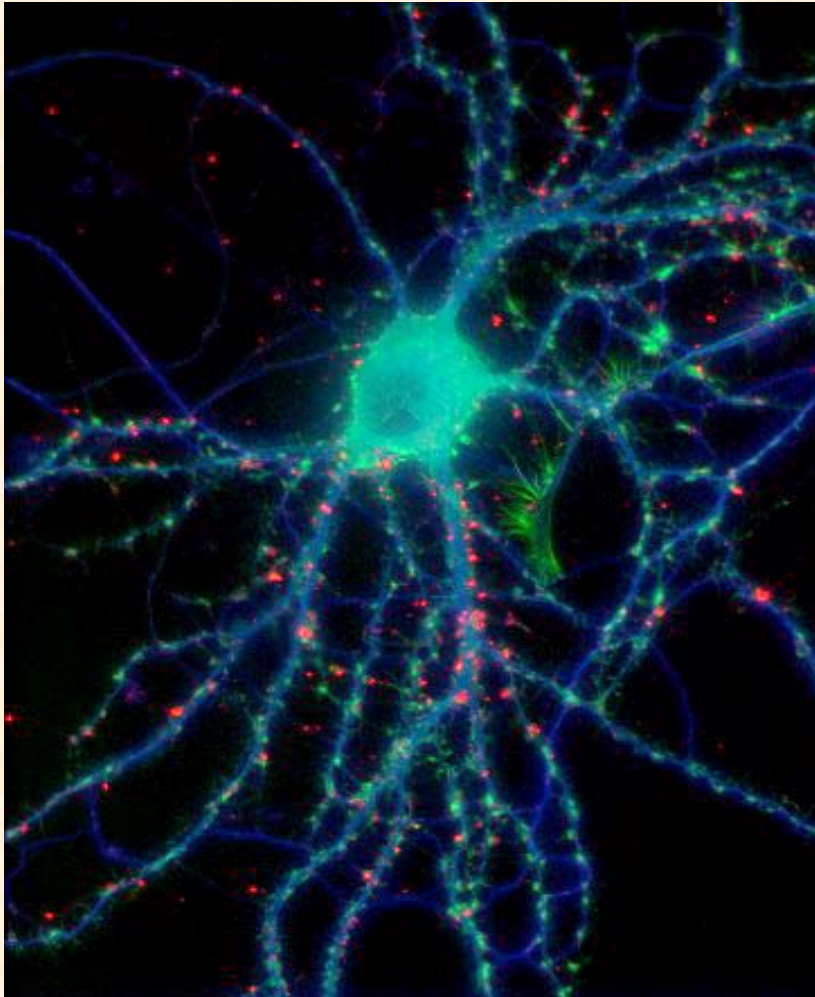
Neurons - Information Processing Cells of the Brain



