Pharmacology of Movement Disorders

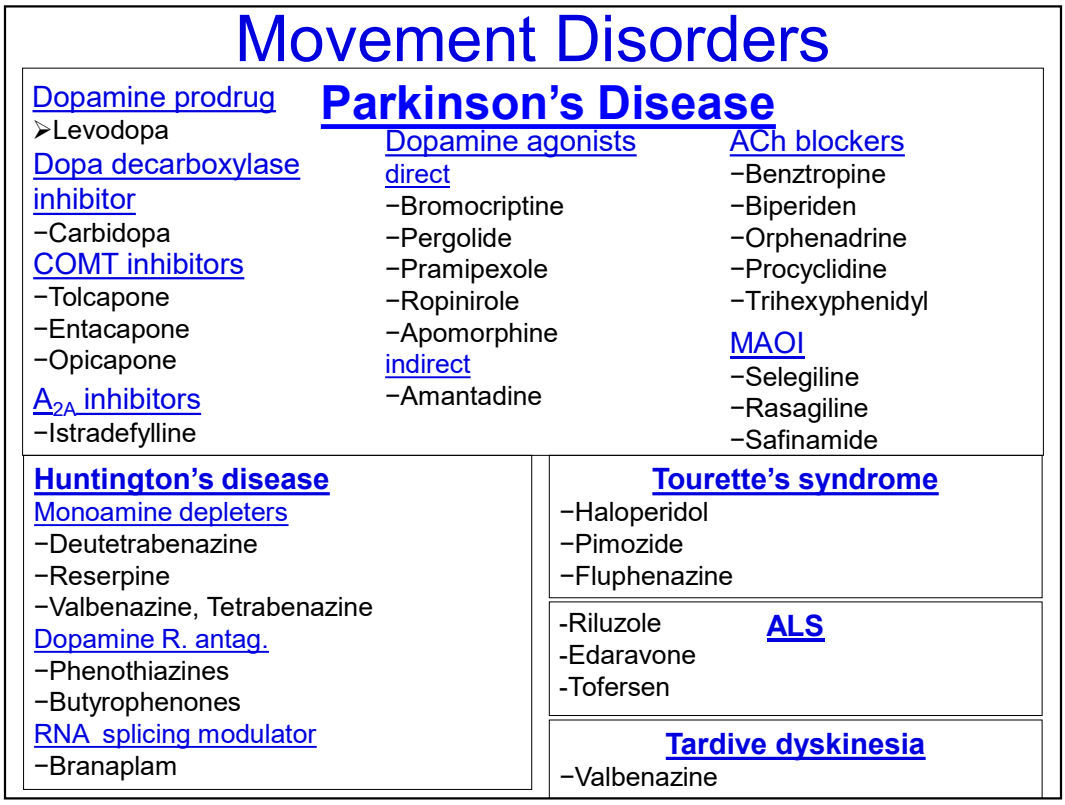
G.J. Klapstein
gloria.klapstein@tu.edu

To check for fda approved drugs, see:

https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/10/neurology

Diseases du jour

- Parkinson's Disease
- Huntington's Disease
- Amyotrophic Lateral Sclerosis
- Tourette's Syndrome



Other drugs include:

- Exelon (rivastigmine tartrate); Novartis; For the treatment of Alzheimer's and Parkinson's disease-related dementia, Approved July 2007
- Neupro (rotigotine); Schwarz Pharma; For the treatment of Parkinson's disease, Approved May 2007; a dopamine agonist of the non-ergoline class of medications indicated for the treatment of Parkinson's disease (PD) and Willis-Ekbom Disease [1] (WED) formerly known as restless legs syndrome

Approved in 2016

Nuplazid (pimavanserin) is thought to exert it's effect through a combination of inverse agonist and antagonist activity at serotonin 5-HT2A receptors and to a lesser extent at serotonin 5-HT2C receptors. Nuplazid is specifically indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. https://www.centerwatch.com/drug-information/fda-approved-drugs/drug/100147/nuplazid-pimavanserin

Approved in 2017

- Austedo (deutetrabenazine) is a vesicular monoamine transporter 2 (VMAT2) inhibitor. Austedo is specifically indicated for the treatment of chorea associated with Huntington's

disease. https://www.centerwatch.com/drug-information/fda-approved-drugs/drug/100197/austedo-deutetrabenazine-

- Ingrezza (valbenazine) is a vesicular monoamine transporter 2 (VMAT2) inhibitor. Ingrezza is specifically indicated for the treatment of adults with tardive dyskinesia. https://www.centerwatch.com/drug-information/fda-approved-drugs/drug/100198/ingrezza-valbenazine
- Radicava (edaravone) is a free radical scavenger. Radicava is specifically indicated for the treatment of amyotrophic lateral sclerosis (ALS). https://www.centerwatch.com/drug-information/fda-approved-drugs/drug/100204/radicava-edaravone
- Xadago (safinamide) is a monoamine oxidase type B (MAO-B) inhibitor. Xadago is specifically indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes. https://www.centerwatch.com/drug-information/fda-approved-drugs/drug/100191/xadago-safinamide

Approved in 2020

- Ongentys (opicapone) is a catechol-O-methyltransferase (COMT) inhibitor.

Ongentys is specifically indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes.

Dec 16, 2021 **FDA Fast Track designation for branaplam for HD**

- Originally developed for Treatment of spinal muscular atrophy (SMA)
- lowers the level of huntingtin protein

Approved September 29, 2022

Relyvrio (sodium phenylbutyrate/taurursodiol) to treat patients with amyotrophic lateral sclerosis (ALS). This drug was **voluntarily removed from the market in April 2024** by its manufacturer, Amylyx Pharmaceuticals, after a global Phase 3 clinical trial (PHOENIX) did not meet its primary or secondary endpoints. While the initial Phase 2 trial showed a benefit, the larger, confirmatory trial failed to replicate those results. Current patients who wish to continue the medication can do so through a free drug program, but it is no longer available for new prescriptions

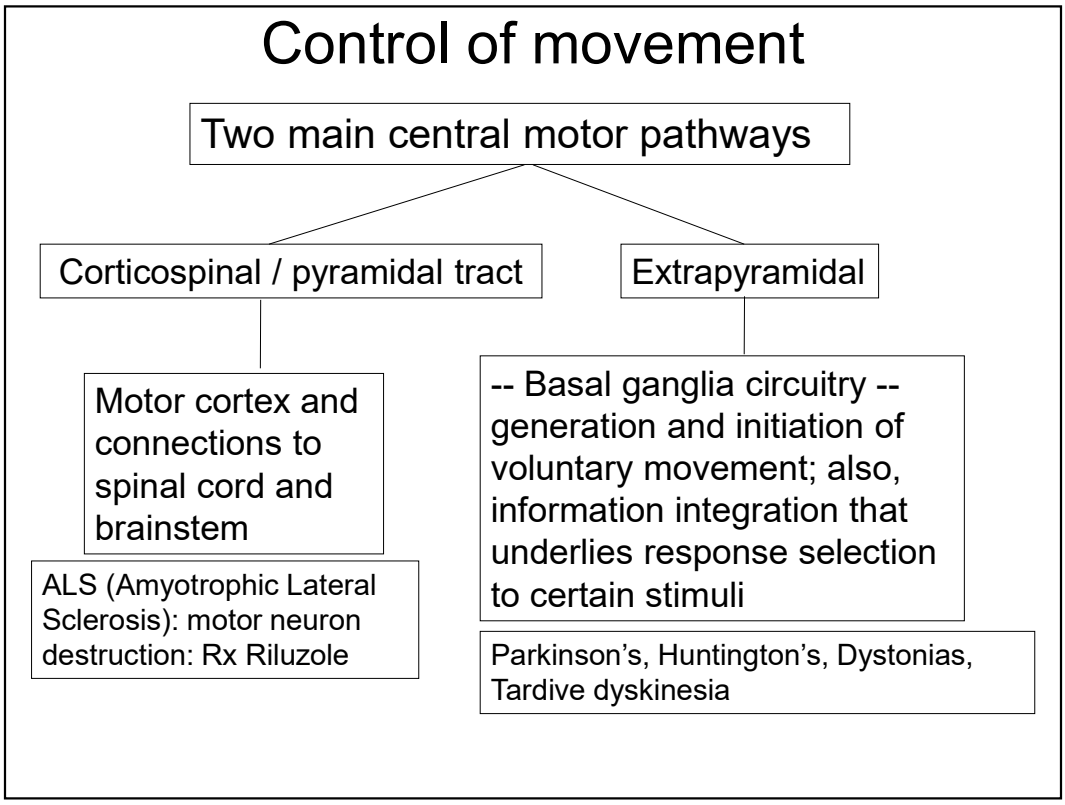
Qalsody (tofersen) approval: April 2023. **What it is:** Qalsody is an antisense oligonucleotide (ASO) therapy. It is the first treatment to target a specific

