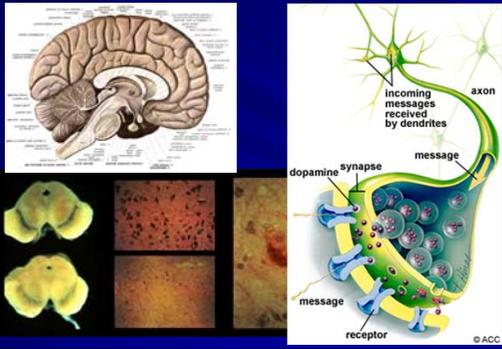


Treatment of Parkinson's Disease: Present and Future

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Neuropathology: Loss of Dopamine-Producing Cells in the Midbrain



PD: symptoms to treat

Motor

- Resting tremor
- Rigidity
- Bradykinesia
- Gait impairment
- Postural instability

Non-motor

- Depression
- Anxiety
- Dementia
- Hallucinations
- Orthostatic hypotension
- Pain
- Fatigue
- Sleep disorders
- Overactive bladder
- Constipation

How do you treat PD?

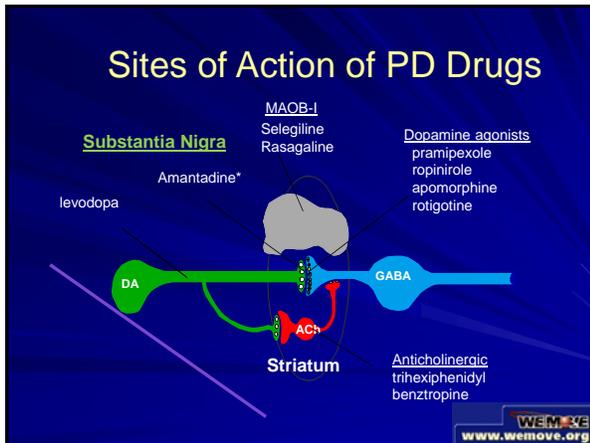
- Medications
- Rehab Therapies
- Exercise
- Education
- Deep brain stimulation (later stages)

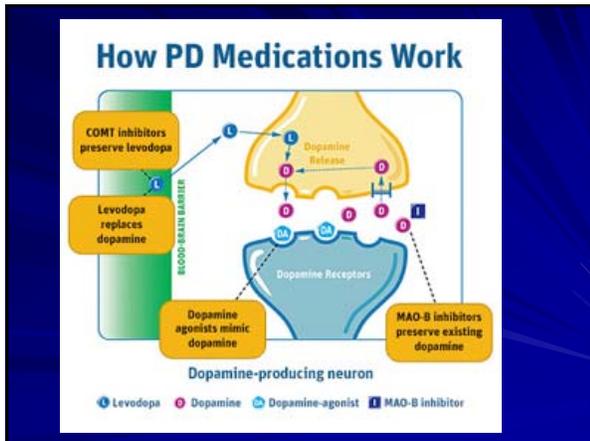
Medication Options for Motor Symptoms

- Replenish dopamine
 - Carbidopa/levodopa (gold standard)
- Mimic dopamine
 - Dopamine agonists
- Increase the brain's own levels of dopamine
 - MAOB-inhibitors
- Other actions
 - Anticholinergic agents
 - Amantadine

What do the PD medications do?

- Mask or reduce the symptoms of PD
 - By impacting the dopamine network
- Medications do not slow progression of or cure the disease
- Medications do not reverse the damage in the brain





What are possible side effects?

- Dizziness, nausea, sleepiness, confusion, hallucinations, leg swelling, constipation, impulsive behavior, low blood pressure, high blood pressure
- Long term side effects of medications
 - Psychosis
 - Motor complications

What are Motor Complications?