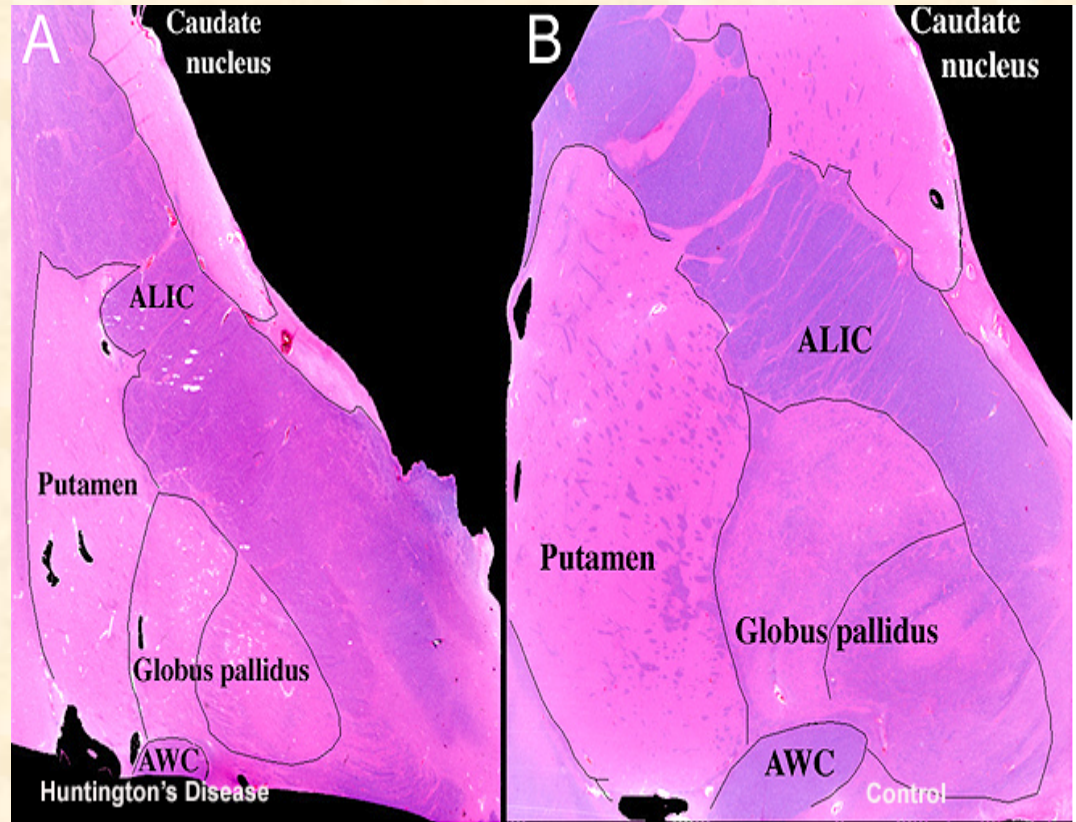
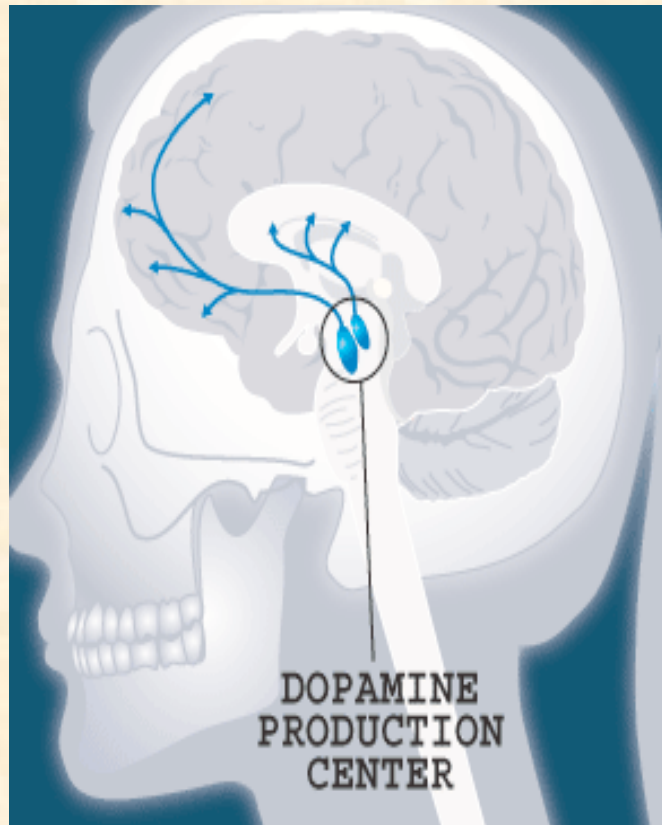
Dopamine Neurotransmission