genetic cause of ALS. **How it works:** It is approved for patients with a mutation in the superoxide dismutase 1 (SOD1) gene, which accounts for approximately 2% of all ALS cases. Tofersen works by binding to the messenger RNA (mRNA) produced by the mutated SOD1 gene, effectively reducing the amount of the toxic SOD1 protein. The FDA granted this approval under the accelerated approval pathway based on a reduction in a biomarker, neurofilament light chain (NfL), which is a sign of nerve damage. Ongoing studies are being conducted to confirm its clinical benefit.

Study Goals

- Be able to identify the various diseases and learn the general pathophysiology for each
- Learn the main drug classes for each disease, and the individual drugs within them
  - Mechanism of action
  - Side effects
  - Pharmacokinetics
  - Drug interactions/Contraindications (!)
- For each individual drug, know what makes it stand out from its class.

Control of movement



Motor control pathways simplified

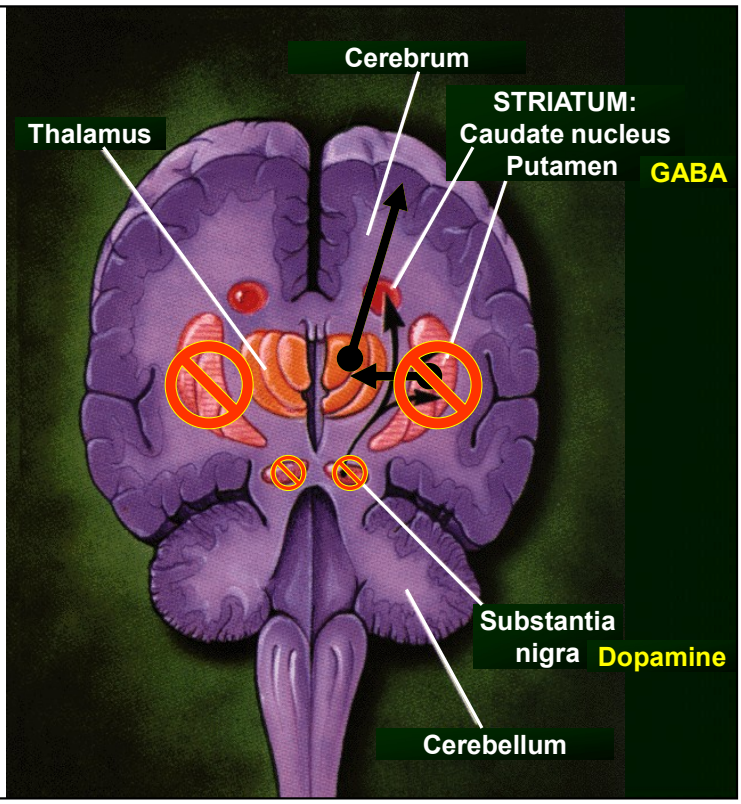
Substantia nigra neurons project to the striatum and release dopamine (inhibitory)

Striatal neurons project to thalamus and release GABA (inhibitory)

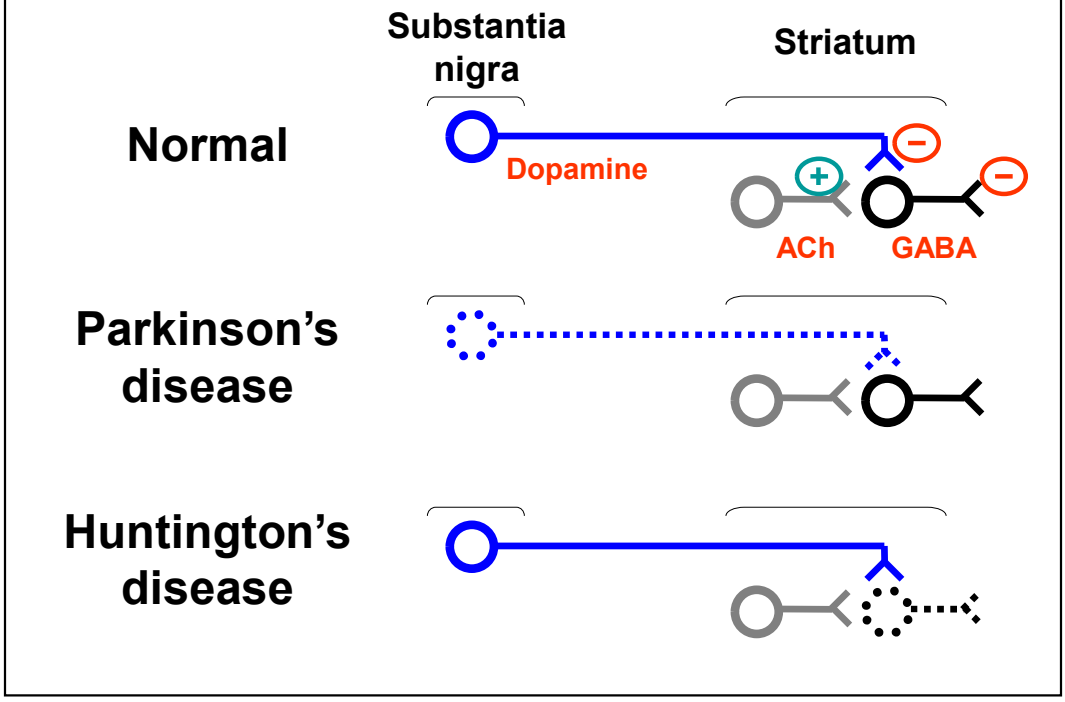
Thalamic neurons project to motor cortex (excitatory)

SN neurons disappear in Parkinson's disease

Striatal neurons disappear in Huntington's disease.



