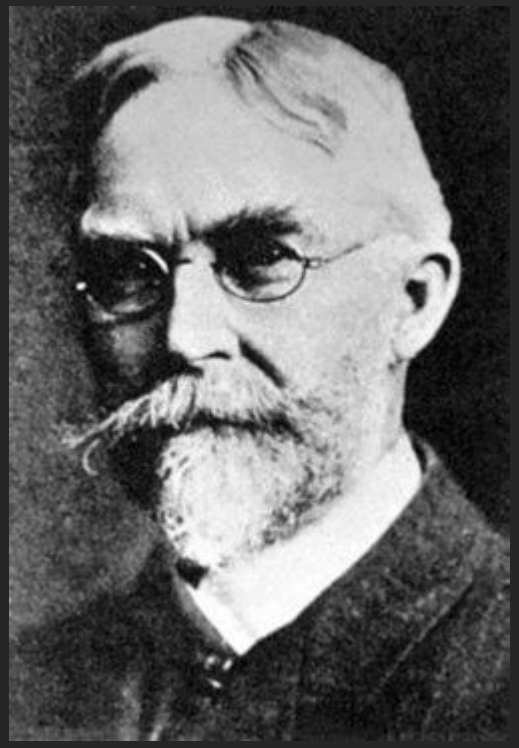
HUNTINGTON'S Disease (HD) [or Huntington's Chorea]



George Huntington
USA 1850-1916

- **HEREDITARY PATHOLOGY (autosomal dominant)**
- **MOTOR INCOORDINATION**
- **COGNITIVE DECLINE IN MIDDLE AGE**

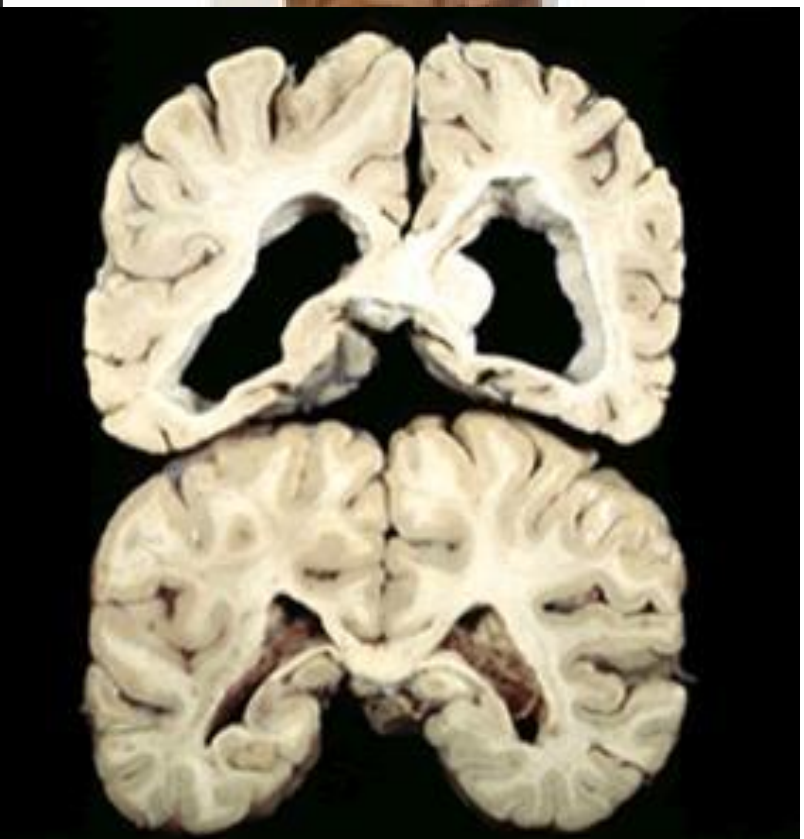
SYMPTOMS

- Chorea - intermittent movements of the limbs, trunk, face & neck
- Personality changes
- Memory impairment

OUTCOME

During 15-30 years person lives with HD; death by immobilization

Repetitive trinucleotide sequence CAG short arm of chromosome 4 in position 16.3 (4p16.3) Autosomal dominant mutation



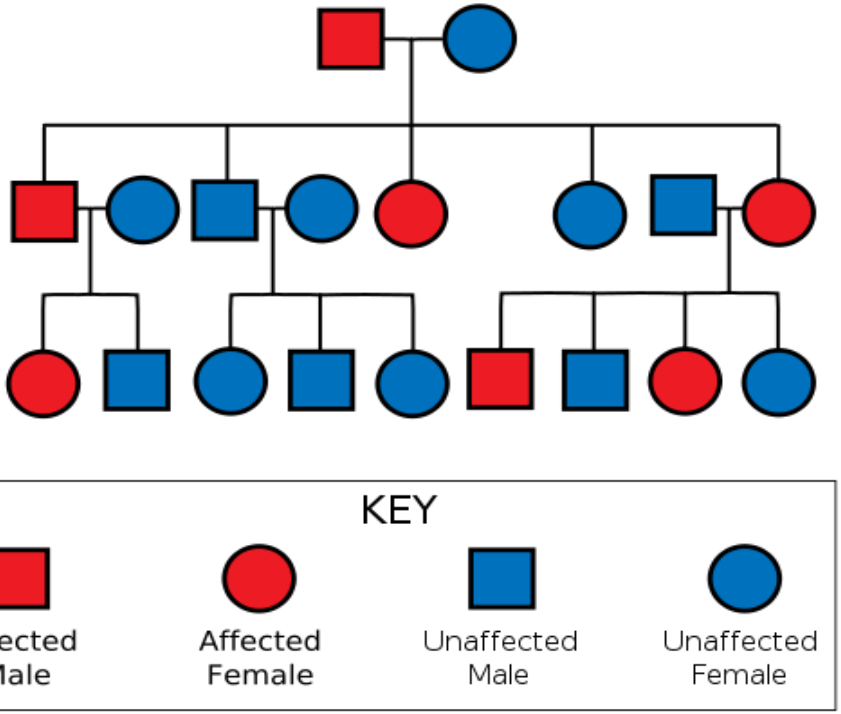


Table 1. Clinical features of Huntington's disease.