Synaptic Transmission

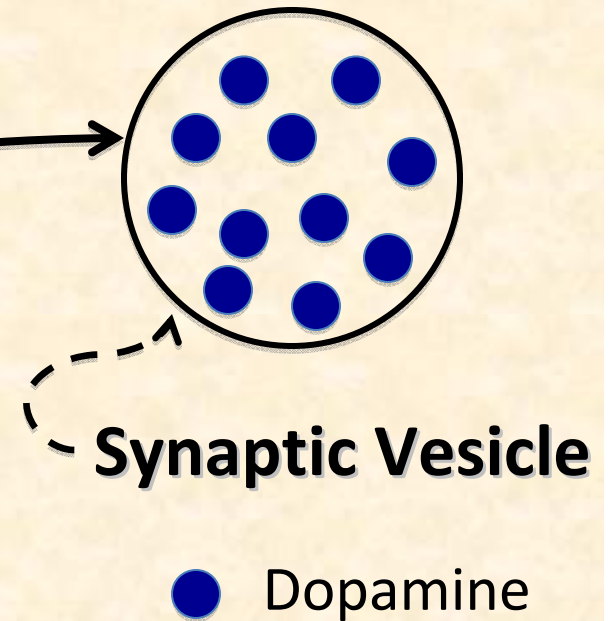
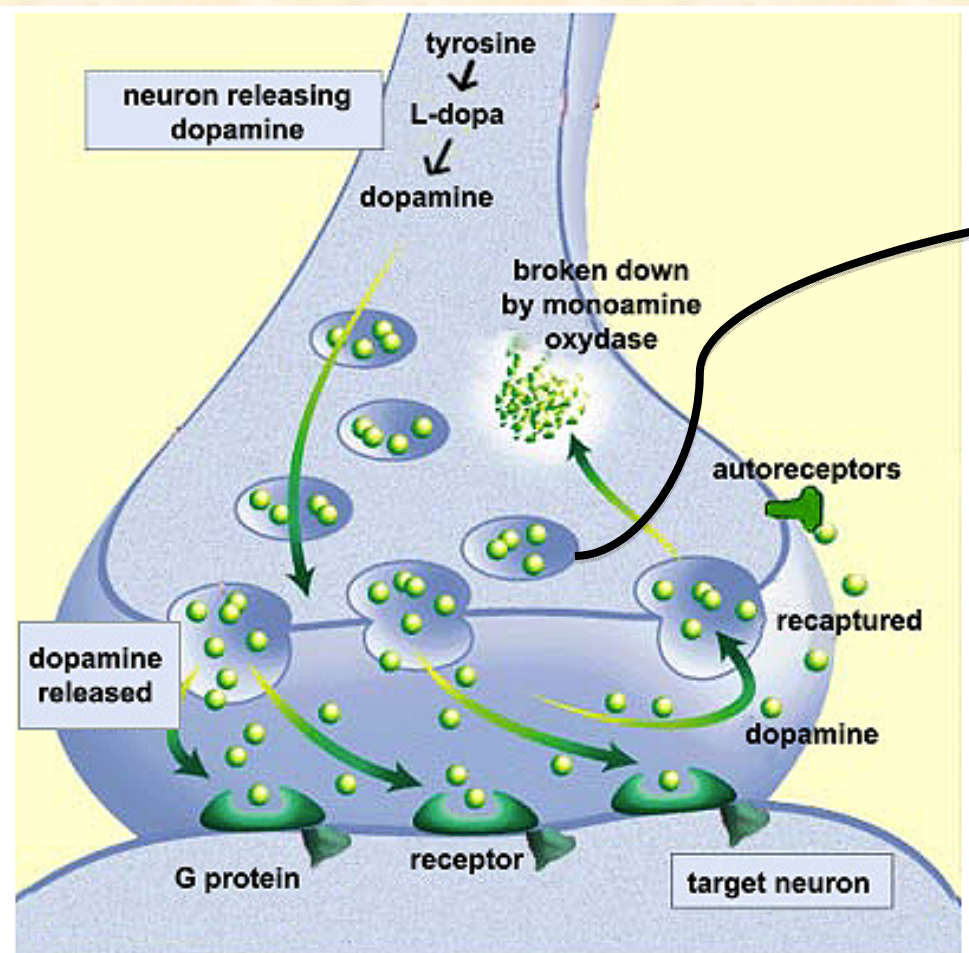


