Hypokinetic Disorders

- **Parkinsonism**
  - Primary Parkinsonism aka Parkinson's Disease
    - History and Epidemiology
      - onset ~50yo
      - Incidence: ? Prevalence: 100/100,000
      - RFs: FHx, male, age, certain occupations (farming, teaching, health care workers)
      - Highly variable course
    - Mechanism
      - unknown etiology w/ most sporadic but some have an AD genetic pattern suggesting that Parkinson's is caused by an unidentified trigger acting upon a genetically susceptible individual
      - loss of dopaminergic neurons projecting from substantia nigra to striatum resulting in decreased movement (however paradoxically there is a tremor which interestingly is the defining feature) with intracytoplasmic inclusions (Lewy Bodies) seen in surviving cells
    - S/S
      - Coarse Resting Tremor (usually the first Sx, tremor is rarely noticed by pt b/c it occurs at rest and when pt does something like picking up a book the tremor goes away as they look at their hand to pick up the book, pts often can actually stop it by focusing all their cerebral energy on it but when pt is distracted and not doing anything the tremor emerges, called "pill-rolling tremor" b/c the wrist is alternating supination/pronation, even though it occurs at rest it actually remits during sleep)
      - Rigidity (often referred to as "stiffness" by patients, if ratchety then called "Cogwheeling" (due to tremor that is superimposed on rigidity) and if smooth then called "Lead-Pipe", check by passively moving a pts arm while the pt mirror's the motion with his/her other arm ("Mirror Test"))
      - Bradykinesia (Difficulty initiating voluntary movements and during execution movement are slow)
      - Micrographia (not more sloppy b/c remember as the pt undergoes an action the tremor goes away, a good way of monitoring pt while on treatment is by having them write the same sentence after each visit and turning the paper to its side visualizing each sentence as a bar graph with the higher bars indicating less micrographia and thus good management)
      - Posture (when pt stands s/he is amobile and rigid w/ a stooped posture, when pushed they are unable to compensate with corrective movements of the trunk and tend to fall ("Postural Instability"))
      - Gait (difficulty initiating first step, walk w/ small shuffling steps ("Marche a Petits Pas"), walk w/ decreased swing in one arm, with arm disuse capsulitis/bursitis forms leading to pain which is usually the main complaint when they refer to their arm, once they start walking they actually speed up having trouble stopping taking them several steps to stop ("Festinating Gait"), difficulty turning using small multiple steps ("Turning en Bloc"))
      - Face (expressionless face w/ decreased blinking ("Masked Facies"), dysarthria/dysphagia, hypophonia)
      - Higher Cortical Function (dementia, personality change)
    - Dx
      - Parkinson's is a clinical dx, confirmation is with improvement with levodopa, often doctors under medicate and as such response is not elicited and diagnosis is falsely ruled out, therefore titrate up to 1g/d to assess clinical response
      - **MRI only when you are considering Parkinsonism Plus Syndromes** (MRI in primary Parkinsonism is usually normal)
    - Tx/Prognosis
      - While therapy does not alter underlying process it does reduce morbidity and mortality but it is far from ideal, there is loss of efficacy after 3yrs with disablement after 10yrs with mortality shortly after (b/f levodopa 2/3 of pts died w/in 7yrs, there is no general agreement on when therapy should be initiated or which drugs should be primarily used at different stages of the disease but below is a common strategy
      - (1) If no Sx then neuroprotective agents (antioxidants, CoQ10, MAO inhibitors, glutamate antagonists, etc)
      - (2) If yes Sx and tremor is the primary Sx then Reuptake Inhibitors (eg. amantadine (Symmetrel)) or anticholinergics (eg. benztropine (Cogentin)) and if not then look at age below
        - <70 yo: start with Dopamine Agonists (eg. pergolide (Permax)) and MAO-B Inhibitors (eg. selegiline (Eldepryl)) then move to Levodopa/Carbidopa
        - >70yo: Levodopa/Carbidopa, NO Dopamine Agonist or MAO-B Inhibitors b/c of SEs of cognitive impairment, etc
      - Early on start Sinemet CR (sustained release) instead of regular sinemet to create more stable dopamine levels which delays the onset of dyskinesia. Later on start Sinemet Regular and because

it has higher bioavailability you usually do 2/3 of the Sinemet CR dose, given in more smaller but more frequent doses
- Surgery (done for younger pts who respond to levodopa but continue to experience significant periods of medication inefficacy)
  - If tremor is the predominate symptom you can do Stereotactic Unilateral Ventrolateral Thalamotomy which reduces tremor in contralateral body (cannot do bilateral b/c of speech abnormalities) NB Deep Brain Thalamic Stimulation (can be done bilaterally with no speech abnormalities)
  - If bradykinesia and dyskinesia are the predominate symptoms you can do Stereotactic Unilateral Pallidotomy specifically GPi which reduces bradykinesia in contralateral body and dyskinesia bilaterally
  - Fetal Transplantation not done much anymore b/c of ethics, cost, difficulty of procedure, need for immunosuppresion
- "End of Dose Deterioration Phenomenon" b/c of ongoing death of dopaminergic neurons eventually dopa cannot be converted into dopamine resulting in progressive increase in reemergence of symptoms after a few hours
- "On-Off Phenomenon" over the course of day there is a sudden reappearance of symptoms (b/c of short t1/2) that increases over time