Motor	Chorea
	Dystonia
	Bradykinesia
	Myoclonus (especially in younger onset patients)
	Gait disorder*
	Dysphagia
	Dysarthria
	Motor impersistence
	Rigidity
Cognitive	Executive dysfunction
	Social cognition deficits
	Inattention
	Dementia
Affective	Irritability
	Impulsivity
	Mood swings
	Depression;
	Apathy
	Psychosis
	Anxiety
	Obsessive/compulsive symptoms
Other	Weight loss
	Incontinence
	Constipation
	Insomnia
	Epilepsy (in younger patients)

* The gait problems in Huntington's disease are typically a result of a range of motor problems that includes chorea, dystonia, ataxia, and a degree of spasticity in some cases.

hat-is-hd/motor-physical-symptoms/

HD Stages

EARLY STAGE

In early stage HD, individuals are largely functional and may continue to work, drive, handle money, and live independently. Symptoms may include minor involuntary movements, subtle loss of coordination, difficulty thinking through complex problems, and perhaps some depression, irritability, or disinhibition.

MIDDLE STAGE

In middle stage HD, individuals lose the ability to work or drive and may no longer be able to manage their own finances or perform their own household chores, but will be able to eat, dress, and attend to personal hygiene with assistance. Chorea may be prominent, and people with HD have increasing difficulty with voluntary motor tasks. There may be problems with swallowing, balance, falls, and weight loss. Problem solving becomes more difficult because individuals cannot sequence, organize, or prioritize information.

LATE STAGE

In late stage HD, individuals require assistance in all activities of daily living. Although they are often nonverbal and bedridden in the end stages, it is important to note that people with HD seem to retain some comprehension. Chorea may be severe, but more often it is replaced by rigidity, dystonia, and bradykinesia. Psychiatric symptoms may occur at any point in the course of the disease, but are harder to recognize and treat late in the disease because of communication difficulties.

https://hdsa.org/what-is-hd/huntingtons-disease-stages/

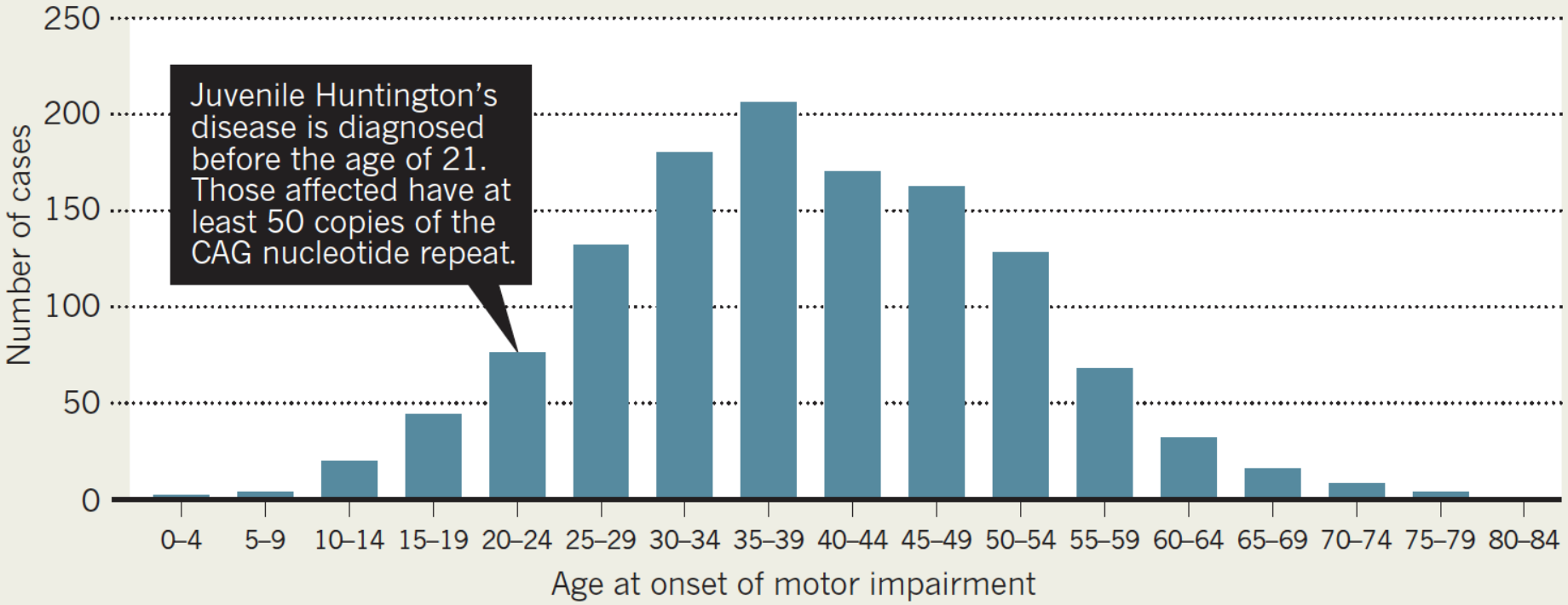
CHARACTERISTICS OF HUNTINGTON'S DISEASE (HD)

