

# Treating Parkinson Disease

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IT'S HOW MEDICINE SHOULD BE®

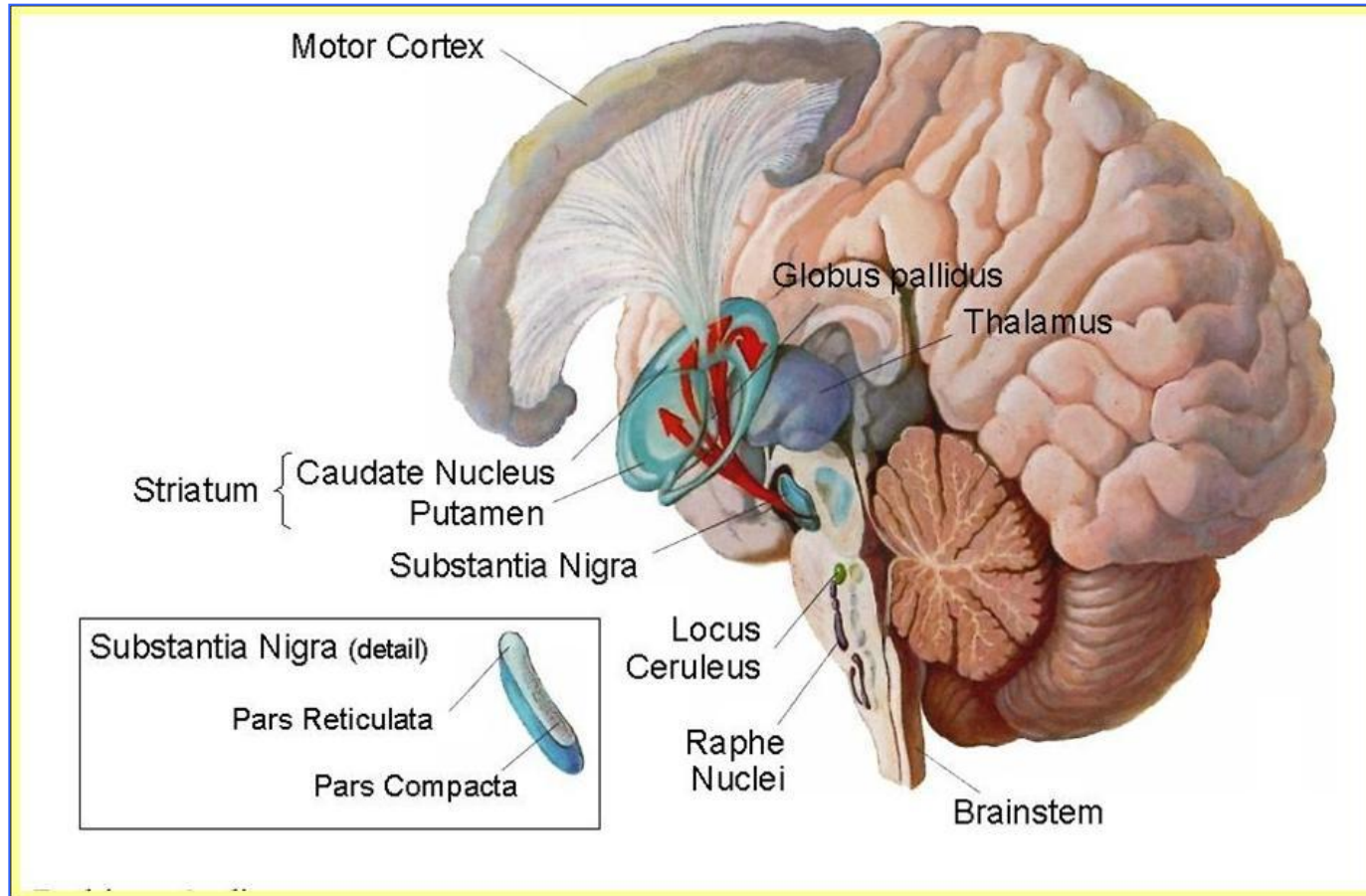
# Outline

- Background
- Why, when, how, and what
- Key points

# Treating Parkinson Disease (PD)

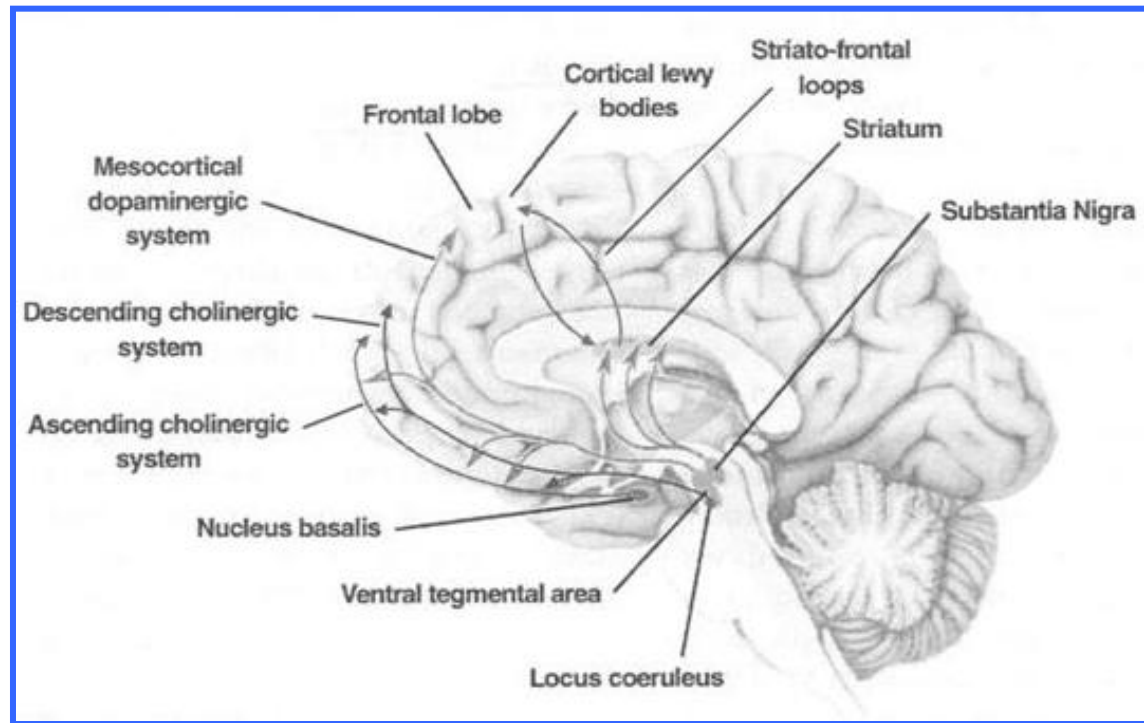
- Neurological substrates of PD
- Neurochemical changes in PD
- Pathology of PD
- Progression of the disorder