Dopamine Neurotransmission

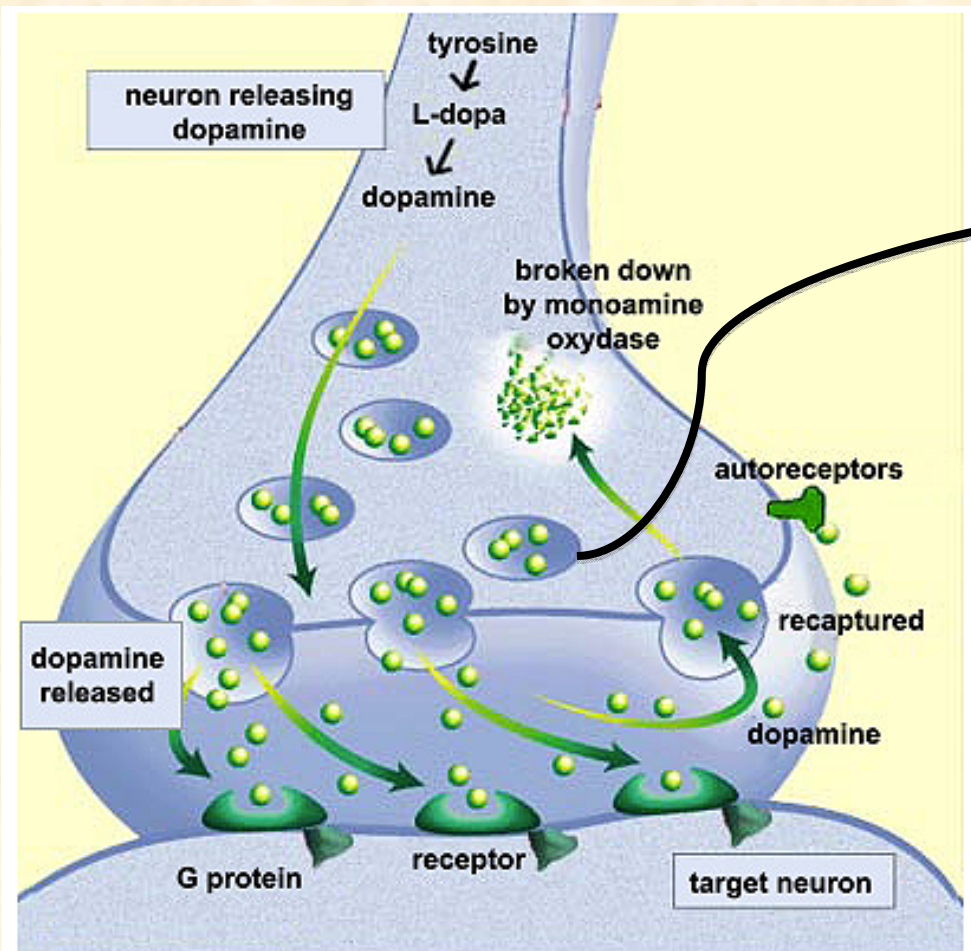


Chorea is thought to occur because of an abnormality in dopamine signalling in the putamen