- Neuronal loss in the caudate/putamen (posterior & anterior)
- Disease onset: 35-45 years
- Genetic alteration on chromosome 4
- Genetic mutation of IT15, which codes for huntingtin (HTT)
- "CAG" - normally repeated 11 to 34 times in gene (number of glutamines expressed in the huntingtin protein)
- HD – CAG repeated $\geq$ 40 times
- Larger number of CAG repeats, earlier age of onset of HD

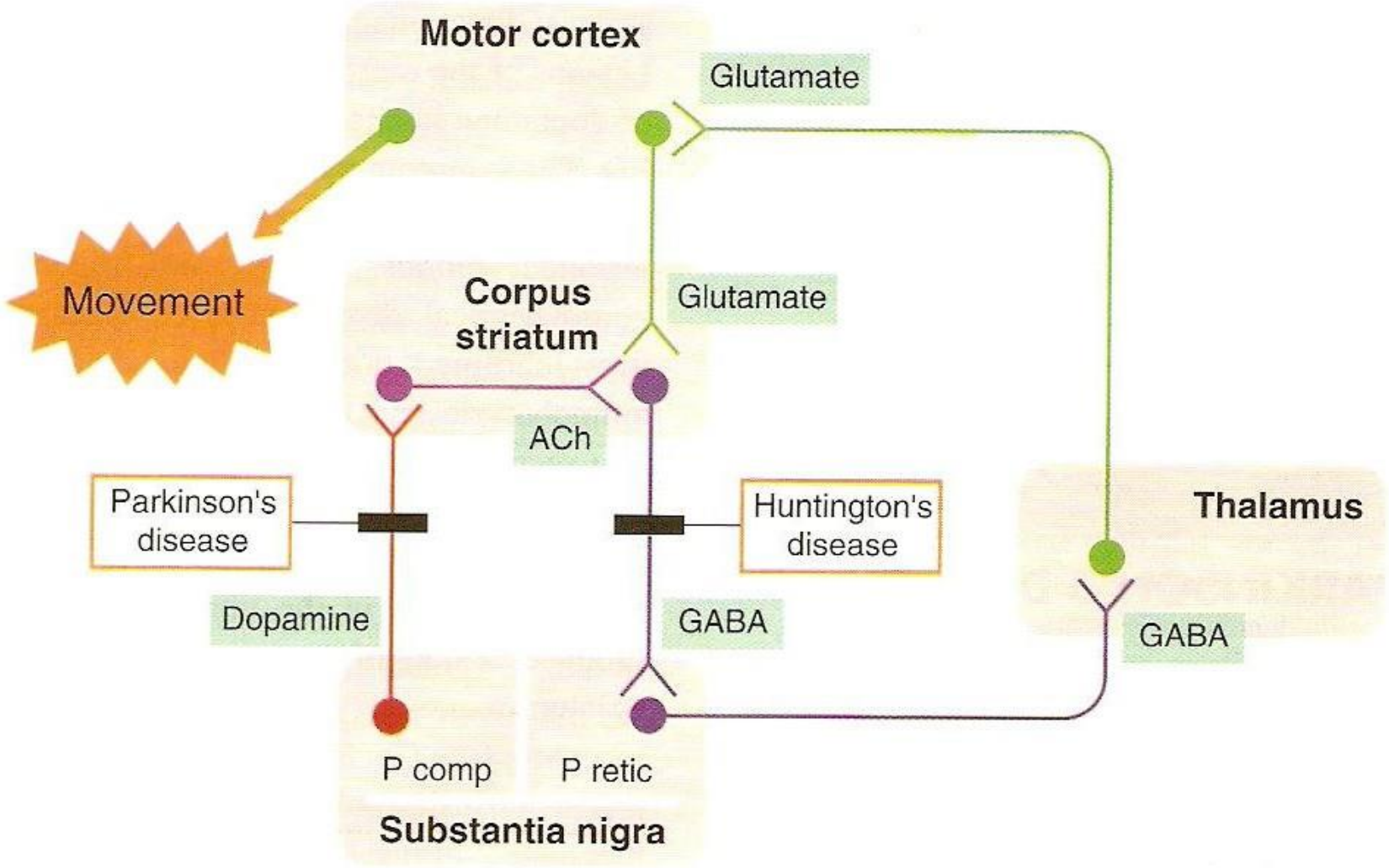
HD – Age of onset distribution

AT THE EXTREMES

Motor impairment associated with Huntington's disease is rare in children and adolescents. People who carry the gene mutation that causes the condition develop symptoms on average at around the age of 40. Huntington's disease can strike later in life, but this is also rare.