# Neurological substrates of PD



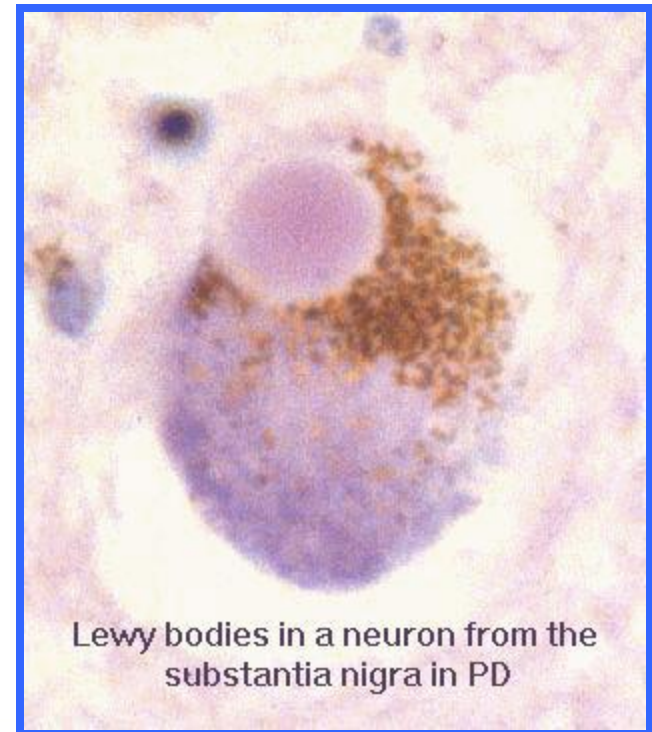
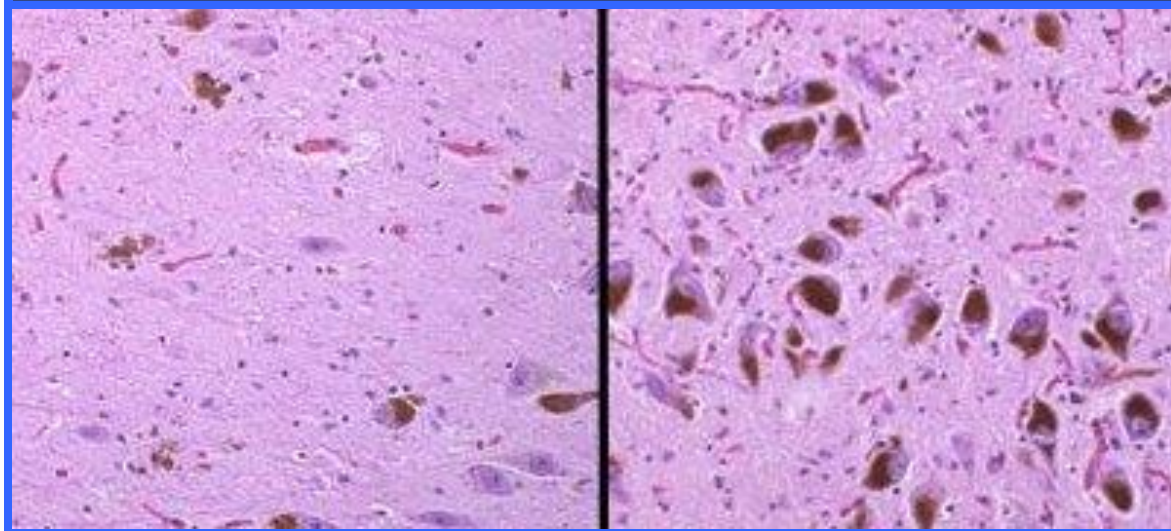
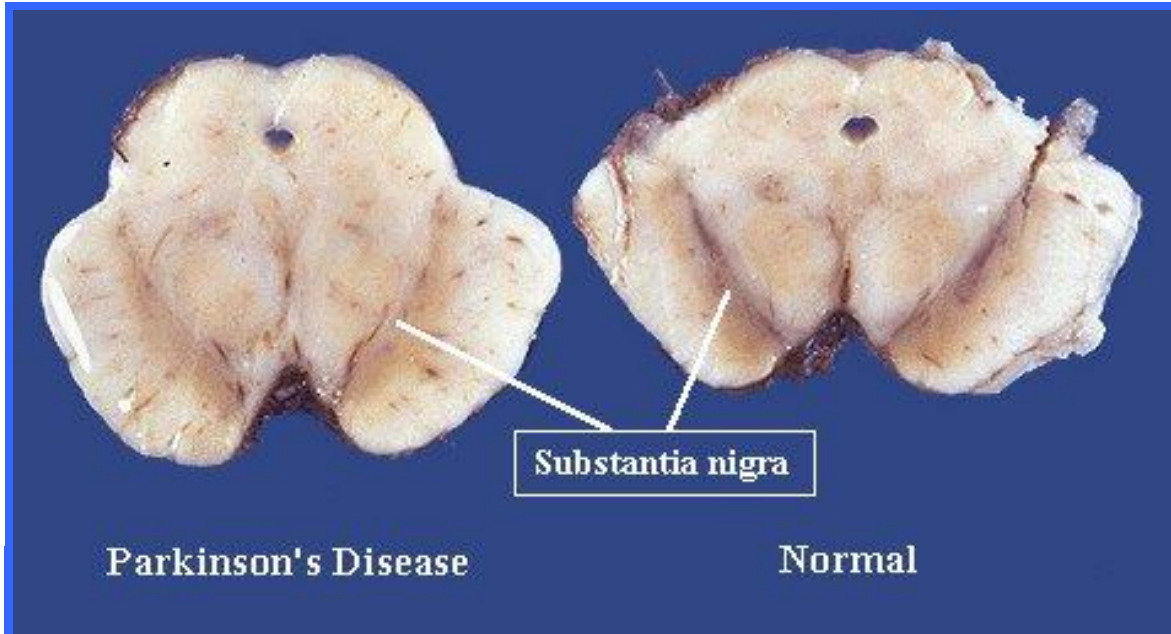
# Neurochemical changes in PD

- Dopamine
- Acetylcholine
- Norepinephrine
- Serotonin
- GABA
- Glutamate

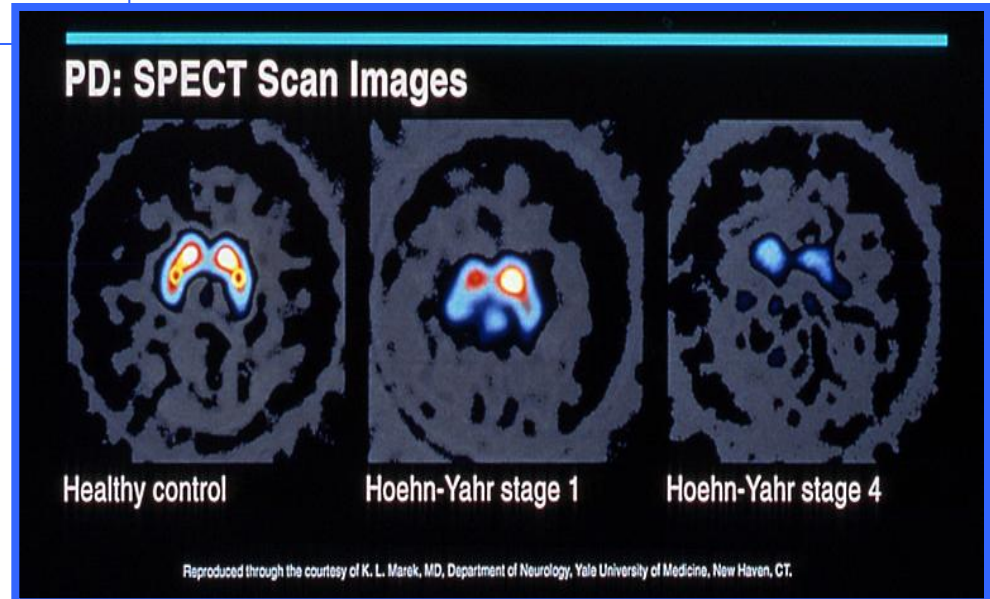
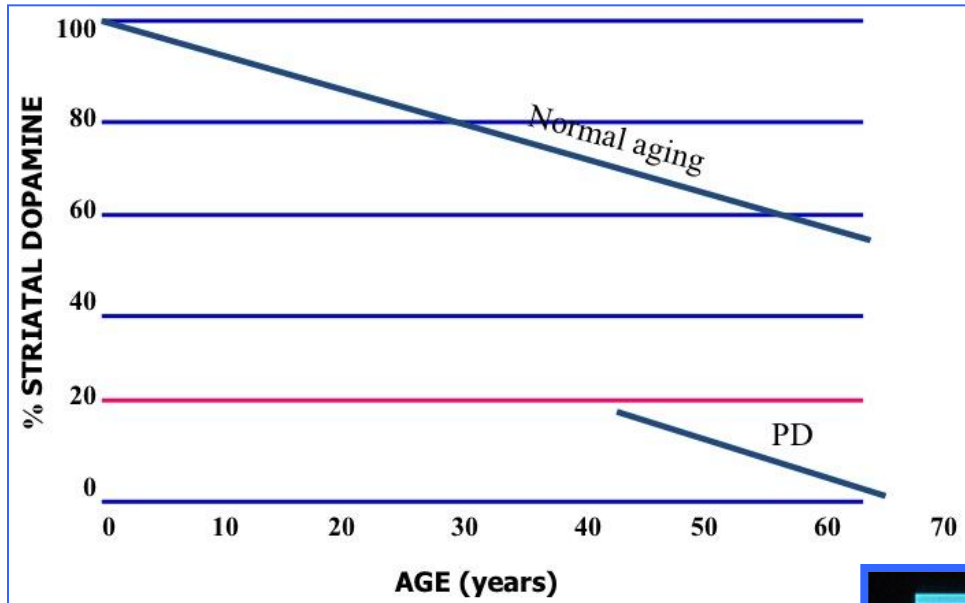