- Secondary Parkinsonism
  - Infections: syphilis, HIV, Spongiform Encephalopathy, "Von Economo Encephalitis" 2/2 1916 influenza pandemic
  - Drugs: dopamine blocking antiemetics esp metoclopramide (most common) and neuroleptics
  - Metabolic: hypercalcemia
  - Toxins: CO, CN-, methanol, ethanol, MPTP toxin found in street drugs, manganese, mercury
  - Trauma: "Punch-Drunk Syndrome" 2/2 trauma to head often seen in boxers (Ali)
  - Ischemia
  - Space Occupying Lesions, Hydrocephalus, Cancer
- Parkinsonism Plus Syndromes **(suggested if unresponsive to levodopa, more symmetric findings, lack of tremor, early dementia, other Sx)**
  - **Lewy Body Disease** (Parkinson's + Hallucinations + Severe Dementia)
  - **Frontrotemporal Dementia (FTD) aka Pick's Disease** (Parkinson's + Change in Personality + Severe Dementia)
  - **Multiple System Atrophy aka Shy Drager Syndrome aka Striatonigral Degeneration aka Olivopontocerebellar Degeneration** (Rapid Parkinson's + Cerebellar Sx + Autonomic Instability)
  - **Progressive Supranuclear Palsy** (Parkinson's + Cerebellar Sx + Vertical Ophthalmoplegia + Bulbar Sx)
  - **Corticobasal Ganglionic Degeneration** (Parkinson's + Limb Apraxia/Dystonia/Myoclonus that progresses to alien limb phenomenon where it functions entirely on its own)
  - **Lytigo-Bodig Parkinsonism-Dementia-ALS Complex of Guam** (Parkinson's + ALS, seen in WWII vets who fought in Guam)
  - **Wilsons** (refer)
  - **NPH** (refer)
  - **CJD** (refer)
  - **Small Vessel Atherosclerosis** (refer)

Hyperkinetic Disorders

- **Myoclonus** (non-rhythmic, lightening fast, abrupt movements that are typically not across many joints and do not involve many muscles such that the movements are not elaborate or coordinated but often described as a simple jerk, Tx: valproic acid)
  - Metabolic/Anoxic/Infectious Encephalopathy
  - Seizure esp in childhood
  - Normal: Falling Asleep, Anxiety, Exercise
- **Chorea** (sudden, non-rhythmic, semi-fast movement that is across many joints and does involve many muscles, usually distal muscles, such that movements look purposeful and are low in amplitude looking like dancing, NB hemichorea if one side of body)
  - Sydenham's Chorea of Rheumatic Fever
  - SEs of OCPs/Parkinson's Meds
  - Dentatorubralpallidoluysian Atrophy
  - Neuracanthocytosis
  - Chorea Gravidarum
  - Huntington's Disease
    - History and Epidemiology
      - characterized by Dr. Huntington in 1872
      - prevalence of ~5/100,000
      - onset ~40yo
    - Mechanism
      - AD mutation of the IT15 gene on chromosome 4 which codes for the protein, huntingtin, whose normal function is unknown, the specific mutation is anticipation aka expansion (>40 copies) of a