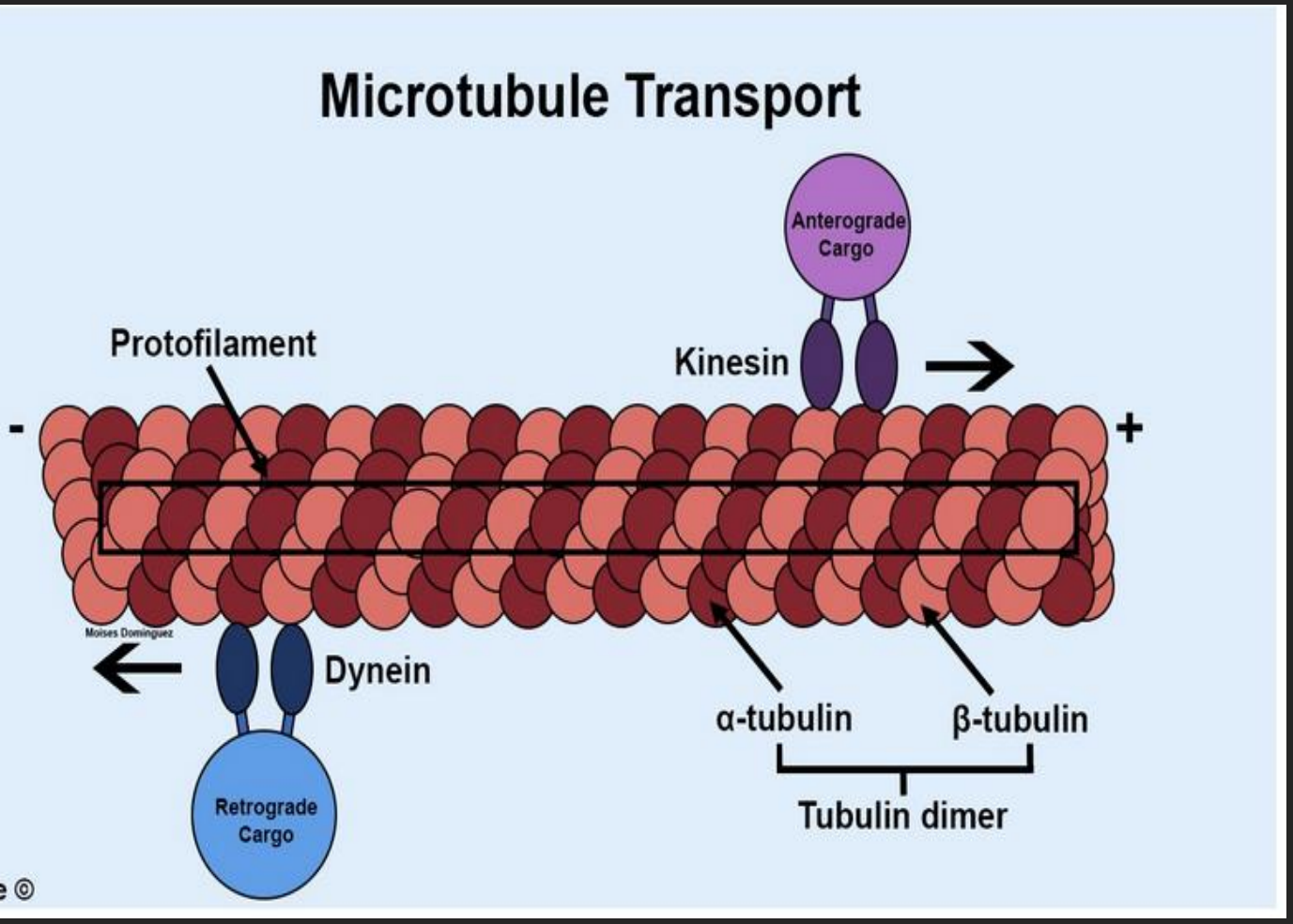
Motor Control and Basal Ganglia
In HD – striatal neurons degenerate



Huntingtin (HTT)

- HTT is involved in axonal transport along microtubules
- HTT acts as an accelerator (*i.e. decreases pausing time*) of axonal transport & it determines the direction the axonal transport (anterograde or retrograde)
- HTT mutation disrupts these axonal transport functions

- HTT protein interacts with more than 400 proteins that function in gene regulation, RNA splicing, vesicle transport & protein degradation