Basal Ganglia connections

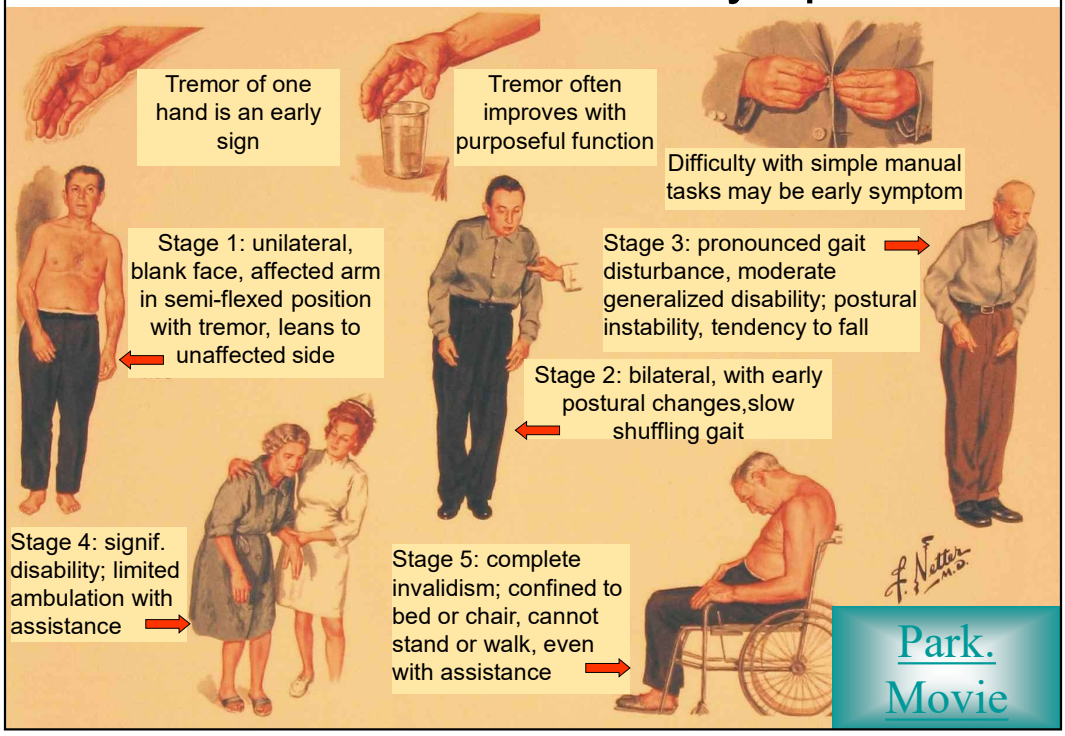


Parkinson's Disease

Parkinson's Disease

- A progressive neurodegenerative disease affecting motor control
- Prevalence ~2% in people > 65 years old
  - third most common neurological disease of the elderly (after stroke and Alzheimer's disease)
- Early symptoms include
  - tremor at rest (pill-rolling)
  - bradykinesia
  - muscle rigidity
  - flat facial affect
- Later symptoms
  - Slow, shuffling gait, postural instability
- can lead to complete immobility and early mortality.

Parkinson's Disease - Symptoms



Parkinson's Disease

- Major neuropathology is loss of dopaminergic neurons in Substantia nigra pars compacta
  - 60-80% of dopaminergic cells lost in most patients
- DA is normally inhibitory on striatal GABAergic neurons, counterbalancing the excitatory cholinergic input to those cells.
  →loss of DA results in more GABA output
- Also some loss of norepinephrine nerve endings in PD
  - May account for sympathetic dysfunction (blood pressure) and non-motor symptoms (fatigue).

In 2003, researchers studying inherited PD discovered that the disease in one large family was caused by a triplication of the normal alpha-synuclein gene on one copy of chromosome 4. This triplication caused people in the affected family to produce too much of the normal alpha-synuclein. This study showed that an excess of the normal form of the protein could result in PD, just as the abnormal form does.

Other genes linked to PD include parkin, DJ-1, PINK1, and LRRK2. Parkin, DJ-1, and PINK-1 cause rare, early-onset forms of PD. The parkin gene is translated into a protein that normally helps cells break down and recycle proteins. DJ-1 normally helps regulate gene activity and protect cells from oxidative stress. PINK1 codes for a protein active in mitochondria. Mutations in this gene appear to increase susceptibility to cellular stress.

LRRK2, which is translated into a protein called dardarin, was originally identified in several English and Basque families and causes a late-onset form of PD. Subsequent studies have identified this gene in other families with PD as well as in a small percentage of people with apparently sporadic PD.

Researchers are continuing to investigate the normal functions and interactions of these genes in order to find clues about how PD develops. They also have identified a number of other genes and chromosome regions that may play a role in PD, but the nature of these links is not yet clear.

From:
http://www.ninds.nih.gov/disorders/parkinsons_disease/detail_parkinsons_disease.htm#57053159, updated Aug 23, 2012.

Parkinson's Disease

- Genetic predisposition is likely
  - α –synuclein (forms intracellular deposits, Lewy bodies)
  - parkin (helps break down and recycle proteins)
  - DJ-1 (gene regulator, protects from oxidative stress)
  - PINK1 (helps parkin induce autophagy of depolarized mitochondria)
  - LRRK2 (regulates CNS-immune system interactions)
- Environmental factors may play a role
  - viral infections
  - neurotoxins
    - drugs (MPTP)
    - pesticides (rotenone)

In 2003, researchers studying inherited PD discovered that the disease in one large family was caused by a triplication of the normal alpha-synuclein gene on one copy of chromosome 4. This triplication caused people in the affected family to produce too much of the normal alpha-synuclein. This study showed that an excess of the normal form of the protein could result in PD, just as the abnormal form does.

Other genes linked to PD include parkin, DJ-1, PINK1, and LRRK2. Parkin, DJ-1, and PINK-1 cause rare, early-onset forms of PD. The parkin gene is translated into a protein that normally helps cells break down and recycle proteins. DJ-1 normally helps regulate gene activity and protect cells from oxidative stress. PINK1 codes for a protein active in mitochondria. Mutations in this gene appear to increase susceptibility to cellular stress.

LRRK2, which is translated into a protein called dardarin, was originally identified in several English and Basque families and causes a late-onset form of PD. Subsequent studies have identified this gene in other families with PD as well as in a small percentage of people with apparently sporadic PD.

Researchers are continuing to investigate the normal functions and interactions of these genes in order to find clues about how PD develops. They also have identified a number of other genes and chromosome regions that may play a role in PD, but the nature of these links is not yet clear.

From:
http://www.ninds.nih.gov/disorders/parkinsons_disease/detail_parkinsons_disease.htm#57053159, updated Aug 23, 2012.

Drug Induced Parkinsonism

- Some drugs can produce Parkinson's-like symptoms
  - Reserpine*, tetrabenazine deplete biogenic monoamines from their storage sites
  - Haloperidol, phenothiazines (antipsychotics)
    - block dopamine receptors
  - MPTP destroys dopaminergic neurons
    - impurity formed during synthesis of MPPP, an analog of meperidine (demerol)
    - metabolized by MAO-B to form the neurotoxin MPP+.

*Reserpine discontinued

MPPP, an analog of meperidine (Demerol), was first illicitly synthesised by a graduate student named Barry Kidston. Kidston had apparently studied a 1947 paper by Albert Zeiring. By reversing the ester of the meperidine skeleton, a drug approaching the potency of morphine was produced. However, the intermediate tertiary alcohol is liable to dehydration in acidic conditions if the reaction temperature rises above -30°C, and since Kidston did not realise this and esterified the intermediate with propanoic anhydride at room temperature, MPTP was formed as a major impurity. MPTP is metabolized to the neurotoxin MPP+ by the enzyme MAO-B, which is expressed in neurons.

The Lancet has a series of MPTP patients

https://www.youtube.com/watch?v=l720wreghqo

https://www.youtube.com/watch?v=cNQS52GoSsk

https://www.youtube.com/watch?v=hXLbpDoyIkY

https://www.youtube.com/watch?v=CYurq-KfOgU

https://www.youtube.com/watch?v=f6yxH2bgkSY

Drugs Classes for Parkinson's Disease

Dopamine prodrug

–Levodopa

–Levodopa + carbidopa (± entacapone)

Direct-acting dopamine agonists

–Bromocriptine } Ergot derivatives

–~~Pergolide*~~ } Ergot derivatives

–Pramipexole } Newer synthetic agents

–Ropinirole } Newer synthetic agents

Other non-ergot -Apomorphine

Bind to dopamine receptors and mimic the action of dopamine

Dopa Decarboxylase inhibitor

–Carbidopa

L-dopa -> dopamine by dopa decarboxylase (which is inhibited by carbidopa)

Catechol-o-methyltransferase (COMT) inhibitors

–Tolcapone

–Entacapone

L-dopa ->3-OMD by COMT (which is inhibited by entacapone or tolcapone)

Will cover details later in lecture

In March 2007, pergolide was voluntarily withdrawn from the U.S. market due to serious valvular damage that was shown in two independent studies.