triplet repeat sequence (CAG) within the gene resulting in a progressive gain of toxic function as the repeat increases (the more repeats the faster progression of disease)
        - abnormal huntingtin accumulates in certain neurons resulting specifically in the loss of ACh neurons within striatum (caudate/putamen) and loss of GABA neurons projecting from striatum to globus pallidus externa
    - S/S
        - gradual emergence of first (1) chorea and (2) psychiatric disorders (ranging from subtle personality changes to mood disorders to outright psychosis) followed by (3) dementia (first Sx in 25% of pts) and then host of other problems very late in course including ataxia, dysarthria, weight loss, bowel/urinary incontinence, et al
    - Dx
        - Genetic Testing: expansion of CAG repeat (NB ethically challenging b/c why inform pts about a disease that has no cure, as such genetic testing is not recommended for children, there have reports of increased suicide after pts have been informed)
        - CT/MRI: caudate atrophy w/ secondary dilation of frontal horns of lateral ventricle
        - CSF: Homovanillic Acid (HVA), a dopamine metabolite, is decreased
    - Tx
        - Genetic/Social Counseling
        - Neuroleptics: commonly used to control chorea/psychosis but the pts are so sedated that the chorea/psychosis is sometimes preferred (esp haldol)
        - Acetylcholinesterase Inhibitors: commonly used to help with dementia but have not been found to halt progression
        - Other: benzodiazepines if agitation, antidepressants if depressed
    - Prognosis
        - Degenerative disorder w/ death ~15yrs from diagnosis 2/2 cardiopulmonary failure or suicide
    - Clinical Studies
        - Neuroprotective Agents
        - Glutaminergic Antagonists
        - Fetal Striatum Transplant
- **Ballismus** (just like chorea but muscles involved are more proximal and thus the movements are high in amplitude and thus look violent and wild, NB called hemiballismus if one side of body, Tx: typically transient lasting days-wks but if Tx is needed then neuroleptics or benzos or even ventrolateral thalamotomy b/c almost always due to a contralateral subthalamic lesion)
    - ?
- **Athetosis** (just like chorea but the movements are much slower and involve more proximal muscles and thus the movements are high in amplitude but look more writhing/squirming/snake-like than violent or wild, NB most pts also have chorea called choreathetosis, Tx: neuroleptics esp haldol)
    - Cerebral Palsy (refer)
- **Dystonia** (just like athetosis but the movements are even slower and involve large portions of the body resulting in very odd, bizarre, grotesque movements/postures, spasms can be sustained for up to several hours or even longer causing contractures and skeletal deformities, 2/2 basal ganglia dsyfxn from decreased dopamine, dystonia can be suppressed by touching the affected body parts, Tx: focal: BOTOX vs generalized: anticholinergics like Benadryl/Artane, dopamine agonists used in Parkinsons)
    - SEs of Neuroleptic Meds
    - Lead Poisoning
    - Hereditary (progressive and multifocal unlike the secondary causes above)
- **Tics** (repetitive acts such as head-shaking, eye-blinking, or sniffing or repetitive vocalizations such as barking, throat clearing, or coprolalia, Tx: neuroleptics esp haldol, clonidine, clonazepam, fluoxetine) & **Stereotypies** (just like tics but are present continuously, termed tardive dyskinesia (TD) if 2/2 neuroleptic use)
    - Tourette and Rett Syndrome
    - Angelman and Prader-Willi Syndrome
- **Fasciculation** (spontaneous contractions of a single motor unit 2/2 denervation, not strong enough to move limb and sometimes not even obvious to pts)
    - Amyotrophic Lateral Sclerosis aka Lou Gehrig's Disease (refer)
    - Polio (refer)
    - Hyperthyroidism
    - Caffeine
    - Stress
    - Sleep Deprivation
- **Restlessness** (?)
    - Restless Leg Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD) (<20yo, S/S: restlessness or jerky movements of LEs, worse w/ later in day and while asleep vs relieved w/ stretching and movement, RFs: IDA, ESRD, pregnancy, Tx: iron, dopamine agonists used in Parkinson's, opioids, gabapentin)
- **Tremors** (rhythmic w/ fixed frequency and amplitude movement)

	Parkinson's/Resting	Cerebellar/Rubral/Intension	Essential/Benign/Familial (most common)	Physiologic	Orthostatic
Worse	Rest	Action (outstretched arm, eyes closed, finger to nose, daily activities like writing, reaching, eating therefore very disabling)	Action	Constant	Volume Depleted
Better	Action	Rest	EtOH	Constant	Fluids
Hz	3-10Hz	1-5Hz	4-8Hz	3-10Hz	16-25Hz
Description	Pill Rolling	Coarse	Fine	Barely Noticeable	
Other S/S	Unilateral Hand/Leg (refer above)	Ataxia Nystagmus Head/Truncal/Low Ext Tremor Voice Tremor Oscillopsia (illusion of moving env)	Vocal Tremor	unique to etiology	
Mechanism	(refer above)	Cerebellar Pathology	AD genetic disorder	Psych: fear, anxiety, fatigue Metabolic: hypoGlu, hyperTH, pheo Toxin Withdrawal: EtOH, AEDs, Li, caffeine, theophylline	
Tx	(refer below)	Gabapentin Stereotactic Unilateral Ventrolateral Thalamotomy reduces tremor in contralateral body (cannot do bilateral b/c of speech abnormalities) Thalamic Stimulation (can be done bilaterally with no speech abnormalities)	Propranolol Primidone Deep Brain Electrical Stimulation of Ventral Intermediate Nucleus of Thalamus	Treat underlying condition	

Therapy: (1) ↑ Dopa or (2) ↓ ACh

2. Life cycle of dopamine

Many of the drugs used to treat PD are secondary agonists, i.e., they influence the synthesis, degradation, and reuptake of dopamine to increase its effective concentration. Therefore, to understand their mechanism of action it is useful to review again how dopamine is made and destroyed. This is schematized in Figure 2.