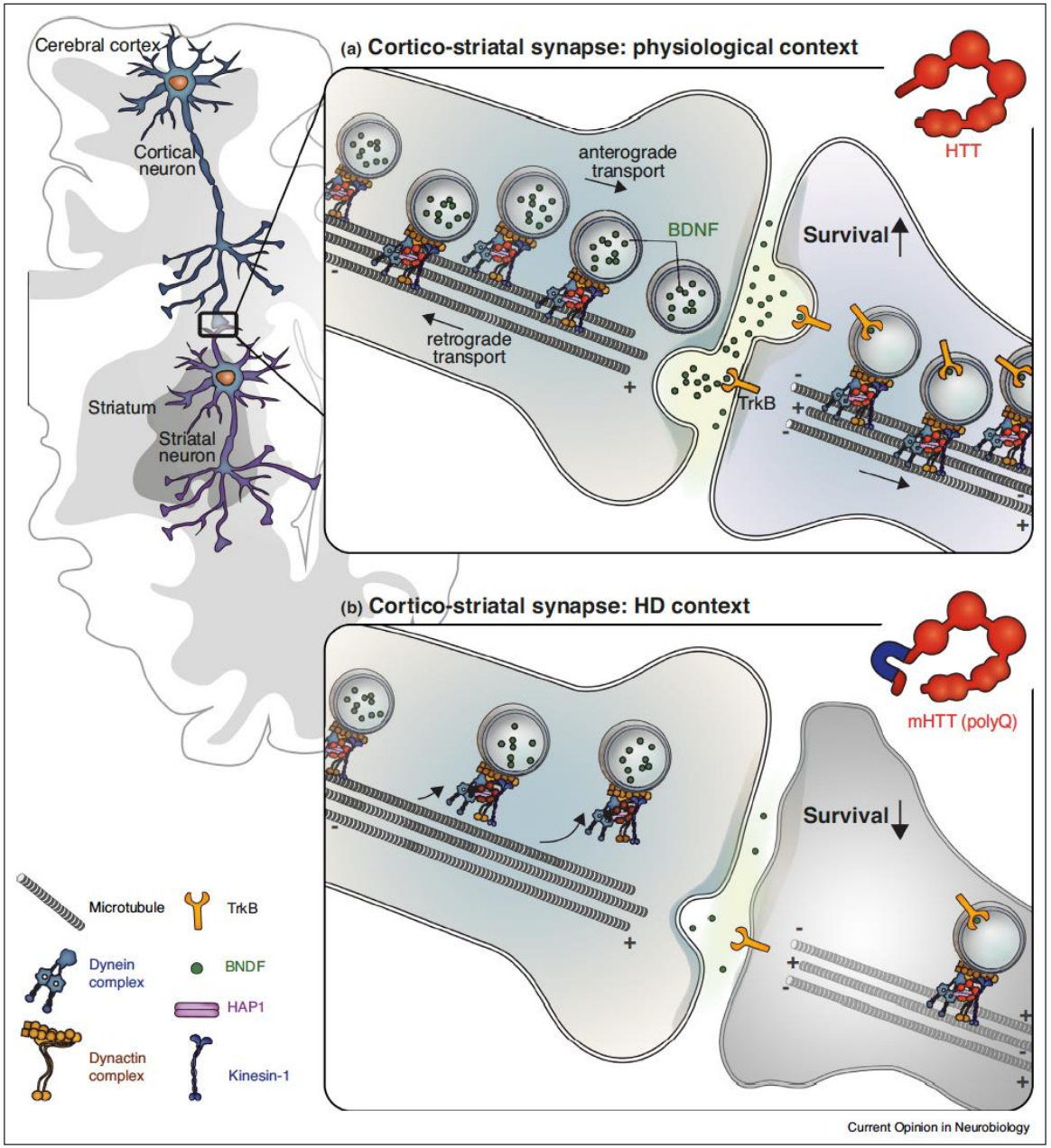
-HTT protein phosphorylation *state* & phosphorylation *location* in protein affects its interaction with kinesin & dynein & therefore the direction of axonal transport

-HTT mutation affects speed of axonal transport & association of vesicles with microtubules

Current Opinion in Neurobiology 2020, 63:122–130

Rita Levi-Montalcini

- BDNF (Brain Derived Neurotrophic Factor) keeps neurons alive by preventing apoptosis
- BDNF is transferred from cortex to the striatum via axon transport
- In HD transport of BDNF is affected



Huntingtin transports vesicles along microtubules toward the synapse. **(a)** Huntingtin facilitates anterograde transport of various vesicles, such as those containing the Brain-Derived Neurotrophic Factor (BDNF). When released at the synapse, BDNF will bind its receptor TrkB, which will be internalized and transported back to the soma of the striatal neurons where it will elicit a survival signal. **(b)** In HD, BDNF-containing vesicles are transported less efficiently because they tend to detach from microtubules. As a result, BDNF release at the synapse, TrkB receptor activation, and survival signaling are all reduced, leading to dysfunction and death of striatal neurons.

Current Opinion in Neurobiology 2020, **63**:122–130

Therapies for Huntington's Disease

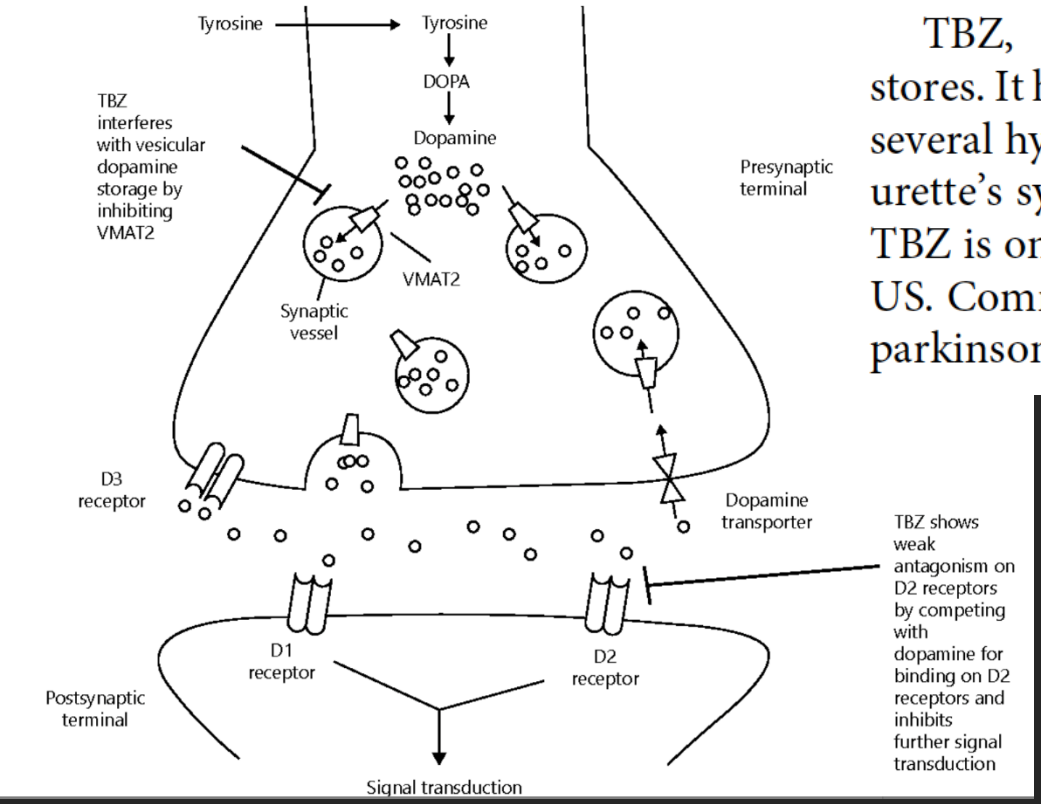
- Drugs are used to treat various **HD symptoms** targeting motor, affective & other symptoms

