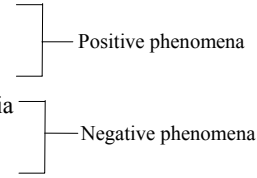


## Things that You Do Not Want to Miss

# Parkinsonism & Parkinsonism Plus Syndromes

## Parkinsonism (James Parkinson, 1817)

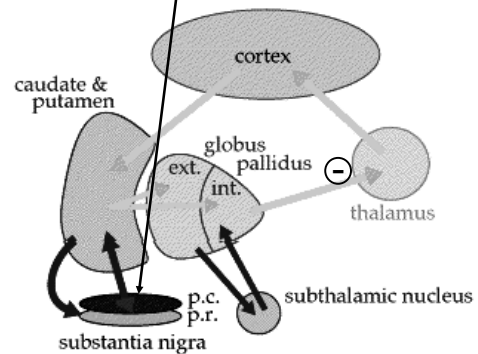
- Six cardinal features
  - tremor at rest
  - rigidity
  - flexed posture
  - bradykinesia-hypokinesia
  - loss of postural reflexes
  - freezing phenomenon
- Definite parkinsonism
  - at least 2 of above (with at least one is either resting tremor or bradykinesia)



## Parkinsonism (Causes)

- Primary parkinsonism
  - sporadic, familial
- Secondary parkinsonism
  - drug-induced
  - hydrocephalus
  - hemiatrophy-HP
  - hypoxia
  - postencephalitic
  - metabolic (hypoparathyroid)
  - trauma
  - tumor
  - vascular
  - toxin (Mn, CO, MPTP...)
- Parkinson-plus syndromes
  - cortico-basal gangl deg (CBGD)
  - dementia syndromes
  - Lytico-Bodig (Guamanian PDA)
  - multiple system atrophy syndromes
    - striatonigral deg
    - Shy-Drager syndrome
    - olivopontocerebellar deg/atrophy (OPCA)
    - motor-neuron dz-parkinsonism
  - progressive supranuclear palsy
- Heredodegenerative dz : Wilson, Huntington, mitochondria dz

## ACh, GABA, and Dopamine



## Parkinson Disease (Diagnosis)

- Due to:
  - deficiency of dopamine in substantia nigra → nigro-striatal pathway.
  - 60% of nigral neurones and 80 % of striatal dopamine lost.
- Initial symptoms, often unilateral to begin:
  - tremor (resting) (70%).
  - rigidity (cogwheel) (10%).
  - akinesia (bradykinesia) (10%).
  - gait disturbance (11%). (TRAP)
- Mean age of onset – 55 yr (20-80 yr) (♂: ♀=3:2)
  - juvenile parkinsonism (<20 yr)
  - young-onset parkinsonism (20-40 yr)

## Parkinson Disease (Epidemiology)

Prevalence rate : 200 per 100,000  
 Incidence rate : 20 per 100,000 (annually)  
 Rare for individuals < 40 years of age  
 ↑ after age 50

At age 70 and above:  
 Prevalence rate : 550 per 100,00  
 Incidence rate : 120 per 100,000 (annually)

Constitute 80% of cases of parkinsonism

In a typical case diagnosis is straight forward

## Parkinsonism (Diagnosis - Difficulties)

### TWO types of difficulties

- To distinguish typical PD from:
  - the secondary parkinsonism, i.e. hydrocephalus, vascular, drugs, toxin...
  - the many parkinson-plus syndromes from other neurodegenerative diseases.
- To distinguish parkinson tremor from other types.

## Parkinsonism (Diagnostic Pearls - Clinical)(1)

- Predominantly unilateral –PD, HA-HP, CBGD
- Symmetric onset –PD, most form of parkinsonism
- Presence of rest tremor –PD, secondary parkinsonism
- Lack of rest tremor –Parkinson-plus syndrome
- Hx of encephalitis –Postencephalitic parkinsonism
- Hx of toxin exposure –Parkinsonism caused by the toxin
- Taking neuroleptics –Drug-induced parkinsonism
- Severe unilateral rigidity, cortical sensory sign, unilateral myoclonus, unilateral apraxia, Alien limb –CBGD
- Orthostatic hypotension, urinary/fecal incontinence –Shy-Drager syndrome

## Parkinsonism (Diagnostic Pearls - Clinical)(2)

- Early loss of postural reflexes, impaired downgaze, deep nasolabial folds, furrowed forehead & eyebrows, nuchal dystonia, abducted arm when walking. –PSP
- Cerebellar dysarthria & dysmetria –Olivopontocerebellar atrophy (OPCA)
- Laryngeal stridor –Striatonigral degeneration
- Lower/upper motor neuron findings –Multiple system atrophy
- Never responded to levodopa –other than PD

## Parkinsonism (Diagnostic Pearls - Clinical)(3)

- Begins with one side favours PD.
  - secondary parkinsonism & Parkinson-plus almost always have symmetric s/s.
  - (exception : CBGD, HA-HP, focal lesion).
- Resting tremor favours PD.
  - secondary parkinsonism & Parkinson-plus rarely have resting tremor.
  - (exception : drug induced parkinsonism).
- Begins with both side and no resting tremor can still be PD.
  - try levodopa.
  - no response to levodopa → other than PD; response to levodopa does not confirm the dx of PD.

## Parkinsonism (Diagnostic Pearls - Clinical)(4)

- Juvenile or young onset → r/o other than PD.
- Onset before 50 yr → higher incidence of genetic aetiology.
- Maternal inheritance → mitochondrial DNA defect.
- DTR usually not impaired; extensor plantar reflex → Parkinson-plus.