Pillon et al., 2003

# Pathology of PD

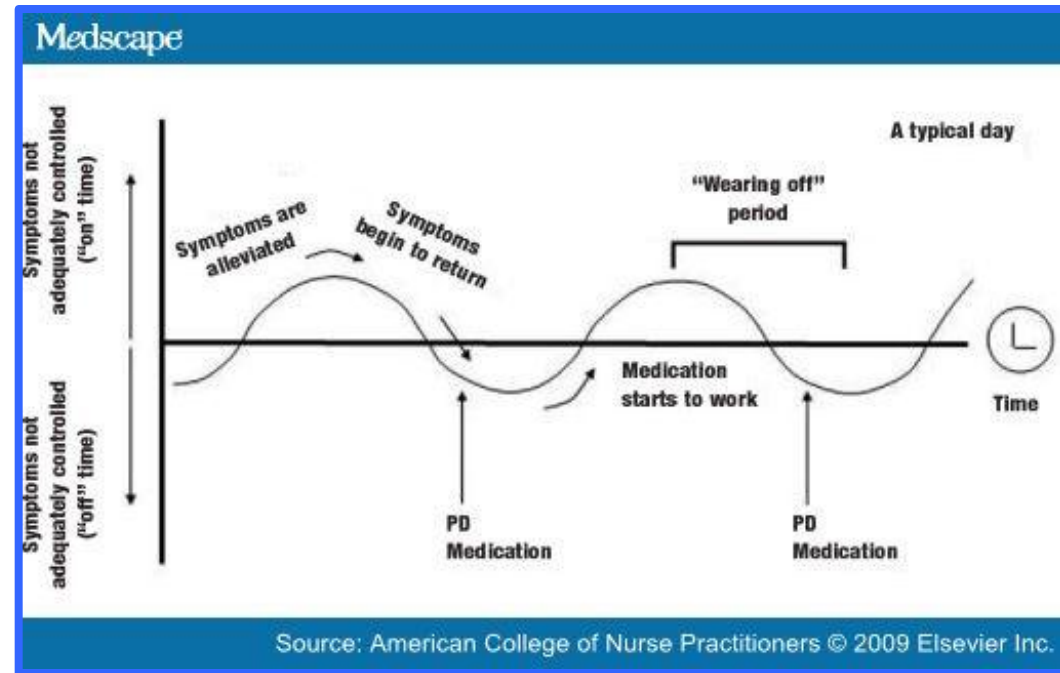


# Progression



# Evolution of symptoms

- Motor fluctuations
  - Wearing off
  - Dyskinesias
- Non-motor features
  - Hallucinations
  - Cognitive changes
  - Autonomic dysfunction
  - Sleep disturbance



# Treatment considerations

## Goal

- Curative
- Neuroprotective
- Symptomatic
- Experimental (research)