^ "MedWatch - 2007 Safety Information Alerts. Permax (pergolide) and generic equivalents". U.S. Food and Drug Administration (March 29, 2007). Retrieved on 2007-03-30.

http://www.fda.gov/medwatch/safety/2007/safety07.htm#Pergolide

Apokyn (apomorphine hydrochloride); Mylan Laboratories; For the treatment of acute, intermittent hypomobility episodes associated with advanced Parkinson's disease, Approved April, 2004

Apomorphine: Nonergot; subcutaneous route useful for rescue treatment in levodopa-induced akinesia/dyskinesia; high incidence of nausea and vomiting

Drugs Classes for Parkinson's Disease

Indirect-acting dopamine agonist

–Amantadine

Increases dopamine release and reduces dopamine reuptake into dopaminergic nerve terminals of substantia nigra neurons (by unknown mechanism). Originally an antiviral agent

MAOI

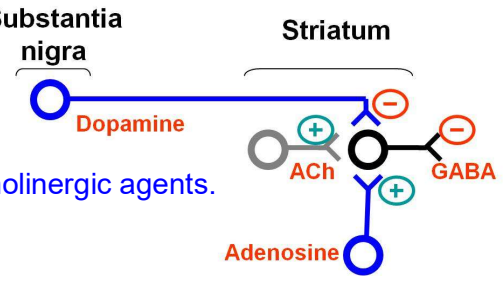
–Selegiline
–Rasagiline
–Safinamide

Inhibits only type B isozyme of monoamine oxidase

ACh Blocking drugs (muscarinic antagonists)

–Benztropine
–Biperiden
–Orphenadrine
–Procyclidine
–Trihexyphenidyl

Have central activity (brain) as anticholinergic agents.



Adenosine A_{2A} inhibitor

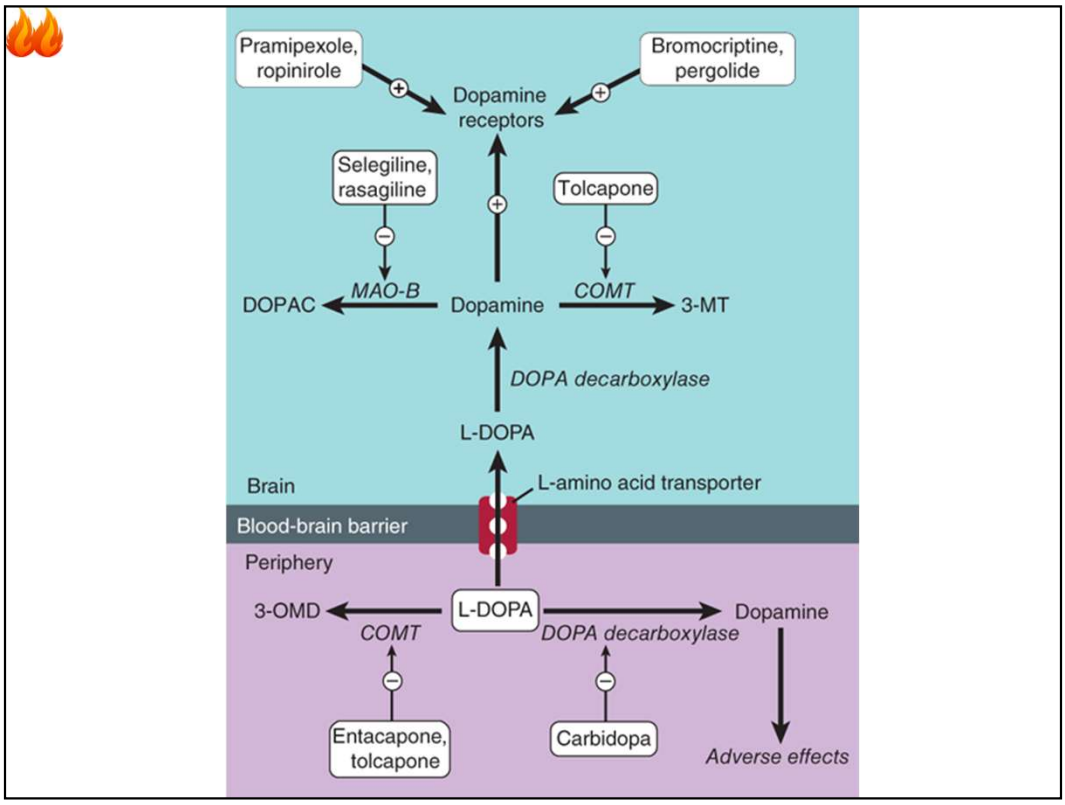
–Istradefylline

A_{2A} and D_2 receptors exhibit reciprocal antagonistic interactions

Will cover details later in lecture

Schiffmann SN, Fisone G, Moresco R, Cunha RA, Ferré S. Adenosine A2A receptors and basal ganglia physiology. Prog Neurobiol. 2007 Dec;83(5):277-92. doi: 10.1016/j.pneurobio.2007.05.001. Epub 2007 Jun 26. PMID: 17646043; PMCID: PMC2148496.

Istradefylline was granted FDA approval on 27 August 2019



Everything on this slide is high yield!

Levodopa (L-dopa)

- L-3,4-dihydroxyphenylalanine, a simple chemical found naturally in plants and animals
- Dopamine does not cross BBB
- Levodopa is a precursor of dopamine
  - –readily crosses BBB
  - –readily decarboxylated (dopa decarboxylase) to form dopamine
    - dopamine does not pass the BBB
- Historic Gold Standard !
- Most efficacious treatment.

Before meds

After meds

Levodopa (L-dopa)

- Readily absorbed from small intestine
  - –depends on rate of gastric emptying and pH
  - –delayed by food
- some other amino acids can compete for transport across BBB

Distribution

- –Plasma levels peak 1-2 hours after oral dose
- –Plasma half life 1-3 hours (patients vary, dosing 3-4 x /day)
- –only 1 – 3 % enters brain across BBB unaltered

Elimination

- –2/3 appears in urine as metabolites within 8 hours
  - homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC).

Levodopa (L-dopa)

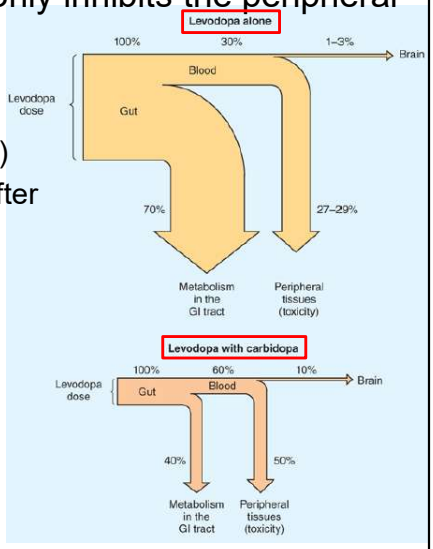
- Best results in the first few years of treatment
  - –1/3 of patients respond well
  - –1/3 respond less well
  - –1/3 do not respond or can not tolerate
- Patient response to L-dopa can decline over time (3-4 years) or stop completely
  - –start at small dose
  - –need to escalate dose as effects diminish
  - –Wearing-off reactions, end-of-dose akinesia, on-off phenomenon
  - –Issue of levodopa toxicity
    - supersensitivity can develop – dyskinesias.

Carbidopa

- Inhibits the L-dopa → dopamine conversion by dopa decarboxylase
- Carbidopa does not pass BBB, so it only inhibits the peripheral conversion of L-dopa
  - –Less peripheral L-dopa → dopamine conversion

    (remember – dopamine does not pass BBB)

    – More L-dopa in plasma to get into brain after oral dose
- Once past the BBB, L-dopa → dopamine
- Combination Rx of L-dopa and carbidopa can reduce the daily dose of L-dopa by 75%
  - –**Sinemet** contains carbidopa and levidopa (1:10 or 1:4).
  - –**Rytary** is an extended release formulation



Levodopa adverse effects

- GI (levodopa alone)
  - –Anorexia, vomiting and nausea in 80% of patients
    - avoid use of antiemetics like phenothiazines because they have extrapyramidal effects (dopamine antagonist)
    - carbidopa combination reduces these effects (<20%)
- CV
  - Tachycardia, ventricular extrasystoles, and rarely atrial fibrillation
    - these effects reduced in presence of carbidopa
  - Postural hypotension (sometimes, usually asymptomatic)
  - Hypertension usually in the presence of non-specific MAOI or sympathomimetics or with large doses of levodopa.

Levodopa adverse effects

- Dyskinesias
  - –Occur in 80% of patients with long term therapy
    - Can consist of chorea, ballismus, athetosis, dystonia, myoclonus, tics or tremor
    - Choreoathetosis of the face and distal extremities is most common presentation
    - Worse at peak plasma [ ]. Extended release formulation may help

Dyskinesias Movie

Behavioral effects

- –More common with Carbidopa (→ ↑ brain dopamine levels)
  - Depression
  - Anxiety / agitation
  - Insomnia / Somnolence
  - Confusion / delusions / hallucinations.