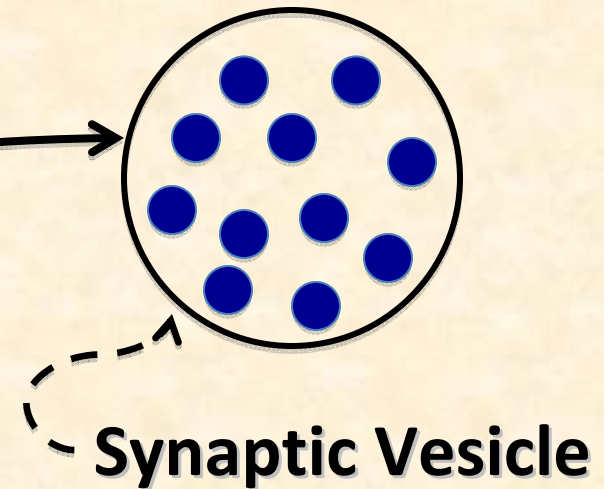
Dopamine Terminal



Dopamine Terminal

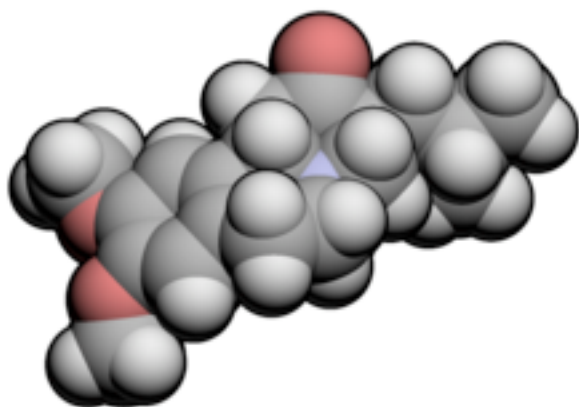