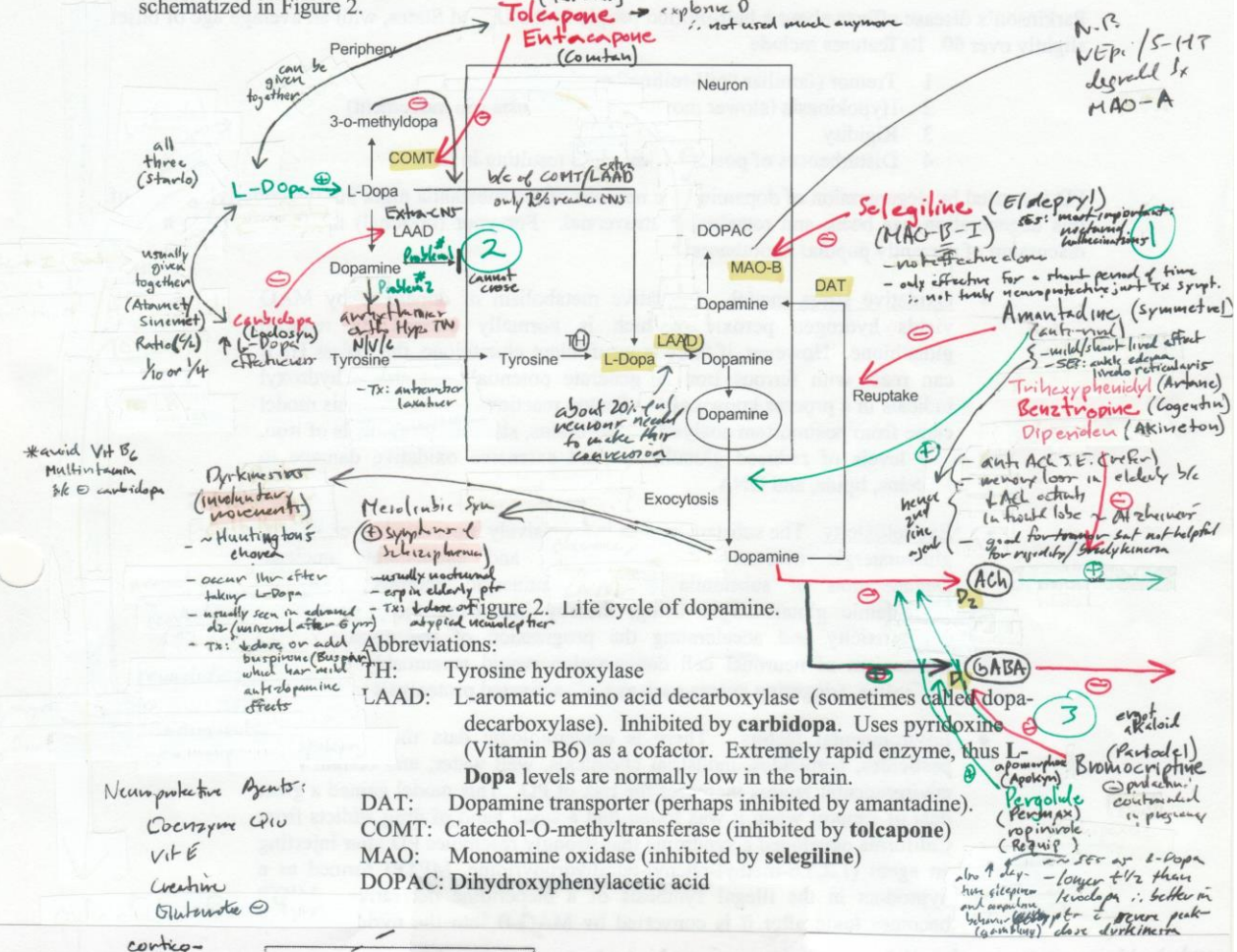

Figure 2. Life cycle of dopamine.

Abbreviations:

TH: Tyrosine hydroxylase

LAAD: L-aromatic amino acid decarboxylase (sometimes called dopa-decarboxylase). Inhibited by **carbidopa**. Uses pyridoxine (Vitamin B6) as a cofactor. Extremely rapid enzyme, thus **L-Dopa** levels are normally low in the brain.

DAT: Dopamine transporter (perhaps inhibited by amantadine).

COMT: Catechol-O-methyltransferase (inhibited by **tolcapone**)

MAO: Monoamine oxidase (inhibited by **selegiline**)

DOPAC: Dihydroxyphenylacetic acid