Drug Holidays

- If adverse effects become too severe, withdraw medicine
  - –withdraw gradually to avoid severe akinesia
  - –break can last between 3 and 21 days
  - –reinstate dose gradually
  - –falling out of favor: depression, venous thrombosis, pulmonary embolism can occur.

L-dopa
Interactions & Contraindicatons

- Interactions
  - –pyridoxine (vitamin B6) enhances the extracerebral metabolism of levodopa
  - –MAOI and levodopa can produce hypertensive crisis if given within two weeks of each other
- Contraindications
  - –do not give to psychotic patients*
  - –patients with angle closure glaucoma
    - levodopa increases intraocular pressure
  - –patients with active peptic ulcers
  - –patients with a history of melanoma
    - No longer considered a contraindication
    - levodopa is a precursor of melanin.

*Pimavanserin covered In antipsychotics lecture

Pimavanserin (Nuplazid) - FDA approved 2016

a non-dopaminergic atypical antipsychotic[1] developed by Acadia Pharmaceuticals for the treatment of **Parkinson's disease psychosis and schizophrenia.** Pimavanserin has a unique mechanism of action relative to other antipsychotics, behaving as a selective inverse agonist of the serotonin 5-HT2A receptor, with 40-fold selectivity for this site over the 5-HT2C receptor and no significant affinity or activity at the 5-HT2B receptor or dopamine receptors.[2] The drug has met expectations for a Phase III clinical trial for the treatment of Parkinson's disease psychosis,[3] and has completed Phase II trials for adjunctive treatment of schizophrenia alongside an antipsychotic medication.[4] On September 2, 2014, the United States Food and Drug Administration granted Breakthrough Therapy status to Acadia's New Drug Application for pimavanserin.[9] It was approved by the FDA to treat hallucinations and delusions associated with psychosis experienced by some people with Parkinson's disease on April 29, 2016.[10]

Dopamine agonists

- Advantages:
  - –No enzymatic conversion required
  - –cross BBB without competing for amino acid transporter
  - –no potentially toxic metabolites
  - –old standards (Ergot derivatives)
    - Bromocriptine
    - Pergolide
  - –Newer agonists (synthetic, non-ergot alkaloids)
    - Pramipexole
    - Ropinirole
  - –Other
    - Apomorphine.

Ergotism Symptoms

The symptoms can be roughly divided into convulsive symptoms and gangrenous symptoms.

Convulsive symptoms

Convulsive symptoms include painful seizures and spasms, diarrhea, paresthesias, itching, headaches, nausea and vomiting. Usually the gastrointestinal effects precede central nervous system effects. As well as seizures there can be hallucinations resembling those produced by LSD (lysergic acid diethylamide, to which the ergot alkaloid ergotamine is an immediate precursor and therefore shares some structural similarities), and mental effects including mania or psychosis. The convulsive symptoms are caused by clavine alkaloids.

Gangrenous symptoms

The dry gangrene is a result of vasoconstriction induced by the ergotamine-ergocristine alkaloids of the fungus. It affects the more poorly vascularized distal structures, such as the fingers and toes. Symptoms include desquamation, weak peripheral pulse, loss of peripheral sensation, edema and ultimately the death and loss of affected tissues.

Dopamine agonists

Bromocriptine (ergot derivative)

Mechanism of action

- –D_2 receptor agonist (partial D_1 agonist)

Absorption and Excretion

- –variable from GI, peak plasma levels 1-2 hours post oral dose
- –excreted in bile and feces

Clinical use

- –can be used as a first line treatment for Parkinsonism
- –commonly used to treat hyperprolactinemia
- –often used in combination with Sinemet
- –build dose up slowly to minimize adverse effects (2-3 months)
- –stop treatments if psychiatric disturbances, cardiac dysrhythmias, erythromelalgia, ergotism, or other intolerable adverse effects.

Dopamine agonists

Pergolide (ergot derivative)

Mechanism of action

- –D_1 and D_2 receptor agonist

Absorption and Excretion

- –Given orally
- –loses effectiveness over time (receptor downregulation?)

Clinical use

- –similar to Bromocriptine, but more effective
- –may benefit patients not receiving levodopa
- –aid patients with response fluctuations to levodopa

Adverse effects

- –frequent at initiation of therapy – resemble bromocriptine.

Ergot derivatives – Adverse Effects

- GI
  - anorexia, nausea and vomiting. Also, constipation, dyspepsia, peptic ulcers and symptoms of reflux esophagitis
- CV
  - Postural hypotension and cardiac arrhythmias
- Dyskinesias
- Mental disturbances
  - Confusion, hallucinations, delusions, and other psychiatric reactions

Miscellaneous

- Headache, nasal congestion, increased arousal, pulmonary infiltrates
- Ergoline-induced symptoms
- Erythromelalgia (pain, redness of extremities), vasospasm, and pleural or retroperitoneal fibroses.

Fibroses can resolve if drug discontinued.

Ergoline; e.g., LSD, hallucinogenic e.g., morning glory

Ergot derivatives – Adverse Effects

- Contraindications
  - Psychotic illness
  - MI history
  - peripheral vascular disease
  - peptic ulcers.

Dopamine agonists

Pramipexole and Ropinirole (synthetic)

Mechanism of action

- –Pramipexole: Preferential affinity for D_3 family of receptors
- –Ropinirole: Pure D_2 receptor agonist

Clinical use

- –Pramipexole
  - used as monotherapy for mild parkinsonism
  - in combination therapies for advanced patients
  - reduces required levodopa dose & smooths response fluctuations
  - Putative neuroprotective effects (scavanges free radicals)
  - Pharmacokinetics: rapid oral absorption, excreted unchanged in urine, gradually increase dose
- –Ropinrole
  - Use similar to pramipexole.

Dopamine agonists

Pramipexole and Ropinirole

Adverse effects

- Ergoline-induced effects unlikely
- Postural hypotension, fatigue, somnolence, peripheral edema, nausea, constipation, dyskinesias and confusion.

Pramipexole: approved July 1997

Ropinerole: approved September 1997

Dopamine agonists

Apomorphine

- Temporary relief of off-period akinesia, especially in advanced disease state
  - –Administer subcutaneous
  - –Rapid onset ~10 minutes, Duration 2 hours
- Adverse effects
  - –Nausea
    - Pretreat with antiemetic trimethobenzamide or domperidone
  - –Dyskinesias, drowsiness, sweating, hypotension

(note: this drug also used to treat erectile dysfunction).

Apokyn (apomorphine hydrochloride); Mylan Laboratories; For the treatment of acute, intermittent hypomobility episodes associated with advanced Parkinson's disease, Approved April, 2004

Monoamine oxidase inhibitors

- MAO-B metabolizes dopamine

  Note: Antidepressant-MAO-inhibitors are either nonspecific or inhibit MAO-A more specifically (MAO-A: Serotonin and Norepinephrine)

- Selegiline,Rasagiline,Safinamide: (somewhat) selective MAO-B inhibitors
  - –retard the breakdown of dopamine
  - –enhance and prolong the antiparkinsonism effects of levodopa
  - –reduce response fluctuations, less severe “off” episodes
  - –lowers necessary dose of levodopa
  - –antioxidant properties?
- Adverse effects
  - –insomnia when taken late in the day
  - –should not be taken with patients on meperidine, tricyclic agents or serotonin reuptake inhibitors or in combination with nonspecific MAO inhibitors (also hits MAO-A at high doses).

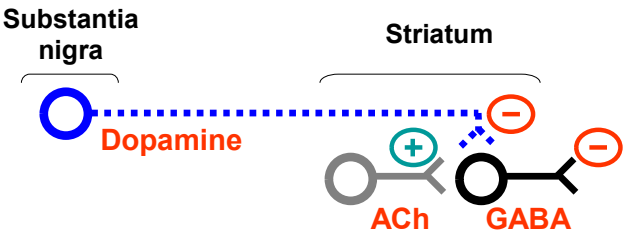
Catechol-o-methyltransferase inhibitors

- COMT metabolizes L-dopa → 3-*O*-methyldopa (3OMD)
- Drugs available
  - –Tolcapone – central and peripheral inhibitor
  - –Entacapone – peripheral inhibitor only
  - –*Stalevo*™ = levodopa+carbidopa+entacapone combination
- Studies indicate improved activity during daily living
  - –reduced response fluctuations with levodopa
  - –↓peripheral dopa decarboxylase → compensatory ↑ in COMT
  - –decreased levodopa clearance
  - –Both have 2 hour half life. Tolcapone has longer duration (admin orally TID while Entacapone is taken QID or 6x daily).