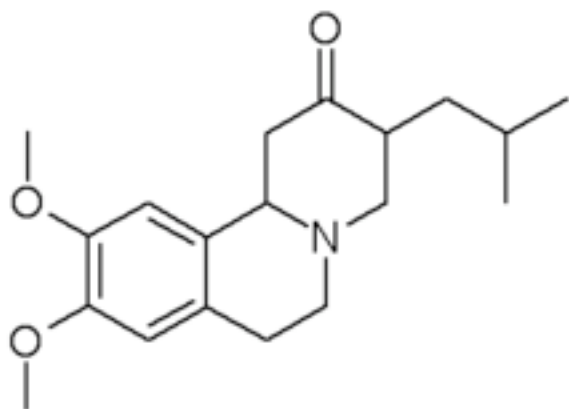


● Dopamine
↓
VMAT 2



Tetrabenazine

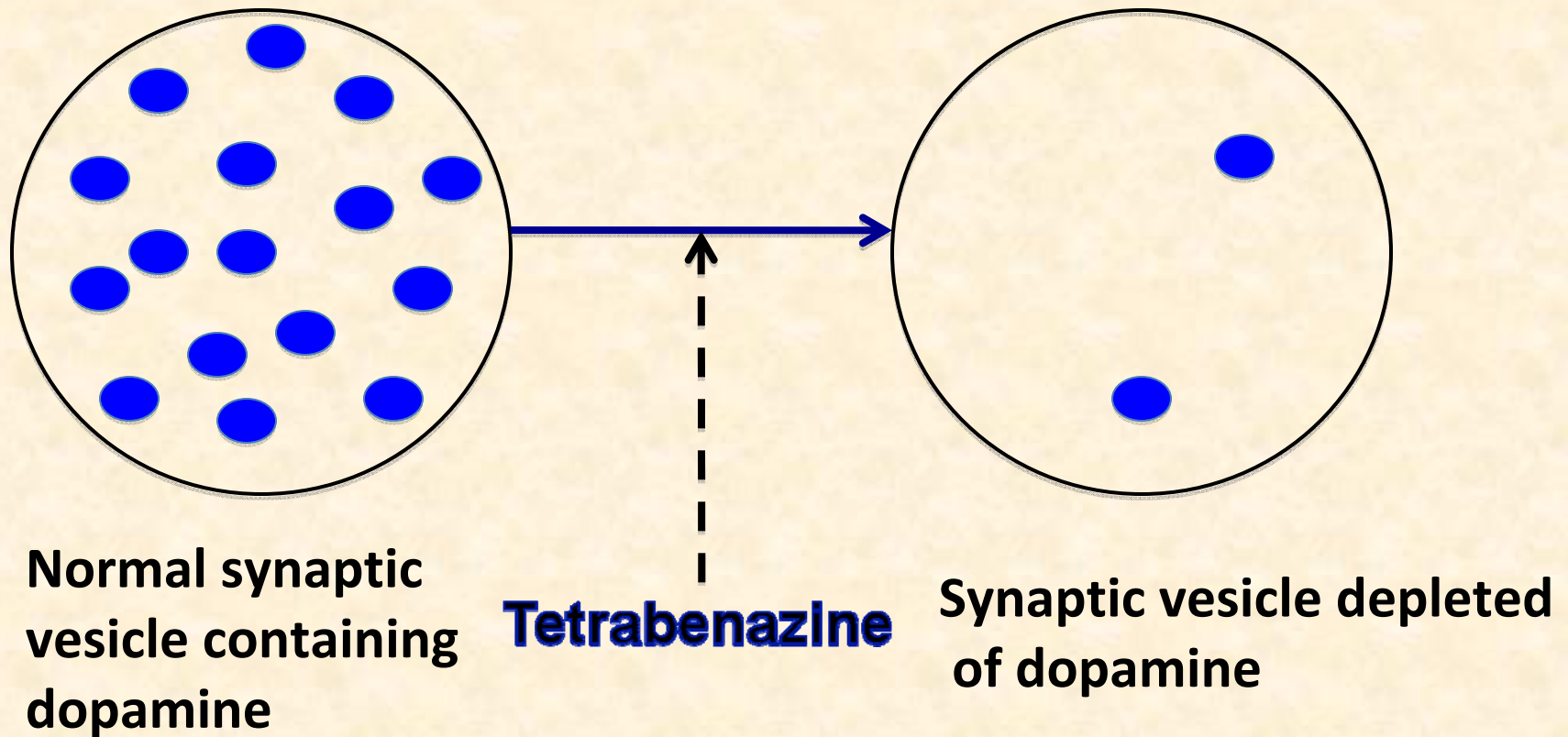
(Prestwick Pharmaceuticals)