Table 2. Drugs currently used in clinical practice to treat the motor features of Huntington's disease.

Symptom	Treatment	Side effect
Chorea	Dopamine receptor antagonists: olanzapine, sulpiride, amisulpiride, haloperidol, risperidone	**Sedation**, [13,14], **parkinsonism and akathisia** [14] and tardive dyskinesias [15] May cause extra pyramidal features, increased appetite/weight gain, irritability*
	VMAT inhibitor: tetrabenazine	**Sedation, insomnia and anxiety, agitation, akathisia, hyperkinesia and depression** [16,17] May potentially cause parkinsonism*
	Cannabinoids: nabilone	**Drowsiness, forgetfulness, sedation, high mood** [18] May potentially cause depression*
	Presumed glutamatergic medications: amantadine	**Irritability, aggressiveness, hallucinations or confusion, increased forgetfulness, sedation, exacerbation of morbid thoughts and anxiety** [19,20]
Dystonia	GABAergic medication: benzodiazepines, clonazepam, diazepam	May potentially cause drowsiness, sedation, depression*
	VMAT inhibitor: tetrabenazine	As above
	Botox (if focal, which is very rare)	Allergic reaction
	As for bradykinesia, consider stopping or reducing doses of drugs being used to treat chorea	
Bradykinesia	Dopamine agonists: levodopa, apomorphine	May potentially cause hallucinations, dyskinesia, drowsiness*
	As for dystonia consider stopping or reducing dose of drugs for chorea	
Myoclonus	GABAergic medication: benzodiazepines	As above
Gait disorder	Presumed glutamatergic medications: amantadine	
	Above therapies if contributing to gait disorder	As above
Dysphagia	Above therapies if contributing to swallowing problems especially chorea	

Side effects highlighted in bold indicate findings from trials of the medication in a Huntington's disease population. VMAT: vesicular monoamine transporter.
*Indicates potential side effects that are commonly associated with this drug but have not been empirically linked to Huntington's disease.

Treatments for Chorea
VMAT2 inhibitors: Tetrabenazine (TBZ) & Deutetrabenazine



TBZ, a VMAT2 blocker, diminishes monoamine stores. It has proven its potential through clinical trials in several hyperkinetic disorders including TD, tic and Tourette's syndrome, dystonia, and myoclonus. Currently, TBZ is only approved for the treatment of chorea in the US. Common side effects include insomnia, depression, parkinsonism, akathisia, and NMS.

Ann Neurosci 2016;23:176–185
DOI: 10.1159/000449184

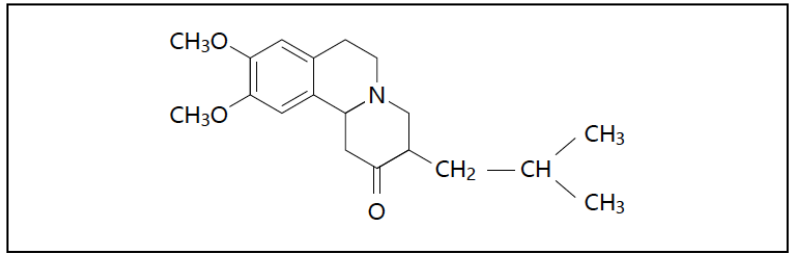


Fig. 1. Structure of TBZ

Deutetrabenazine

Deutetrabenazine (deuTBZ) is approved for the treatment of HD, in addition to TD. DeuTBZ is chemically identical to TBZ, except for the replacement of two hydrogen atoms with deuterium. Replacing hydrogen with deuterium decreases the CYP2D6 metabolism of TBZ, resulting in a longer half-life, less frequent dosing, and more stable serum drug levels.

Curr Treat Options Neurol (2018) 20: 44
DOI 10.1007/s11940-018-0529-y

Treatments for Dystonia

Medications affecting	Cholinergic system	GABAergic system		Dopaminergic system
	Trihexyphenidyl	Baclofen	Clonazepam	Tetrabenazine
Dosage form (tablet)	2 mg, 5 mg	10 mg, 20 mg	0.5 mg, 1 mg, 2 mg	12.5 mg, 25 mg
Dosing	TID	TID	BID	TID
Side effects	**Central**: sedation, memory impairment, psychosis, chorea **Autonomic**: blurred vision, urinary retention, constipation, dry mouth	Drowsiness, dizziness, nausea, fatigue	Sedation, depression, nocturnal drooling, behavioral disinhibition	Parkinsonism, depression, suicidality
Caution	Contraindicated in angle-closure glaucoma	Abrupt discontinuation can trigger baclofen withdrawal syndrome (psychosis and/or seizure)	Abrupt discontinuation can trigger withdrawal including seizure; tachyphylaxis rare in dystonia	FDA recommends *CYP2D6* genotyping when using the dose > 50 mg/d