Catechol-o-methyltransferase inhibitors

- May alter uptake of L-dopa into CNS
  - –COMT metabolizes levodopa into 3-methyldopa which competes for active transport across BBB
- Adverse effects
  - –↑ levodopa toxicity (dyskinesias, nausea, and confusion)
  - –Diarrhea, abdominal pain, orthostatic hypotension, sleep disturbances, and orange urine
  - –Tolcapone may be hepatotoxic.
    - Death from acute hepatic failure is rare, but requires signed patient consent and monitoring of liver function q. 2 weeks during first year.

ACh Blocking drugs



Clinical use

- –May improve tremor and rigidity
- –Little effect on bradykinesia
- Start at low dose and gradually increase
- Common antimuscarinic drugs (responses may vary)
  - –Benztropine
  - –Biperiden
  - –Orphenadrine
  - –Procyclidine
  - –Trihexyphenidyl.

ACh Blocking drugs

Adverse effects (antimuscarinic effects !)

–CNS: drowsiness, mental slowness, inattention, restlessness, confusion, agitation, delusions, hallucinations and mood changes

–dryness of the mouth, blurring of vision, mydriasis, urinary retention, nausea, vomiting, constipation, tachycardia, increased intraocular pressure

Contraindications

–prostatic hyperplasia

–obstructive gastrointestinal disease

–angle-closure glaucoma.

Alison J. Yarnall et al. Anticholinergic Load: Is there a Cognitive Cost in Early Parkinson's Disease?, *Journal of Parkinson's Disease* (2015). DOI: 10.3233/JPD-150664

-no increased risk in PD patients

A study found a greater risk of dementia, in particular Alzheimer's disease (AD), in individuals using anticholinergic medications regularly.

a 2020 study by UC San Diego School of Medicine researchers found an association between anticholinergic medications and increased risk of Alzheimer's disease. Another study cited by authors reported that taking just one strong anticholinergic medication for three years was associated with a 50 percent increase in the odds of developing dementia over the 11-year study period.

A_{2A} Antagonist

Istradefylline

- –Analog of caffeine
- –Selective antagonist of adenosine A_{2A} receptor

Clinical use

- –Use as adjunct to levodopa/carbidopa
- –Reduces off-periods
- –Long half life (~66 hrs), so once daily (q.d.) dosing

Adverse effects

- –Nausea, sleeplessness (like caffeine!)
- –Overdose leads to hallucinations, agitation, dyskinesia

VMAT2 inhibitor

Valbenazine

- –Indicated for treatment of tardive dyskinesia
  - •Discussed in Dr. Zwerin's Schizophrenia lecture
- –Vesicular monoamine transporter 2 (VMAT2) inhibitor
  - •Exact mechanism unknown
- –See antipsychotics lecture

Adverse effects

- –Somnolence

Deep Brain Stimulation

- Indicated mainly for patients who have stopped responding well to medications.
- Electrodes implanted into subthalamic nuclei or globus pallidus
- Connected by lead wires to pulse generator in chest wall
- contraindicated in patients with secondary or atypical parkinsonism, dementia, or failure to respond to dopaminergic medication
- Adaptive DBS approved February 2025

Unlike traditional DBS which delivers constant stimulation, aDBS detects specific brain patterns associated with symptoms and delivers precisely calibrated electrical pulses to keep symptoms at bay. This adaptive approach aims to provide better symptom control and reduce side effects by only stimulating the brain when needed

Focused Ultrasound Treatment

- Minimally invasive procedure that uses sound waves to precisely ablate a small target in the brain, which can help to reduce tremors
  - Ventral intermediate nucleus of thalamus to control resting tremor
  - Globus pallidus interna or pallidothalamic tract to control bradykinesia, rigidity, dyskinesia
- Unilateral approved in 2021
- Bilateral (6 months apart) approved 2025

AI info (2025)

Focused Ultrasound for Parkinson's Disease: A Review for Medical Professionals

Mechanism of Action

Magnetic resonance-guided focused ultrasound (MRgFUS) is a non-invasive, stereotactic surgical technique that uses high-intensity ultrasound energy to generate a precise, localized thermal lesion in targeted brain tissue. The procedure relies on the convergence of multiple low-energy ultrasound beams, which individually pass harmlessly through the skull. At the focal point, the combined energy is sufficient to raise the temperature to a level that causes thermal ablation of the targeted tissue, effectively disrupting the neural circuitry responsible for specific Parkinson's disease (PD) symptoms. Real-time feedback from magnetic resonance imaging (MRI) is crucial for this process, providing continuous anatomical guidance, target verification, and thermal monitoring to ensure the lesion is created with sub-millimeter precision and to minimize damage to adjacent structures.

FDA-Approved Indications and Targets

MRgFUS has evolved as a treatment for PD, with a growing number of FDA approvals:

Unilateral Thalamotomy: Initial approvals were for the treatment of

medication-refractory, tremor-dominant PD. The target for this procedure is the ventral intermediate nucleus (VIM) of the thalamus. Ablation of the VIM interrupts the abnormal oscillatory activity in the cerebello-thalamo-cortical circuit, which is implicated in the generation of rest tremor.

Unilateral Pallidotomy: Subsequent approvals expanded the indication to include other motor symptoms such as bradykinesia, rigidity, and dyskinesia. This is achieved by targeting the globus pallidus interna (GPi) or the pallidothalamic tract. Disrupting these pathways helps to normalize the activity in the basal ganglia motor circuit.

Staged Bilateral Treatment: The most recent and significant approval in July 2025 by the FDA, based on data from a multi-site clinical trial, allows for staged bilateral treatment. This is a crucial advancement as PD is a systemic disease affecting both sides of the body. The procedure is typically performed in two separate sessions, spaced at least six months apart, and most commonly targets the pallidothalamic tract (PTT). This bilateral approach allows for more comprehensive symptom management, including bilateral tremor, dyskinesia, and other motor fluctuations.

Patient Selection and Considerations

MRgFUS is a viable option for a select patient population. Ideal candidates are those with:

Medication-refractory motor symptoms: Specifically, patients with tremor, rigidity, or dyskinesia that are not adequately controlled by optimal medical therapy.

A good levodopa response: This suggests the motor symptoms are responsive to dopaminergic stimulation, which can be an indicator of a positive response to lesioning of the basal ganglia circuitry.

Anatomical suitability: The procedure requires a clear pathway for the ultrasound beams to pass through the skull. Patients are screened with a CT scan to assess skull density ratio (SDR), as a low SDR can impede the ultrasound's passage and render the procedure ineffective.

General health status: Candidates must be able to lie still in the MRI scanner for the duration of the procedure (typically 2-4 hours) and must not have contraindications to MRI.

Comparison with Deep Brain Stimulation (DBS)

MRgFUS offers a distinct alternative to DBS, each with its own advantages and disadvantages:

FeatureMRgFUSDBS**Invasiveness**Non-invasive (no incision, no implanted hardware)Surgical (requires burr holes, implanted leads, and a pulse

generator)**Mechanism**Permanent thermal ablation of tissueContinuous electrical stimulation**Reversibility**Irreversible and permanentReversible (can be turned off or removed)**Post-procedure care**No ongoing programming or battery maintenanceRequires regular programming and battery replacements**Immediate Effect**Often immediate and dramatic symptom reliefEffects are dependent on post-operative programming**Side Effects**Potential for immediate, but often temporary, side effects (e.g., numbness, gait changes, dysarthria)Potential for surgical complications (e.g., hemorrhage, infection) and stimulation-related side effects (e.g., dysarthria, paresthesia)**Targeting**Currently approved for specific ablative targets (e.g., VIM, GPi, PTT)Can be targeted to a wider range of structures and adjusted post-operatively

Export to Sheets

Emerging Research and Future Directions

Beyond thermal ablation, focused ultrasound is a platform technology with other potential applications in PD. Current clinical trials are exploring its use to:

Temporarily open the blood-brain barrier (BBB): This could allow for the non-invasive delivery of large-molecule therapeutics, such as neuroprotective agents, growth factors, or gene therapies, that would otherwise be unable to cross the BBB.