## Modality

- Medication
- Surgery
- Non-pharmacologic

## Target symptom

- Motor
- Non-motor

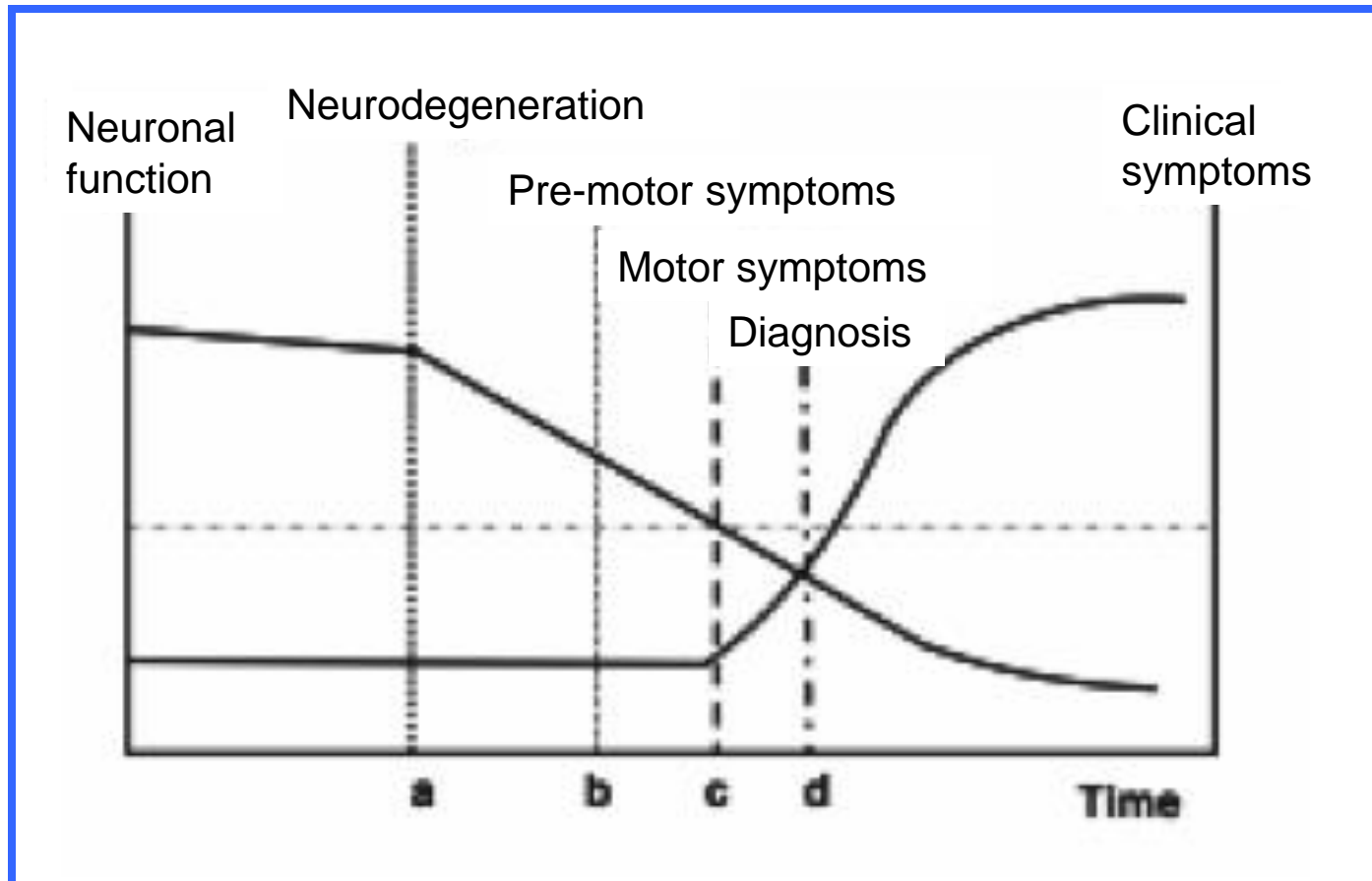
## Stage of PD

- Early
- Middle
- Advanced

# Why treat PD?

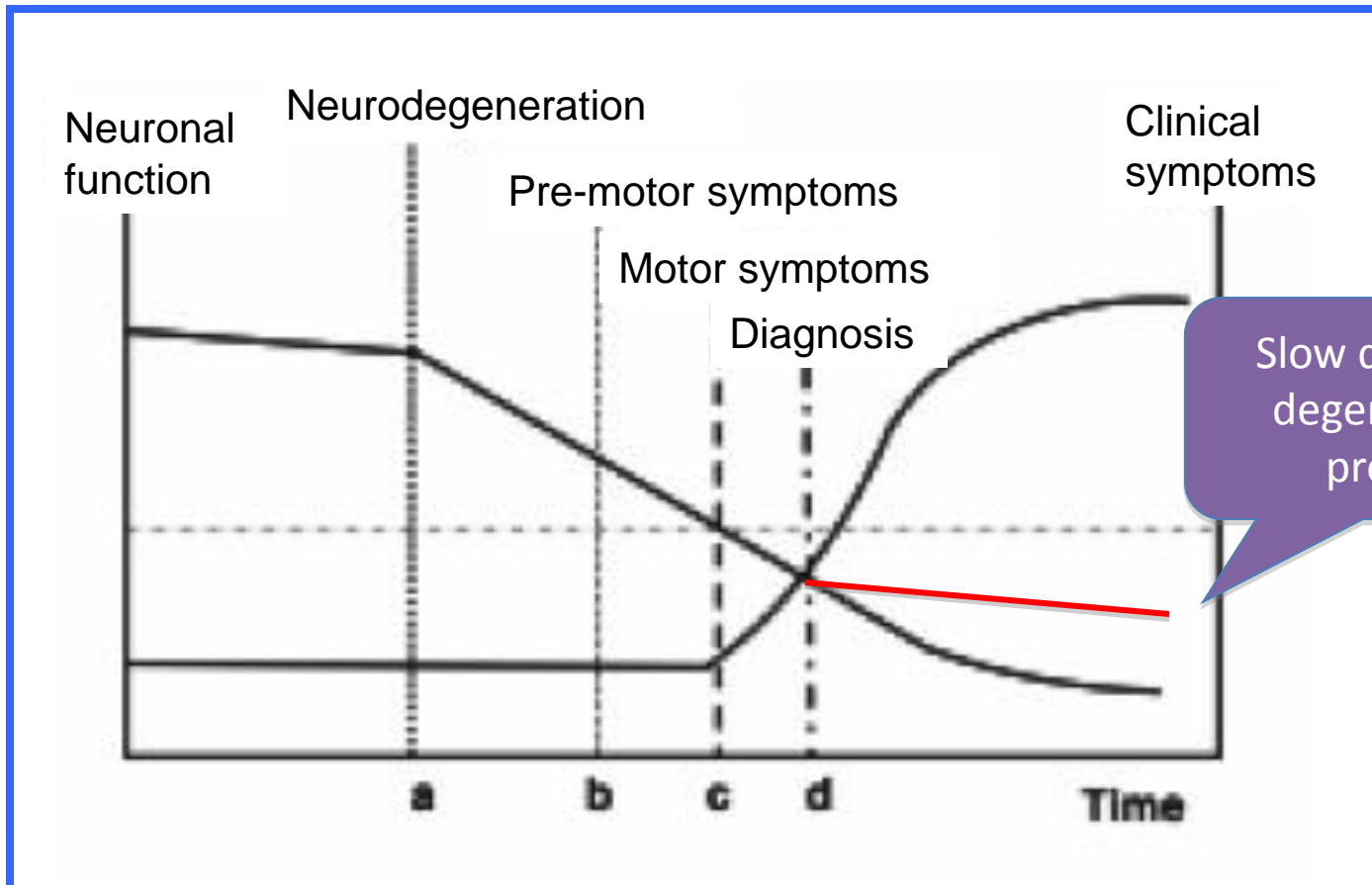
- Improve motor and non-motor symptoms
- Improve quality of life
- Continue productivity in workplace
- Enhance ability to perform activities of interests and activities of daily living
- Ease caregiver stress
- Good medications and therapies are available

# When should we treat PD?



# When should we treat PD, once diagnosed?

- No “right” answer or time...highly individual
- Depends on
  - Degree of functional impairment
  - Employment demands
  - Patient’s well-being
  - Presence of specific symptoms
    - Gait and balance problems
    - Pain, cramps, rigidity
    - Tremor



# Neuroprotection

- No clear established interventions
- Medications being studied
  - Coenzyme Q<sub>10</sub>
  - Rasagiline (MAO-B inhibitor)
  - Glutamate antagonists
  - Creatine
  - Isradipine

# How do we treat PD?

- Medications
  - Neuroprotective (?)
  - Symptomatic
    - Monotherapy
    - Adjunctive therapy and
- Surgery
- Non-pharmacological
  - Physical, occupational, and speech therapies
  - Exercise



Multi-disciplinary  
approach

Individualized  
regimen



# Factors influencing treatment selection

- Age
- Type and severity of symptoms
- Degree of disability
- Concern for specific medication side effects
- Concern for long-term complications
- Patient attitudes towards medications

# What?

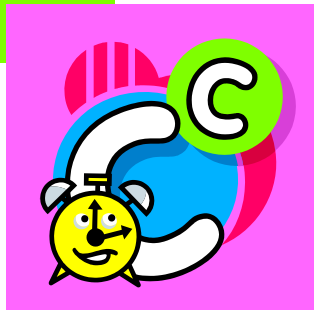
## The ABC's of PD medications



Anticholinergics, Amantadine, (Apomorphine)