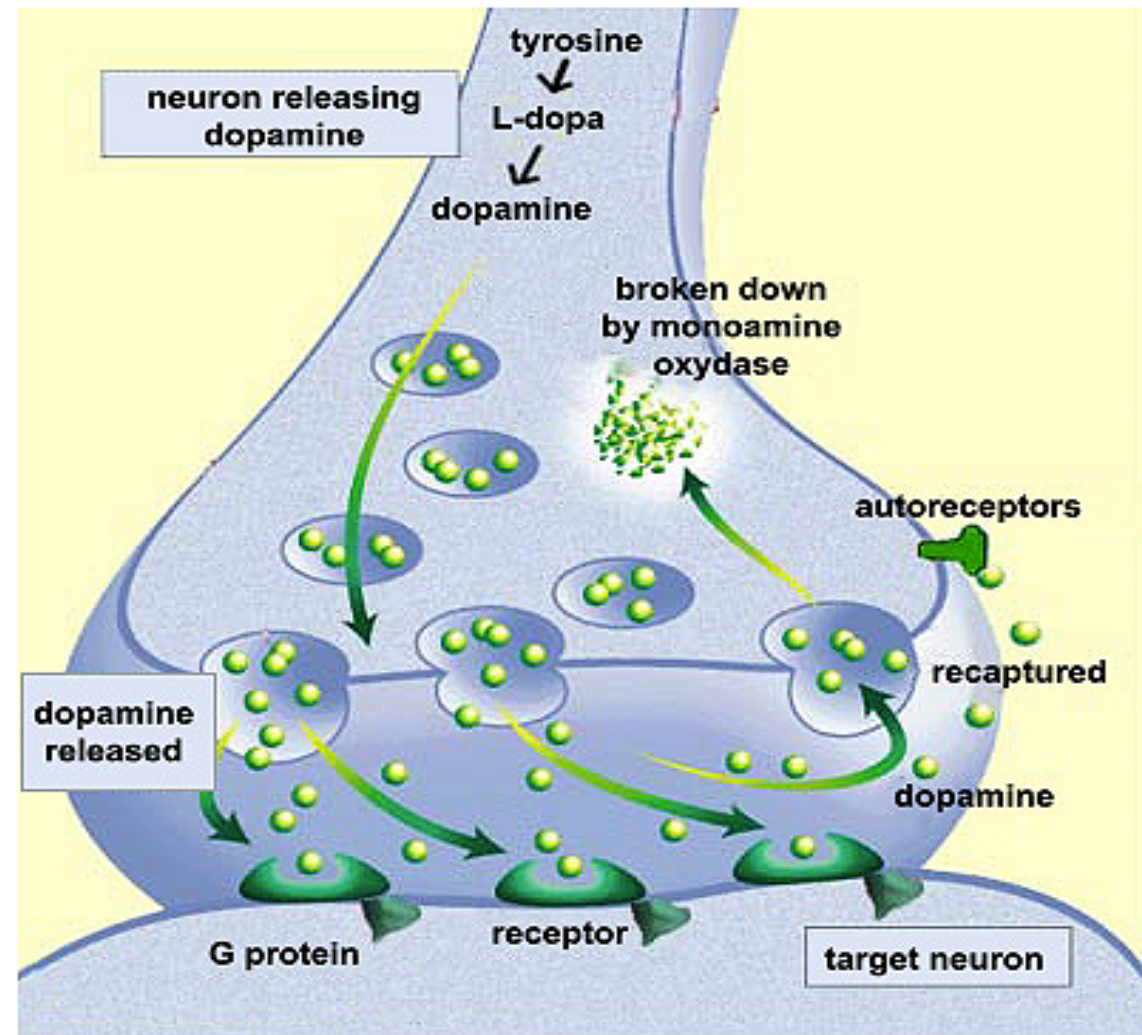
Tetrabenazine

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



Action of Tetrabenazine



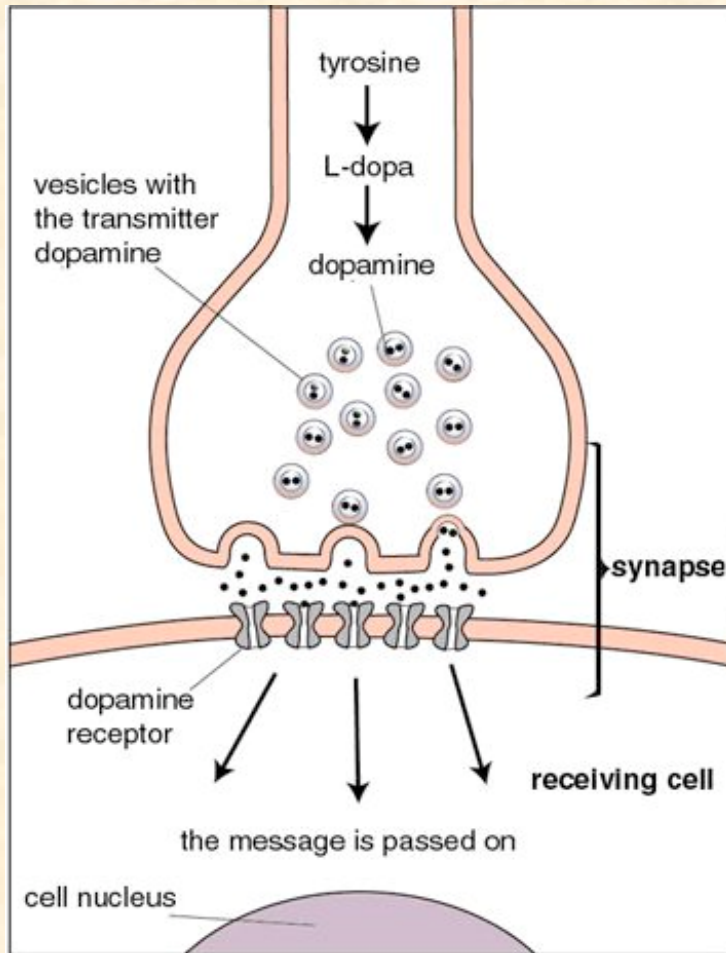
Atypical Antipsychotics

Atypical anti-psychotics

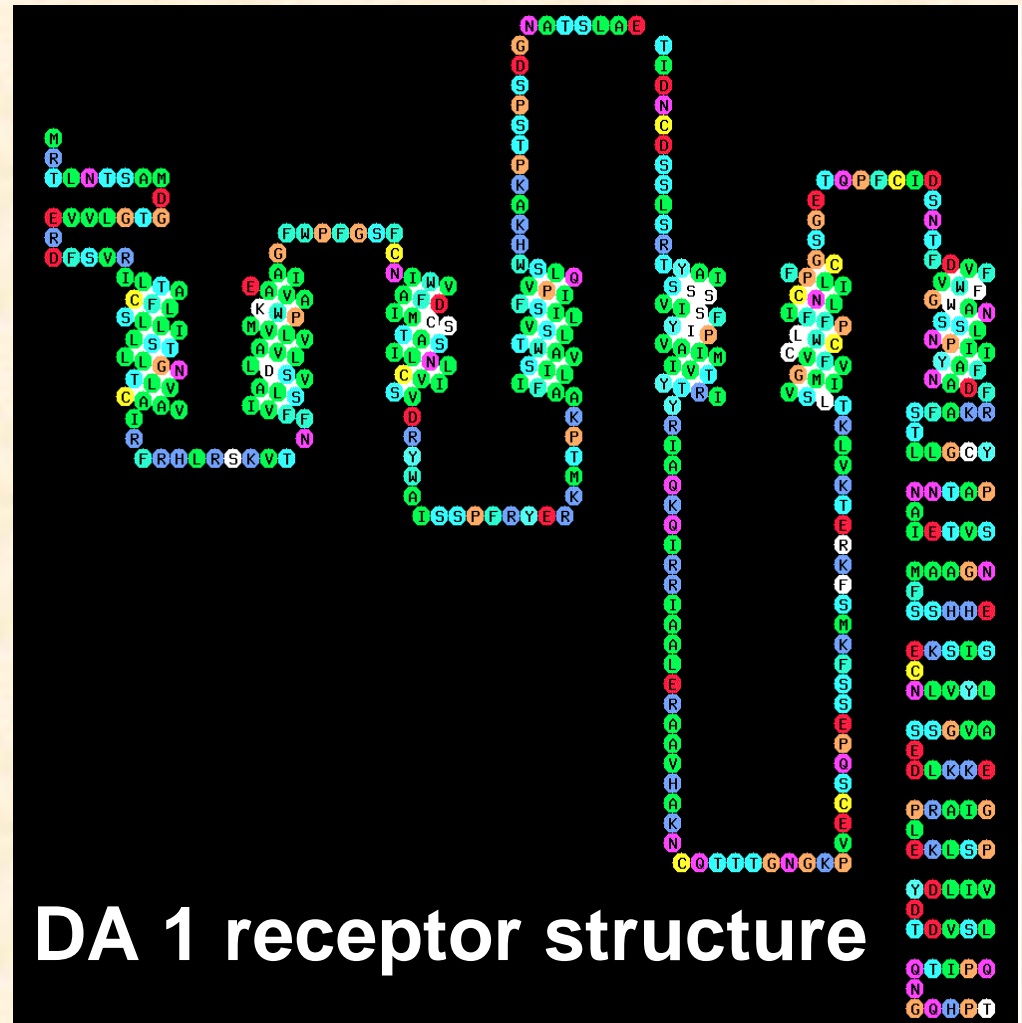
- 1. risperidone (Risperdal)**
- 2. quetiapine (Seroquel)**
- 3. ziprasidone (Geodon)**
- 4. clozapine (Clozaril)**

Block dopamine receptors

Dopamine Receptors



DA 1, DA 2 – motor
DA 3 – DA 5 – other functions



DA 1 receptor structure

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;