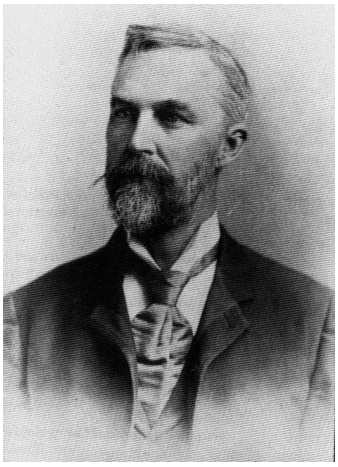
Targeting of alpha-synuclein: FUS is being investigated as a means to enhance the delivery of anti-alpha-synuclein antibodies to the brain, aiming to address the underlying pathology of the disease.

Neuromodulation: Low-intensity FUS can be used to alter neuronal activity without causing ablation, offering a reversible, non-invasive alternative to traditional neuromodulation techniques.

In summary, MRgFUS represents a significant advance in the neurosurgical management of PD. The recent approval of staged bilateral treatment greatly expands its utility, providing a new non-invasive option for patients with complex motor symptoms. As with any ablative procedure, careful patient selection and a multidisciplinary team approach are essential to maximize benefit and mitigate risk.

Huntington's Disease

Huntington's Disease

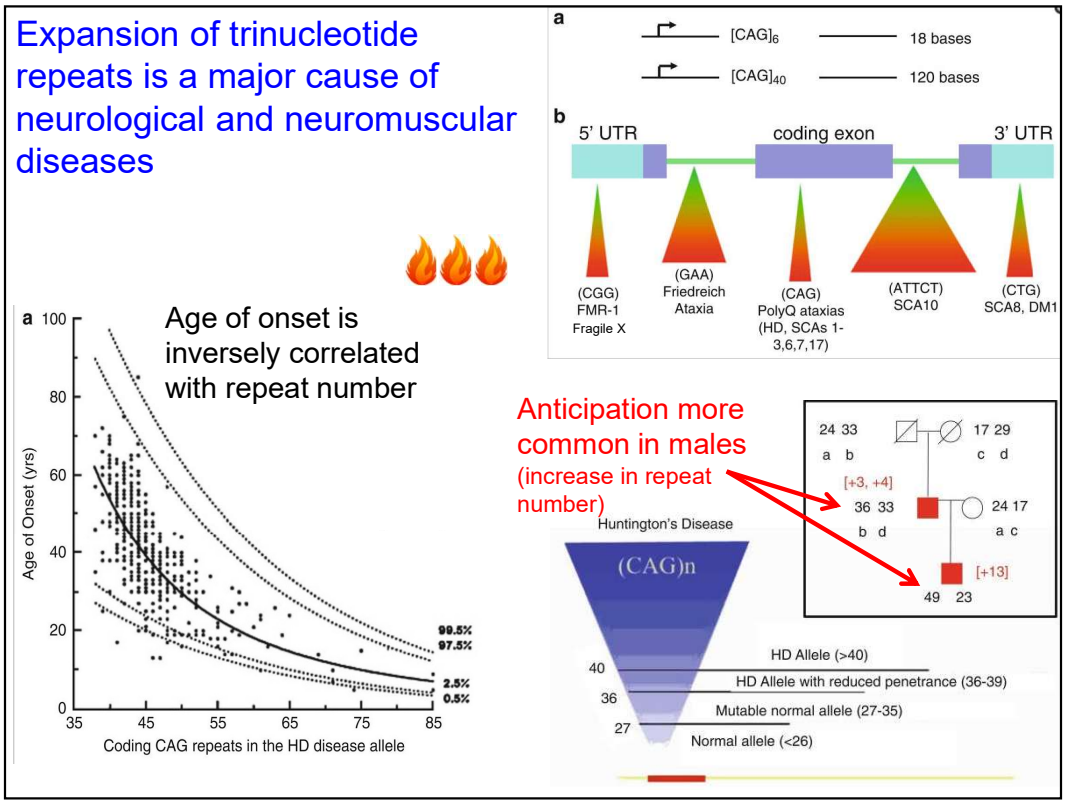


George Huntington
1872

- hereditary - autosomal dominant
  - •CAG triplet repeat disorder (glutamine)
  - •HTT gene codes for huntingtin protein
- prevalence is ~ 1 in 10,000 with
  >150,000 "at risk" in the US
- adult onset primarily -- juvenile variant
- progressive course with fatal outcome

- chorea (later bradykinesia)
- metabolic abnormalities
- cognitive impairment
- psychiatric symptoms

- neurological disorder
- striatum and cortex most affected.



From:

A Brief History of Triplet Repeat Diseases

Helen Budworth and Cynthia T. McMurray

Methods Mol Biol. 2013; 1010: 3–17.

doi: 10.1007/978-1-62703-411-1_1

PMCID: PMC3913379

NIHMSID: NIHMS545434

Trinucleotide repeat expansion disorders caused by triplet repeats in coding and noncoding gene regions. (**a**) Inheritance of disease genes and parent–child transmission causes rapid expansion of repeat regions. (**b**) Triplet repeats residing in coding and noncoding sequences of a gene have significant impact on human health and underlie many severe neurological disorders

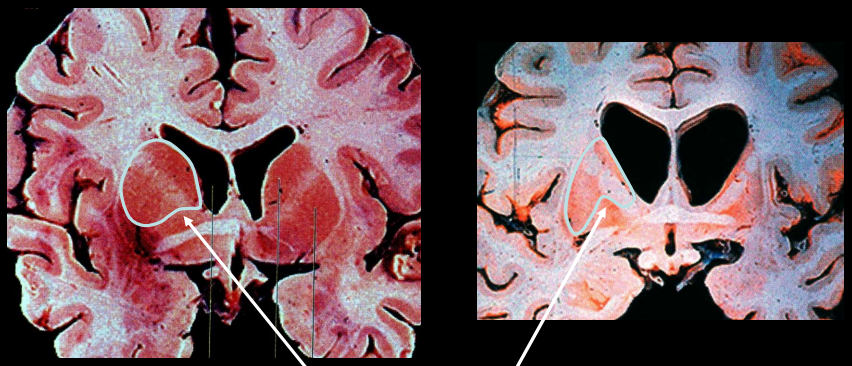
Effect of repeat number on age of onset and anticipation. (**a**) Age of onset is inversely correlated with repeat number. Increasing CAG repeats in the HD disease gene decreases the age of onset of symptoms of the disease. Early onset/juvenile HD symptoms can be seen at repeat numbers above 60.

Effects of CAG expansion in the huntingtin gene. A representative two-generation pedigree of an HD family. *Squares* are males; *circles* are females. *Red boxes* indicate affected individuals. *Open circles* are unrelated spouses. *Black numbers* represent CAG repeat number in each allele of the affected family members. *Small black letters* indicate the alleles present in father-to-son transmission. The *number in brackets*represents the size of the CAG expansion during inheritance. The relationship between HD and CAG repeat number (*left*). In this schematic representation of the HD gene, the *open bar* represents the coding region of the Huntington's gene (called huntingtin); the *small red bar*indicates the position of the CAG repeat stretch located within the N-terminal portion of the coding sequence. The *inverted triangle*represents an increasing number of CAG repeats. The *base of triangle* represents unaffected individuals with 6–26 CAG repeats; *lines*indicate unaffected carriers for disease with 27–35 CAG repeats; and the *top part of the triangle* indicates affected individuals with 36–120 CAG repeats

Postmortem Brain Slices

Normal Brain

HD Brain



Huntington's Movie

Striatum

Huntington's Movie 2

www.sciam.com/dec2002

Huntington's Disease

- No effective treatments
  - Clinical trials have been uniformly disappointing
  - non-pharm. supportive therapy improves quality of life
- Branaplam granted orphan drug status for HD in Oct 2020
  - Originally developed for spinal muscular atrophy (SMA), but clinical trial stopped by Novartis in July 2021
  - Lowers huntingtin protein levels (Oct. 2020)
  - HD patient trials planned for 2021

Up-to-date May 2011 recommends tetrabenazine as an initial treatment

Xenazine (tetrabenazine); Prestwick Pharma; For the treatment of chorea due to Huntington's disease, Approved August 2008

Ingrezza (valbenazine) is a vesicular monoamine transporter 2 (VMAT2) inhibitor. Ingrezza is specifically indicated for the treatment of adults with tardive dyskinesia.