MAO B Inhibitors

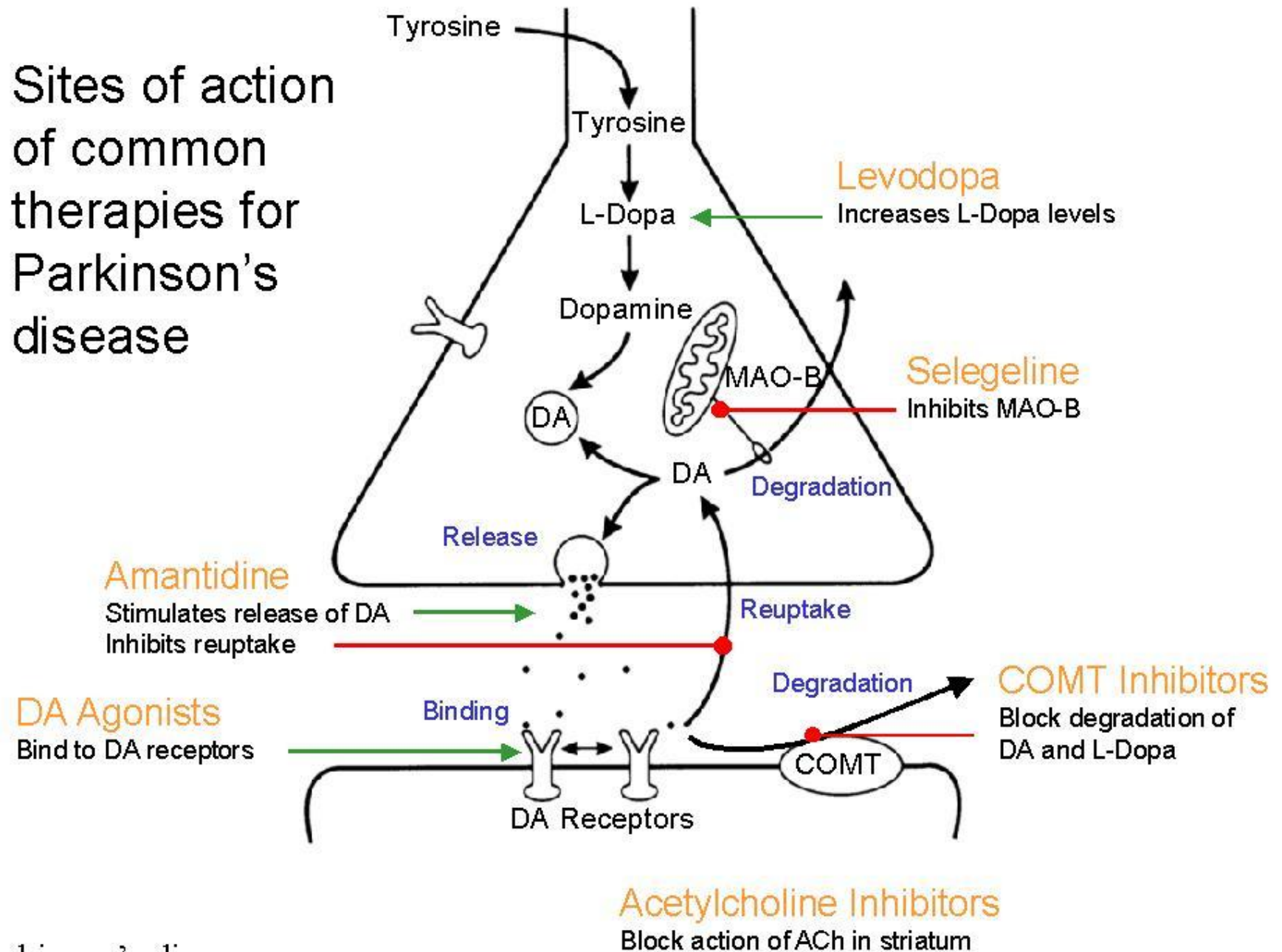


COMT inhibitors



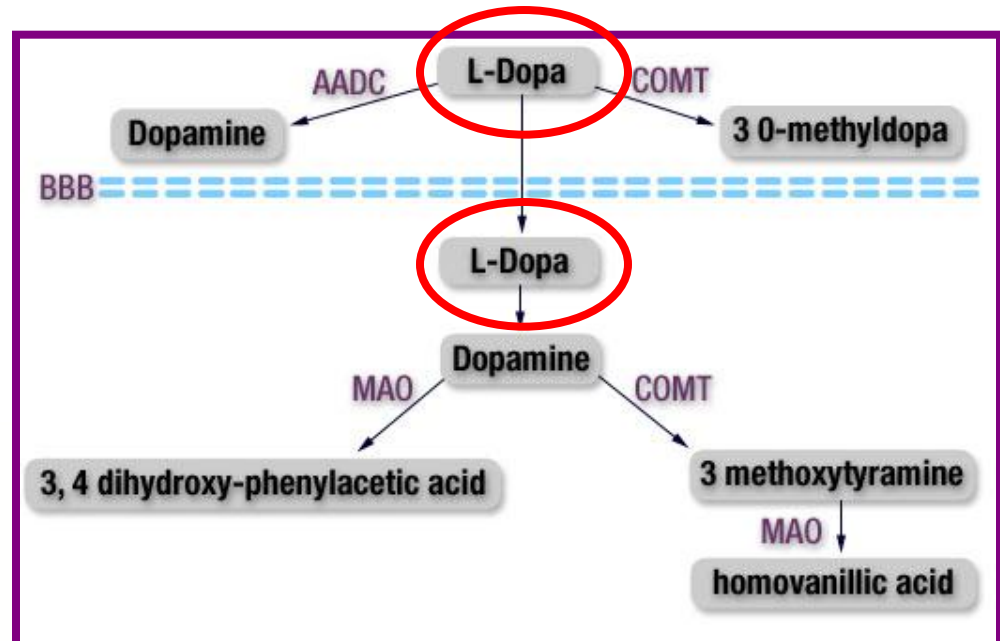
Levodopa, Dopamine agonists

# Sites of action of common therapies for Parkinson's disease



# Levodopa

- Mechanism:
  - Levodopa (L-Dopa) → Dopamine
  - Active transport across blood brain barrier
  - Combined with carbidopa or benserazide (decarboxylase inhibitors) to prevent rapid peripheral conversion to dopamine
- Rationale:
  - Most effective drug for PD motor symptoms
  - “Gold standard”



# Levodopa

- Sinemet (carbidopa/levodopa) 10/100, 25/100, 25/250
  - Immediate release (IR)
- Sinemet CR (carbidopa/levodopa) 25/100, 50/200
  - Controlled release (CR)
- Parcopa 10/100, 25/100, 25/250
  - Orally disintegrating tablets
- Stalevo  
 (carbidopa/levodopa/  
 entacapone) 50, 100, 150
  - Combination medication



# Levodopa

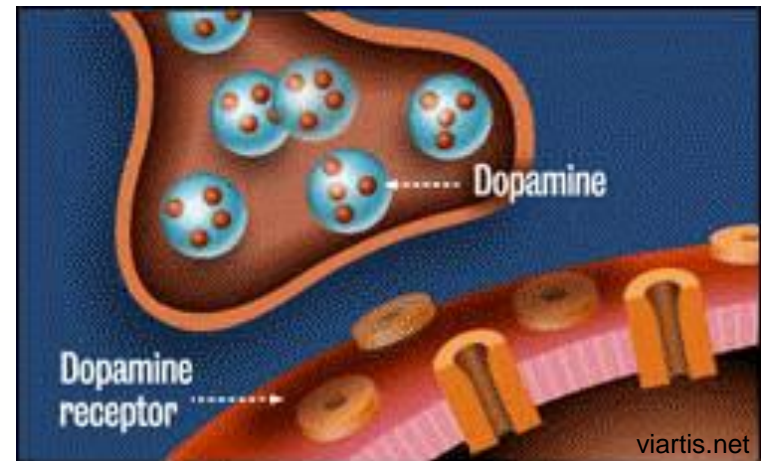
- Sinemet IR
  - Onset of action 20-40 min, duration 2-4 hrs
- Sinemet CR
  - Onset of action 30-60 min, duration 3-6 hrs
  - Bioavailability ~70% of Sinemet IR
- Absorbed in small intestine
- Protein competition
- Average dose: 400-600 mg/day
- Side effects:
  - Nausea, hypotension, somnolence, dyskinesias, hallucinations

# When should levodopa be used?

- Early monotherapy
  - Older age
  - In younger individuals, depending on treatment goals
  - More effective than dopamine agonists in early PD studies though more frequent motor complications
  - No evidence of faster decline in clinical study
- Adjunctive therapy
  - With other PD medications (e.g., anticholinergics, amantadine, dopamine agonists, MAO-B and COMT inhibitors)
- Still considered gold standard of symptomatic treatment

# Dopamine agonists

- Mechanism:
  - Act directly on pre and post-synaptic dopamine receptors
  - Two types: ergot vs. non-ergot dopamine agonists
  - Do not require metabolic conversion like levodopa
  - Do not interact with protein
  - Longer action than levodopa



# Different dopamine agonists

- Bromocriptine (Parlodel)
- Pergolide (Permax)
- Cabergoline (Dostinex)
- Pramipexole (Mirapex)
- Ropinirole (Requip)
- Rotigotine (Neupro)

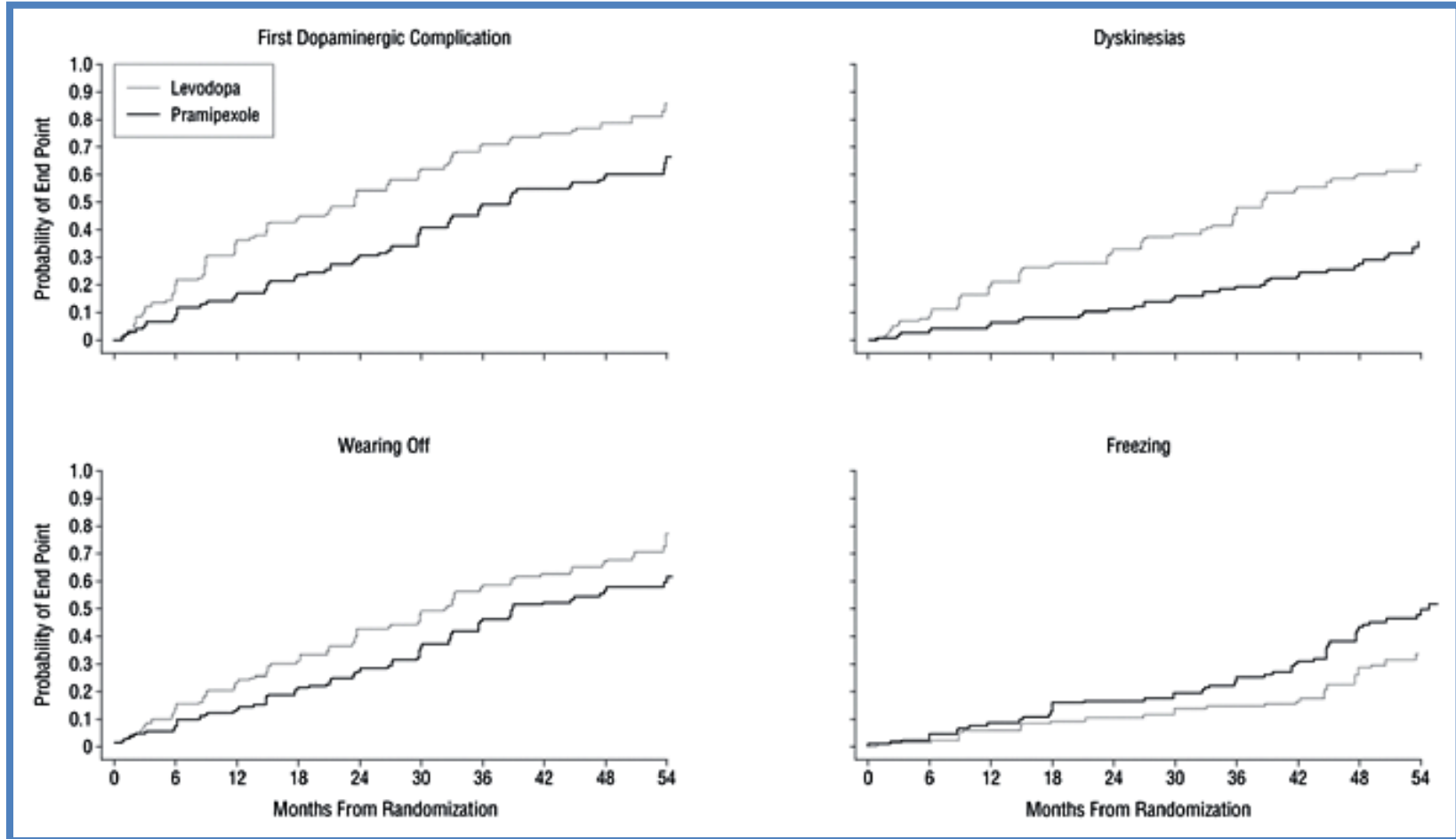
Ergot medications  
Not typically used currently