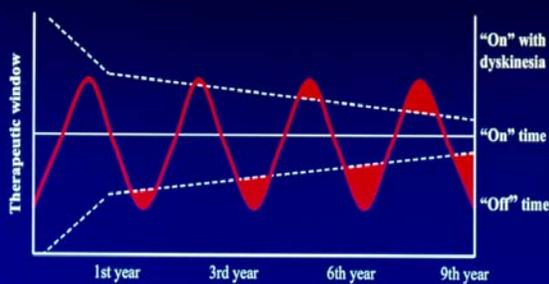
■ Motor fluctuations

- end of dose "Wearing OFF"
- unpredictable "ON-OFF", "Yo-Yo-ing"
- dose failures
- freezing

■ Dyskinesias

- Extra involuntary movements
- Usually peak dose side effect
- 50% of patients after 5 years have them
- 80-90% of patients after 10 years have them

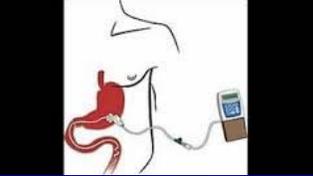
The Therapeutic Window Narrows Over Time



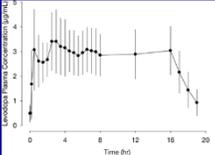
How do you treat motor complications?

- Take doses of levodopa closer together
- Add MAOB-I or COMT-I
 - Slows dopamine metabolism to make dose last longer
- Lower levodopa dose to make dyskinesias go away
 - If dose too low patient turns OFF
- Duopa levodopa pump
- Deep Brain Stimulation

Duopa Levodopa Pump

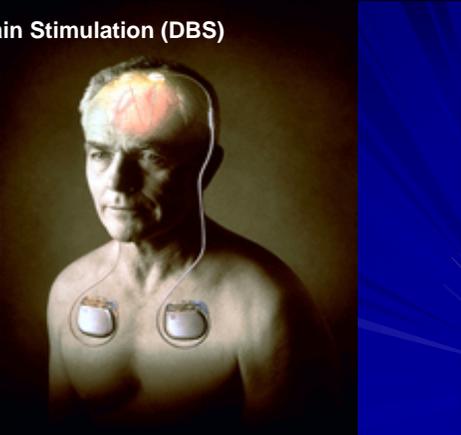


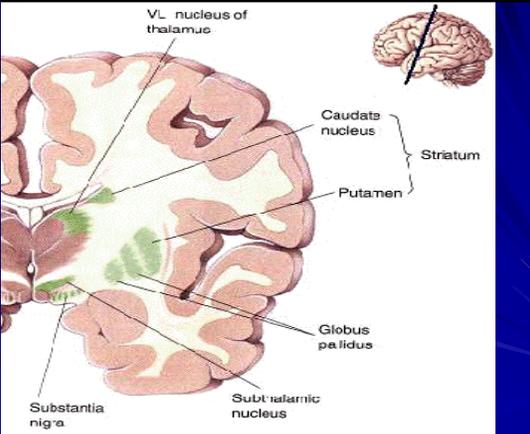
- Stomach empties slowly
- Pills take too long to kick in
- Pills don't absorb (dose failure)

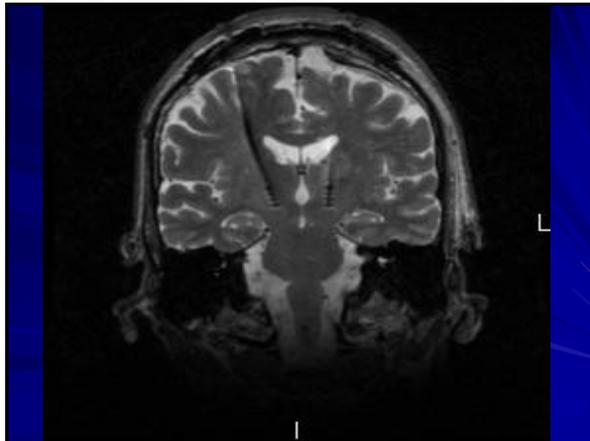


Time (h)	Levodopa plasma concentration (µg/ml)
0	1.5
2	3.5
4	3.8
6	3.2
8	3.5
10	3.2
12	3.0
14	3.0
16	1.5
18	1.2
20	1.0
22	1.5
24	1.5

Deep Brain Stimulation (DBS)







What does DBS do?