Termsarasab *et al. Journal of Clinical Movement Disorders* (2016) 3:19
DOI 10.1186/s40734-016-0047-6

SYMPTOMATIC THERAPY

- FLUOXETINE (irritability, depression)
- CLONAZEPAM and VALPROIC Acid (myoclonic convulsions)
  BACLOFEN (GABA agonist)
- CLOZAPINE, RISPERIDONE (psychosis, hallucinations)

RESERPINE, TETRABENAZINE (movement)

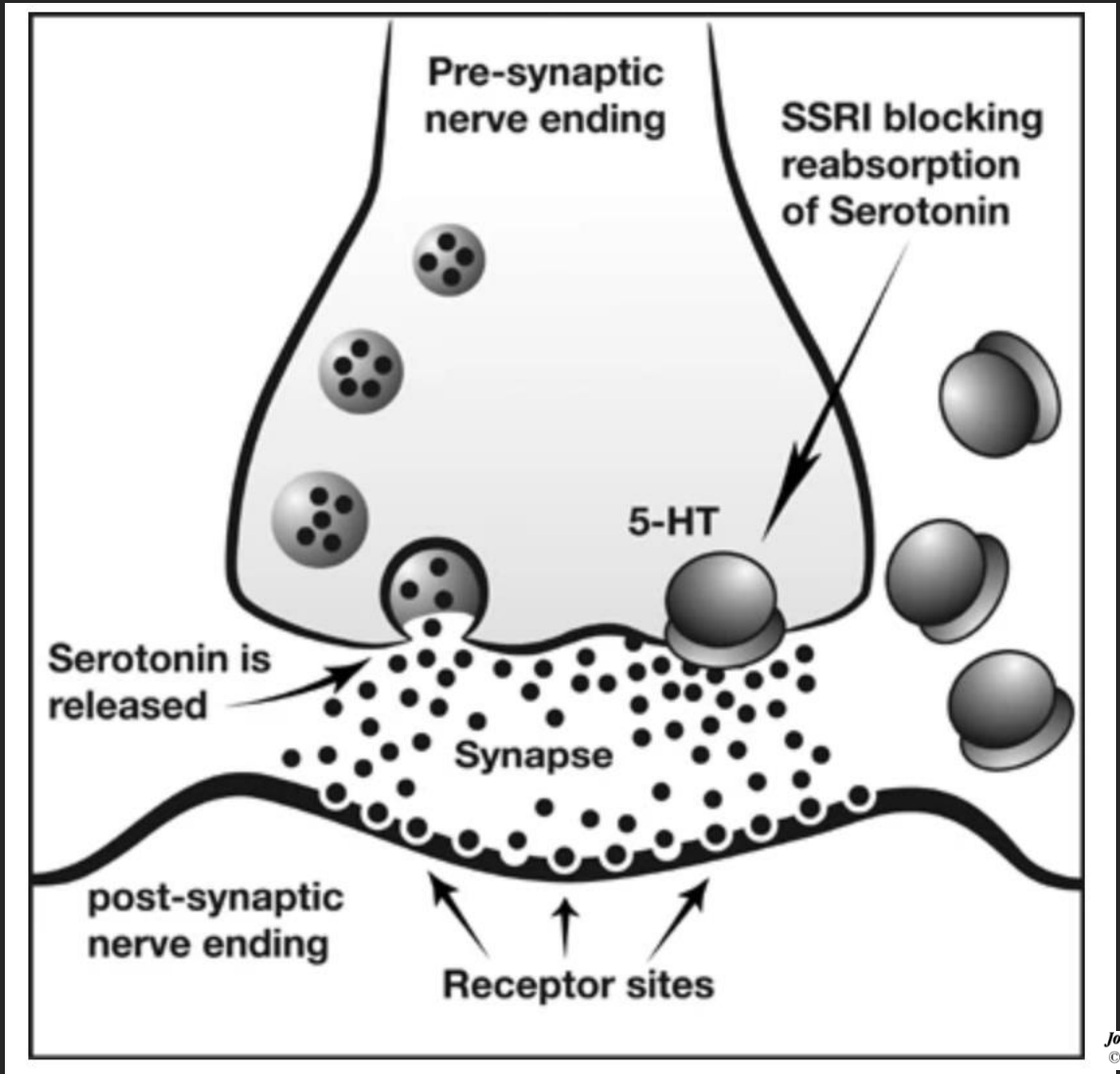
Caloric requirement

Table 3. Drugs currently used in clinical practice to treat the affective features of Huntington's disease.

Symptom	Treatment	Side effect*
Depression	Standard antidepressants including mirtazipine, fluoxetine, citalopram and venlafaxine	Weight gain, fatigue, drowsiness, insomnia
	Monoamine oxidase inhibitors	Weight gain, anxiety, fatigue
Anxiety	Citalopram	As above
	Lorazepam	
Irritability	Olanzapine, risperidone	As in Table 2
	Quetiapine	Confusion, drowsiness
	Sodium valproate	Weight gain, tremor, extrapyramidal features
	Carbamazepine	Depression, irritability, insomnia, drowsiness, nausea
	Lamotrigine	Anxiety, irritability, depression
	Lithium	Fatigue, tremor, weight gain, sweating
Impulsivity	Atomoxetine	Insomnia, drowsiness, irritability
Apathy	Modafinil	Anxiety, depression, insomnia
	Amantadine	As in Table 2
	Standard antidepressants including mirtazipine, fluoxetine, citalopram and venlafaxine	As above
Psychosis	Atypical neuroleptics: olanzapine, sulpiride, amisulpiride, haloperidol, risperidone	As in Table 2

*Owing to the lack of empirical research in this area and/or the failure of such studies to report the side effect profile, the side effects reported here reflect potential side effects that are commonly associated with these drugs, although they have not been empirically linked to Huntington's disease.