Non-ergot medications  
Typically used\*\*

Problems with patch so taken  
off market

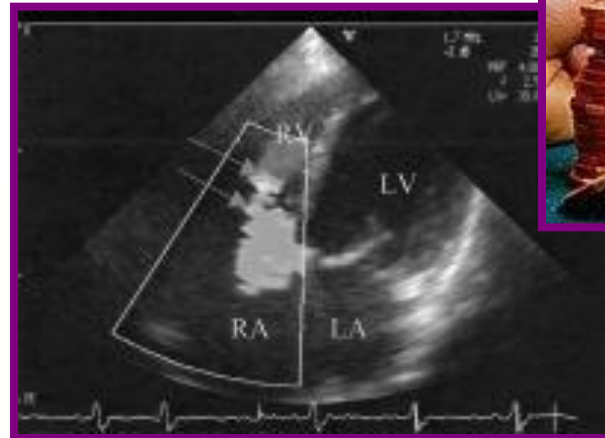
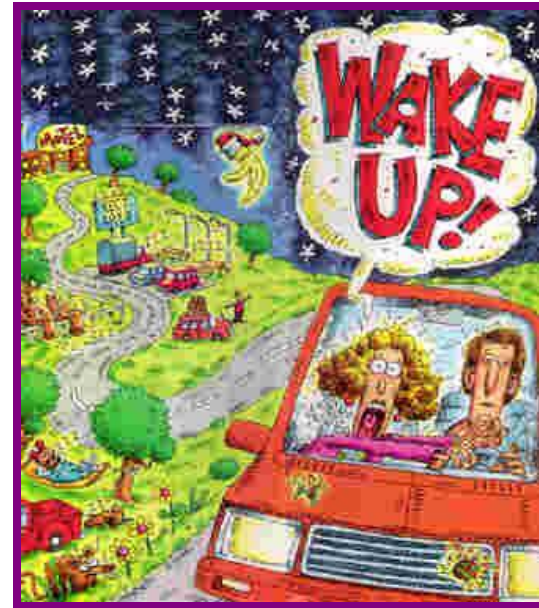


# Dopamine agonists in early PD



# Dopamine agonists

- Side effects
  - Nausea, vomiting
  - Dizziness, hypotension
  - Edema
  - Sedation, “sleep attacks”
  - Hallucinations, psychosis
  - Impulse control disorders (gambling, etc)
  - Valvular fibrosis

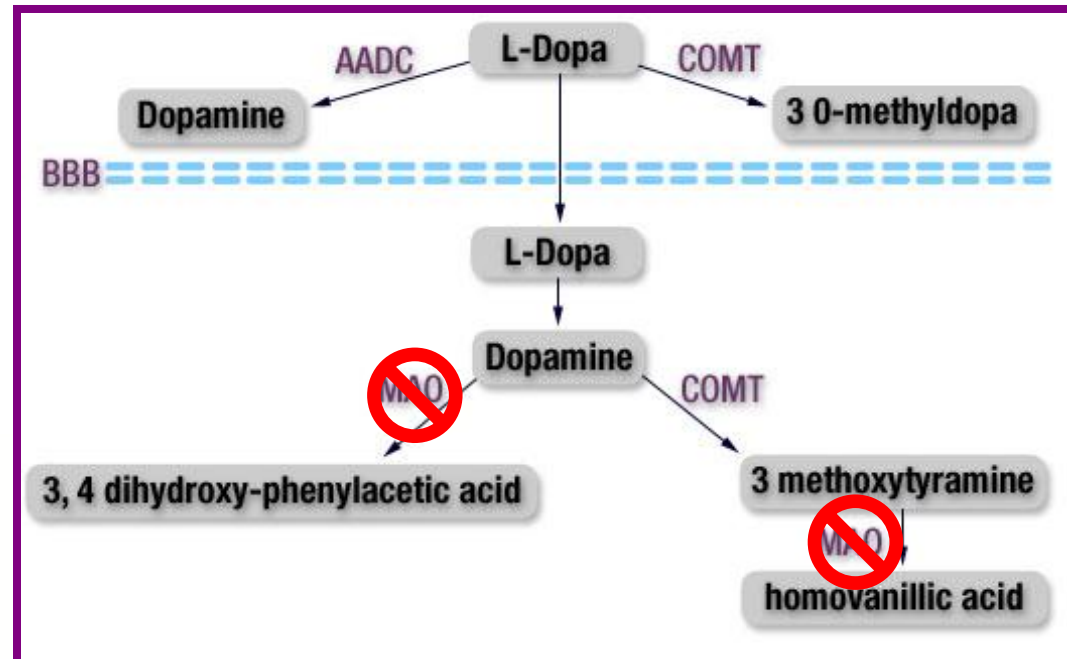


# When should dopamine agonists be used?

- Early monotherapy
  - Fewer motor complications and dyskinesias (vs. levodopa)
  - Not as effective as levodopa for motor symptoms
  - Take longer to titrate
  - Possibly more side effects
- Add on to other PD medications (adjunctive therapy)
  - Longer duration of action
  - Useful in smoothing out motor complications

# MAO B inhibitors

- Selegiline (Eldepryl)
- Rasagiline (Azilect)
- Mechanism:
  - Blocks the MAO B enzyme that breaks down dopamine



# MAO B inhibitors

## Selegiline

- Dose: 5 mg twice daily
  - Not given at night due to amphetamine metabolite
- Zydys selegiline
  - Buccal absorption
  - Dose: 1.25-2.5 mg/day
- Side effects
  - Dizziness, insomnia, nausea, hypotension
- Contraindication: Demerol

## Rasagiline

- Dose: 0.5-2 mg once daily
- Side effects
  - Dizziness, nausea

# When to use selegiline?

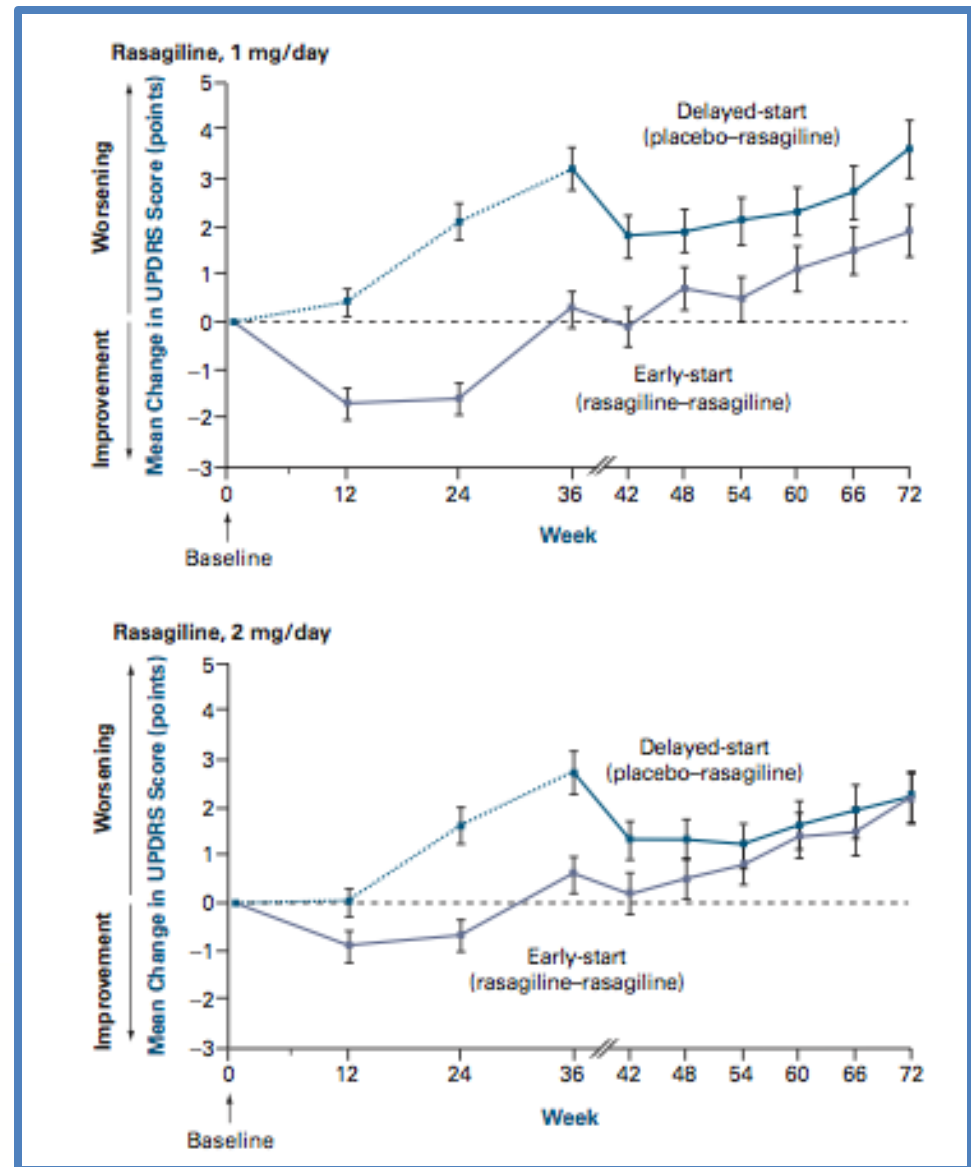
- Early monotherapy
  - Mild symptomatic effects
- Advanced disease - adjunctive therapy
  - But “not efficacious” for preventing motor complications
- Positive effect on freezing of gait?