Huntington's Disease

- Drugs which impair dopaminergic neurotransmission often alleviate chorea
  - deplete monoamines by blocking vesicular monoamine transporter
    - tetrabenazine, reserpine
    - valbenazine (also VMAT2 inhib.) – for chorea and tardive dyskinesia
  - block dopamine receptors (atypical neuroleptics (antipsychotics))
    - olanzapine, risperidone, aripiprazole are helpful, especially in patients with both chorea and agitation or psychosis
    - clozapine is helpful, but risk of agranulocytosis, so don't use it
    - quetiapine not helpful for chorea, except at very high doses
  - if refractory to atypical neuroleptics, try 1st gen neuroleptics
    - phenothiazines, butyrophenones
- Dopamine-like drugs exacerbate chorea
  - e.g., Levodopa.

Xenazine (tetrabenazine); Prestwick Pharma; For the treatment of chorea due to Huntington's disease, Approved August 2008

Ingrezza (valbenazine) is a vesicular monoamine transporter 2 (VMAT2) inhibitor. Ingrezza is specifically indicated for the treatment of adults with tardive dyskinesia. In 2024, the FDA approved a new "sprinkle" formulation of valbenazine (Ingrezza) for the treatment of chorea associated with Huntington's disease.

Huntington's Disease

- Rigidity and bradykinesia do not require treatment
  - L-dopa doesn't help akinetic-rigid syndrome in HD
- for patient with psychosis or disruptive behavior,
  - try quetiapine, olanzapine, risperidone
    - covered in antipsychotics lecture
- for depression
  - try tricyclic antidepressants or SSRIs
    - covered in antidepressants lecture
- no known treatment for dementia in HD

ALS

ALS (Amyotrophic Lateral Sclerosis)

- “Lou Gehrig’s disease”, “Stephen Hawking’s disease”
- Cause not known: 10% of cases are familial
- Rapidly progressive, invariably fatal
- Both upper and lower motor neurons die
- Loss of strength, loss of voluntary movement
- Death from respiratory failure
  - Usually 3-5 years after onset
  - 10% of patients survive more than 10 years
  - Mechanical ventilation may be necessary

ALS (Amyotrophic Lateral Sclerosis)

- Riluzole (Rilutek)
- Prolongs survival by several months
- Mechanism not completely known
  - inhibitory effect on glutamate release
    - myorelaxant and sedative at high dose
    - anticonvulsant at moderate dose
  - NMDA antagonist (non-competetive)
  - inactivates voltage-gated sodium channels
  - interferes with intracellular events following excitatory amino acid receptor activation
- Well absorbed p.o., $t_{1/2}$ ~12 hours
- hepatic metabolism
  - cytochrome P450, CYP1A2
  - use with caution in patients with hepatic insufficiency
- common adverse effects: asthenia, dizziness, GI disorders, and elevations in liver enzyme activities.

ALS (Amyotrophic Lateral Sclerosis)

- Edaravone
- Free radical scavenger
  - Delays disease progression
  - Also used following acute ischemic stroke

- Tofersen (Qalsody)
- antisense oligonucleotide
  - first treatment to target a specific genetic cause of ALS
  - approved for patients with a mutation in the superoxide dismutase 1 (SOD1) gene (in 2% of all ALS cases)

Tourette's Syndrome

Gilles de la Tourette's Syndrome

- A chronic disorder involving multiple tics
  - complex genetic inheritance pattern
- Treatment
  - haloperidol most effective (covered in antipsychotics lecture)
    - start with small dosage
  - other treatments may be effective
    - Fluphenazine (dopamine antagonist, antipsychotic)
    - Clonazepam (sedative-hypnotic)
    - Clonidine (α2 agonist)
    - Carbamazapine (antiepileptic, antidepressant)
    - Ropinirole may be useful (dopamine agonist)
    - Botox for focal motor tics
  - Deep Brain Stimulation (DBS) of thalamus.

DBS for Tourette's Movie

What is DBS? See: http://www.uhhospitals.org/services/neurology-and-neurosurgery/institute/our-centers/movement-disorders/health-library/health-article?contentTypeId=135&contentId=38

http://www.uhhs.com/DisplayContent.aspx?PageID=337

Patient Experiences Symptom Resolution Following Brain Surgery

CLEVELAND, April 1, 2004: A neurosurgical team at **University Hospitals of Cleveland (UHC)** has, for the first time in North America, applied a new surgical approach to the treatment of **Tourette Syndrome**, resulting in the immediate and nearly complete resolution of symptoms for the patient, who has suffered from this neurologic disorder since he was a child.

"We were genuinely amazed at the patient's response," says **Robert J. Maciunas, MD,** neurosurgeon at UHC and professor at Case Western Reserve University School of Medicine. He has used the technique called **Deep Brain Stimulation (DBS)** for the treatment of Parkinson's disease and tremor, and was impressed with this patient's dramatic reaction: the disappearance of the jerking motions, muscle tics and grunting associated with his **Tourette's**. "This technique holds great promise for patients suffering from this movement disorder, which often is diagnosed in childhood or early adolescence and can be completely debilitating."

Jeff Matovic, a Lyndhurst, Ohio, resident who grew up in Bay Village, was six years old when he was diagnosed with Tourette Syndrome, a neurobehavioral disorder characterized by sudden, repetitive muscle movements (motor tics) and vocalizations (vocal tics). Though standard therapy with medication controlled his movements for much of his boyhood, his condition severely worsened with age.

Prior to brain surgery, physicians at **University Hospitals Movement Disorders Center** mapped out regions of Jeff's brain, through MRI (magnetic resonance imaging) scans and 3-D computer images. Their goal was to locate the safest and most direct route to reach the cells inside the thalamus portion of the brain, involved in controlling Jeff's movements. By placing electrodes around those cells to deliver continuous high-frequency electrical stimulation, control messages are rebalanced throughout the movement centers in the brain. The electrodes are connected from the brain through wires under the skin (beneath the scalp, neck and upper chest) to an implanted battery just beneath the collarbone. In Jeff's case, since both sides of his body were affected by the movement disorder, he has electrodes implanted on both sides of his brain and tiny battery packs implanted on each side of his chest.

The doctors at University Hospitals of Cleveland are careful to point out that not everyone with Tourette Syndrome requires treatment. The first line of treatment is medication, which can be very effective. Surgical treatment is considered a last resort, and it is not clear how effective deep brain stimulation will ultimately prove for patients with this particular disorder.

In the United States, the Food and Drug Administration has approved deep brain stimulation for the treatment of

Parkinson's disease, essential tremor and dystonia. "We've seen very positive responses in patients with Parkinson's disease. Studies of the DBS technique show that this stimulation can significantly reduce tremor and other symptoms in about three quarters of appropriately selected patients with Parkinson's." says **Brian N. Maddux, MD, PhD**, Jeff's neurologist at UHC and assistant professor at Case School of Medicine. "Patients with a different movement disorder called dystonia can take three months to respond to the electrical stimulation. We didn't know how Jeff would respond. Within hours after the stimulator was turned on, we observed the ceaseless movements become completely relaxed and he was able to walk normally. We were awestruck."

Physicians at University Hospitals of Cleveland have submitted a report of this case for consideration for publication in a peer-reviewed journal. They hope to further explore the application of DBS to other patients with Tourette Syndrome. It is estimated that approximately 200,000 Americans have Tourette Syndrome, though experts believe it is a movement disorder that often remains undiagnosed.

End