- Reduces tremor, rigidity, and bradykinesia
- Reduces OFF time
- Reduces dyskinesias
- Allows reduction of PD medication

- Does not help memory, speech, balance problems, freezing of gait
- Does not cure PD

Non-medication treatments

- Physical therapy: PT
 - Improve balance, gait, mobility, endurance
- Occupational therapy: OT
 - Improve activities of daily living, dexterity
- Speech therapy: ST
 - Improve voice volume, articulation, swallowing
- Exercise
 - Symptom reduction and slows disease progression

The Future: Treatments Under investigation

Treating PD Symptoms



The first image shows three people with tremors, with the caption "Symptom of Parkinson's Disease". The second image shows a person with a stooped posture, a common motor symptom of Parkinson's disease.

New Formulations of Levodopa

- ND0612
 - Subcutaneous levodopa continuous infusion
 - Small patch pump device
 - Steady blood levels for over 24 hours
- CVT-301
 - Levodopa inhaler
 - Rescue medication for OFF times
 - Takes effect in 5 to 10 minutes

Prosavin

- Gene therapy
 - Phase 1 and 2 studies completed
- The gene therapy serum is injected in the region of the brain called the striatum
- Converts targeted cells into a replacement set of dopamine nerve cells
- Shows promise. Too early to know all safety concerns and if effective long term

Slowing Progression of PD

Clinical Trial: STEADY PD III

- Purpose: to determine if isradipine slows progression of early PD
- Isradipine
 - Calcium channel blocker, BP medication
 - Blocks calcium channels in dopamine neurons that keeps the neurons working over time
- Study currently underway here at MCW
 - Enrollment closed

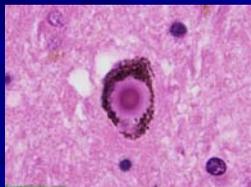
Clinical Trial: SURE-PD

- Purpose: to determine if inosine can slow progression of early PD
- **Inosine**
 - raises uric acid levels
 - Uric acid is a potent brain anti-oxidant
 - People with higher uric acid levels have lower risk of PD
 - PD patients with higher uric acid levels have slower disease progression
- Currently enrolling patients here at MCW

Slowing progression of PD

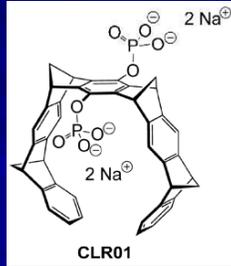
- Growth factors
 - GDNF
 - No effective way found to deliver in target brain region
- Gene therapy
 - Turn neurons into growth factor factories
- Stem Cells
 - Create cells to make growth factors
 - Create cells to make dopamine (just treating symptoms???)

Attacking the Lewy Body



CLR01

- The “molecular tweezers”
- Prevents alpha synuclein from clumping into lewy bodies
- Promising results in animal models of PD



NPT200-11

- A compound that binds to alpha synuclein, rendering it less toxic
- Has shown promise in animal models of PD
- Phase 1 study in people completed!
 - First human trial
 - Assessed safety and dosing
 - Studied in 55 healthy volunteers
 - Doses well above those thought to be needed to treat PD were well tolerated

Nilotinib

- Chemotherapy drug
- Small study of 12 PD patients
- Seemed to reverse the effects of PD in some cases
 - Motor improvement
 - Cognitive improvement
- Cautious optimism
 - Small study
 - Not blinded or placebo controlled

Immune Therapy

- Alpha synuclein vaccine (**PD01A**)
 - One early study in PD patients
 - Induce the immune system to dispose of alpha synuclein so lewy bodies don't form
 - Cautious optimism
 - Encephalitis as a side effect in AD studies
- Alpha synuclein targeted antibody (**PRx002**)
 - Does not stimulate the whole immune system
 - May be safer?

Conclusions

- PD can be successfully treated for many years with a combination of medication, rehab therapies, exercise, education.
- Current treatments improve symptoms and quality of life.
- Research brings hope that future treatments may be able to slow down the disease process in addition to improving the daily symptoms of PD.