# When to use rasagiline?

- Early monotherapy
  - Symptomatic benefit
  - Improved quality of life
  - Once daily regimen
  - Side effect profile showed no increased risk in elderly patients
  - Expensive
- Advanced disease - adjunctive therapy
  - Reduces “off” time

# What about neuroprotection and rasagiline?

- Both doses superior to placebo
- Rasagiline 1 mg met all 3 primary outcomes of the delayed start study
- But rasagiline 2 mg dose did not (unclear why?)

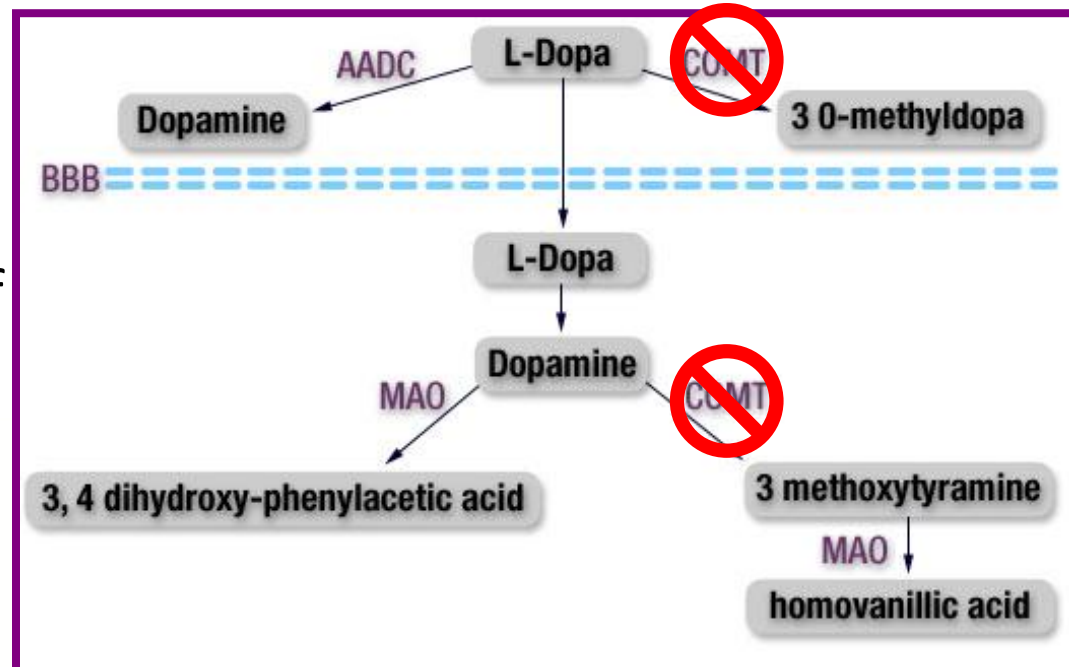


# COMT inhibitors

- Tolcapone (Tasmar)
- Entacapone (Comtan)
- Stalevo (carbidopa/levodopa/entacapone)

- Mechanism:

- Blocks the enzyme that breaks down levodopa
- Extends the duration of levodopa's action

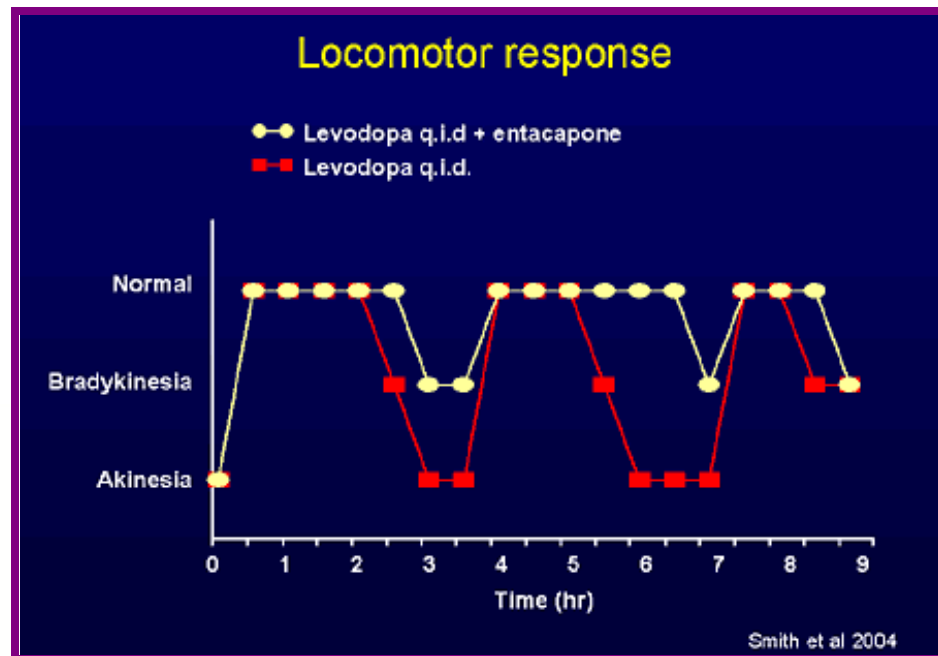


# COMT inhibitors

- Doses
  - Tolcapone (Tasmar) 300-600 mg/day
  - Entacapone (Comtan) 200 mg (up to 8 times/day)
  - Stalevo (carbidopa/levodopa/entacapone) 50, 100, 150
- Side effects
  - Nausea, dyskinesias, diarrhea, orange discoloration of urine
  - Fatal hepatitis in 3/60,000 patients with tolcapone → Written consent, liver function test monitoring

# When to use COMT inhibitors?

- Early treatment
  - Continuous dopaminergic stimulation theory → fewer motor fluctuations over time?
- Advanced treatment
  - To increase “on” time, decrease wearing off



# Anticholinergics

- Trihexyphenidyl (Artane)
- Benztropine (Cogentin)
  
- Proposed mechanism:
  - Restore balance of acetylcholine and dopamine
  
- Historical use of belladonna in 19<sup>th</sup> c. for PD



# Anticholinergics

- Doses (range)
  - Trihexyphenidyl (Artane) 2-12 mg/day
  - Benztropine (Cogentin) 1-8 mg/day
- Side effects often limit their use
  - Dry mouth, blurred vision, hypotension, cardiac arrhythmias, urinary retention, constipation
  - Confusion, hallucinations
- Contraindications
  - Closed angle glaucoma



# When to use anticholinergics?

- Young patients with tremor
  - Effective for tremor +/- rigidity or dystonia
  - No effect on akinesia or postural instability
- Early monotherapy or adjunctive therapy
- Inexpensive
  