Treatment of Depression
Selective Serotonin Reuptake Inhibitors (SSRIs) Fluoxetine



Journal of Perinatology 2005; 25:595–604

Table 4. Drugs used to treat other features of Huntington's disease: a summary of the treatments available to help manage aspects of Huntington's disease that extend beyond the motor, cognitive or psychiatric domains.

Weight loss	Dietary supplements
	Olanzapine and other atypical neuroleptics
	Sodium valproate
Sleep problems	Olanzapine
	Z-drugs
	Amitriptyline
	Modafinil in the morning
	(Sodium oxybate)
Incontinence	Oxybutynin
Constipation	Fybogel
	Senna
	Movicol
Epilepsy	Sodium valproate
	Carbamazepine
	Lamotrigine

Treatment of Irritability & Seizures
Valproate & Carbamazepine

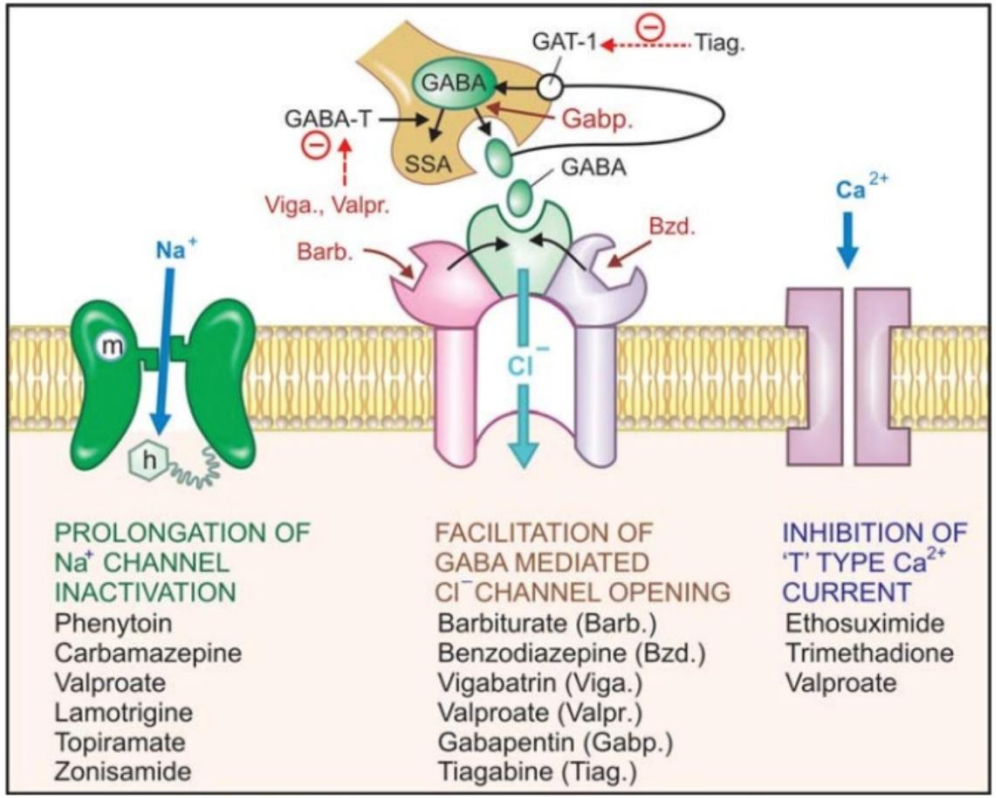


Fig. 30.2: Major mechanisms of anticonvulsant action
m: Activation gate; h: Inactivation gate; GABA-T: GABA transaminase; SSA: Succinic semialdehyde; GAT-1: GABA transporter

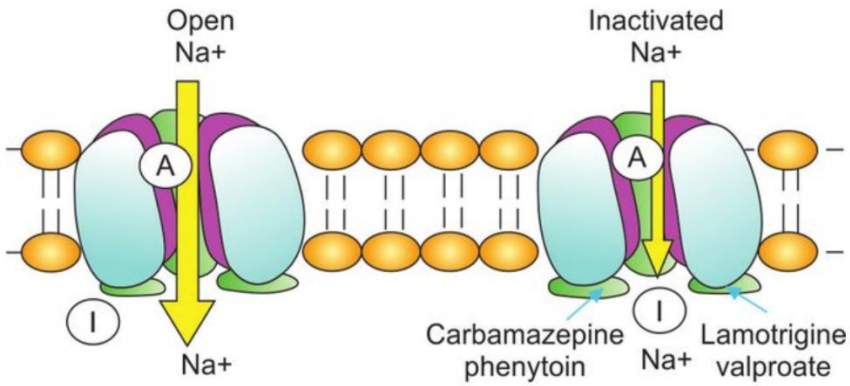
http://www.pharmacy180.com/article/antiepileptic-drugs-1147/

Valproate

- Enhances GABA transmission
- Inhibits Na^+ & Ca^{++} channels

Carbamazepine

- Inhibits Na^+ channels



December 2016 · Journal on Recent Advances in Pain 2(3):90-93
DOI: 10.5005/jp-journals-10046-0050