- *Not good for:*
  - Elderly or cognitively impaired patients

# Amantadine (Symmetrel)

- Mechanism:
  - Antiviral agent
  - Unique actions on dopamine system via dopamine receptors and indirectly through glutamate
- Doses: 100-300 mg/day
- Dose adjustments in renal impairment and elderly
- Side effects
  - Nausea, dizziness, edema, confusion, livedo reticularis, insomnia

# When to use amantadine?

- Early monotherapy
  - Mild to moderate improvement in functional disability, bradykinesia, rigidity
  - Variable improvement in tremor
- Advanced disease as adjunctive therapy
  - Improves dyskinesias

# Strategies for treating early PD

- Single dopaminergic drug with mild effects
  - Amantadine, selegiline, rasagiline, pramipexole, ropinirole
  - Low dose levodopa
- Anticholinergics for tremor
- Non-pharmacological therapies
- Research trials for potential neuroprotective agents

# Strategies for treating advanced PD

- Define the motor complication
- Motor fluctuation
  - Wearing off of doses
  - Early morning akinesia
  - Night-time “off”
- Dyskinesias
  - Peak dose dyskinesia
  - Diphasic dyskinesia
  - “Off” period dystonia



# Motor fluctuation diary

Time	Meds	Asleep	Off	On	On with dyskinesia
MN-1:00 A		X			
1:00-2:00 A		X			
2:00-3:00 A		X			
3:00-4:00 A			X		
4:00-5:00 A		X			
5:00-6:00 A	Sinemet 25/100, Mirapex 0.5 mg		X		
6:00-7:00 A			X		
7:00-8:00 A				X	
8:00-9:00 A				X	
9:00-10:00 A			X		
etc...					

# Strategies for treating advanced PD

## Wearing off

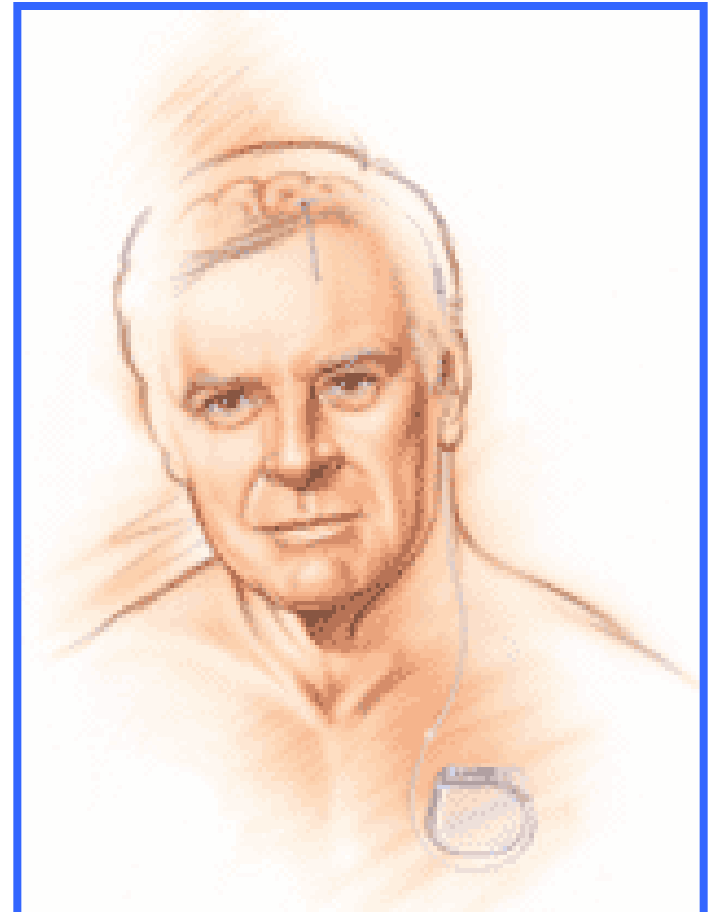
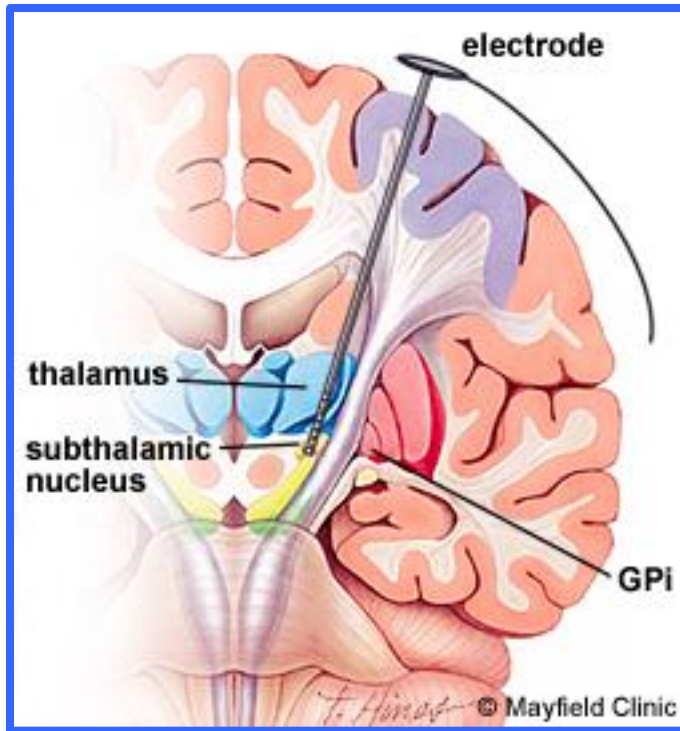
- More frequent doses
- Longer acting medications (dopamine agonists, rasagiline)
- Combined medications (above, COMT inhibitors)
- Monitor diet – protein intake
- Take levodopa on empty stomach

## Dyskinesias

- Discontinue medications (selegiline, entacapone, anticholinergics)
- Smaller (more frequent) doses
- Add agonist, reduce levodopa
- Add amantadine
- Surgery

# Surgery for PD

- Types of procedures
  - Ablative procedures
  - Deep brain stimulation
  - Experimental



# Surgery for PD – Good candidates

- Age  $\leq$  75 yr
- Advanced PD
- Good response to levodopa
- Motor complications or marked tremor
- Medical treatment not satisfactory
- No psychiatric illness (psychosis, mood)
- No cognitive impairment
- No major medical problems
- Good support system
- Realistic goals and expectations

For more info on  
Rush's PD Surgery  
program

Leo Verhagen,  
MD, PhD

# Strategies for non-motor symptoms

## Mood

- Depression/anxiety – medications, counseling
- Adjust PD medications if related to wearing off

## Impulse control disorders

- Reduce and discontinue dopamine agonists
- Use levodopa
- Antipsychotics

## Hallucinations

- Review medication list, exclude medical problem
- Reassurance, non-confrontational strategies, night-lights
- Antipsychotics (quetiapine [Seroquel], clozapine [Clozaril])
- Cognitive medications (donepezil [Aricept], rivastigmine [Exelon], etc)

## Cognitive changes/dementia

- Keep active mentally (and physically)
- Reduce or discontinue medications that can impair cognition
- Cognitive medications (donepezil [Aricept], rivastigmine [Exelon], galantamine [Razadyne], memantine [Namenda])

# Strategies for non-motor symptoms

## Blood pressure

- Orthostatic hypotension
- Increase fluids
- Elevate head of bed, increase salt and caffeine, pressurized stockings
- Medications – fludrocortisone (Florinef), midodrine (Proamantine), pyridostigmine (Mestinon)

## Bladder

- Limit night-time liquids
- Bladder medications – Ditropan, Detrol, Sanctura, etc
  - Watch for cognitive effects of medications
- Protective garments, condom catheters
- Exclude infections

## Bowels

- Diet, increase fluids, exercise
- Stool softeners, constipation paste
- Polyethylene glycol

# Key points

- Parkinson's disease is more than just a motor disorder
- Symptomatic treatments are available for both motor and non-motor symptoms and along all stages of PD
- Treatment of PD involves a multi-disciplinary approach
- Regimens must be individualized
- Goal to use the lowest but most effective dose without side effects

# Key points

- While there are very good symptomatic medications available, we have many unmet needs...
  - Smoother and longer responses
  - Better treatments for non-motor and non-levodopa responsive symptoms
  - Neuroprotective agents
  - A cure