PD constitutes 80% of cases of parkinsonism

## Parkinsonism (Diagnostic Pearls – Lab)

- Acanthocytes, ↑ creatine kinase – Neuroacanthocytosis (more chorea)
- MRI: many lacunes – Vascular parkinsonism
- MRI: tiger’s eye in pallidum – Hallervorden-Spatz disease
- MRI: caudate atrophy – HD, neuroacanthocytosis
- MRI: ↓ T2 signal in striatum – Multiple system atrophy
- MRI: midbrain atrophy – PSP
- MRI: huge ventricle – NPH
- Abnormal autonomic function test, denervation on sphincter EMG – Shy-Drager syndrome

## Parkinsonism (Diagnosis - Difficulties)

### TWO types of difficulties

- To distinguish typical PD from:
  - the secondary parkinsonism, i.e. hydrocephalus, vascular, drugs, toxin...
  - the many parkinson-plus syndromes from other neurodegenerative diseases.
- To distinguish parkinson tremor from other types
  - essential tremor (postural & kinetic)

## Parkinsonism

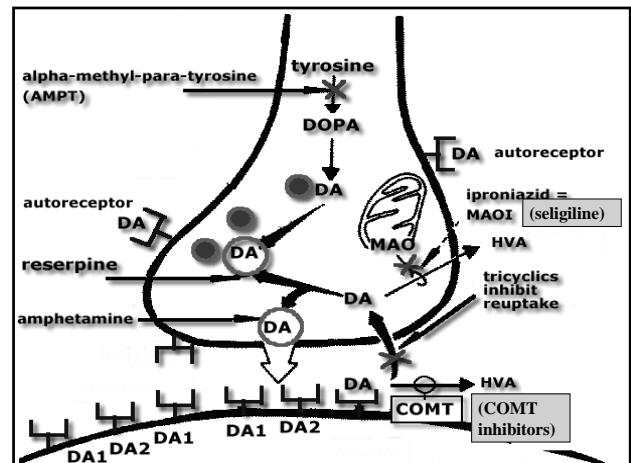
### Update on Pharmacotherapy

## Parkinson Disease (Treatment Options)

- Pharmacological treatments
- Non-pharmacological treatments
  - Physiotherapy
  - Psychiatric counseling
- Surgical treatments
  - Ablative: thalamotomy, pallidotomy
  - Restorative: embryonic dopaminergic tissue implants
  - Deep brain stimulation: thalamus, pallidal, subthalamic nucleus

## Parkinson Disease (Available Medication)

- Monoamine oxidase-B inhibitor – selegiline
- Dopamine releaser – amantadine
- Dopamine agonists – bromocriptine, ropinirole, cabergoline
- COMT inhibitor – tolcapone, entacapone
- Anticholinergics – trihexyphenidyl
- Levodopa – sinemet (standard/slow release)



### Parkinson Disease (Pharmacotherapy – General Principles)

- Principles on treating PD used also for the Parkinson-plus syndromes.
- Treatment is lifelong; medication and doses change with time as adverse effects and new symptoms encountered.
- Levodopa remains the most effective anti-parkinson medication.
- General agreement – *dopa-sparing strategy*
  - early use of levodopa responsible for later response fluctuations and other complications.
- Symptomatic treatment only needed when symptoms are troublesome.

### Parkinson Disease (Major Outcomes after 5 years of Levodopa)

Smooth good response	25% (n = 83)
Troublesome fluctuations	43% (n = 142)
Troublesome dyskinesias	19% (n = 67)
Toxicity at therapeutic/ subtherapeutic dosages	4% (n = 14)
Total or subtotal loss of efficacy	8% (n = 27)

36 patients (11%) had both troublesome fluctuations & dyskinesias.

### Parkinson Disease (Stages)

- EARLY – no functional impairment.
- MILD – honeymoon period.
- MODERATE – multiple drugs, occupational and social activities affected.
- SEVERE – side effects from drugs, resistant to therapy, reduced quality of life.
- LATE – dependent in ADL, wheelchair or bed bound.

### Parkinson Disease (Pharmacotherapy)

- Early – no functional impairment
  - no medication is needed.
  - the use of **seligiline** at this stage based on the fact that it slows the progress of PD lacks proof.
  - one of several symptomatic drugs in early stage of PD to delay the use of levodopa.
  - MAOB enzyme inhibitor
  - dosage: 5mg od
  - relatively safe when given alone; together with levodopa ↑ the possibility of dopaminergic toxicity.

### Parkinson Disease (Pharmacotherapy)

- Mild – with functional impairment
- Start antiparkinsonian medication if there is:
  - threat to employment.
  - threat to ability to handle domestic, financial or social affairs.
  - threat to handle activities of daily living.
  - appreciable worsening of gait or balance.

*Discussion and decision to be made between patient and physician.*

### Parkinson Disease (Pharmacotherapy)

- Mild – with functional impairment
  - Available options:
    - seligiline
    - dopamine releaser (amandatine)
    - dopamine agonists (bromocriptine, ropinirole, cabergoline, lisuride)
    - anticholinergic (trihexyphenidyl)
      - appropriate if tremor is the predominant complaint

## Parkinson Disease (Amandatine)

- Mild indirect dopaminergic agent:
  - acts by augmenting dopamine release from storage sites, possibly also by blocking reuptake of dopamine into the presynaptic terminals.
- Effective within days, but short-lived in advanced PD (fall-off effect); effective in 2/3 of cases.
- Dosage: 100 mg bd ~ 200 mg bd.
- S.E.: livedo reticularis (knee), ankle edema, visual hallucinosis.
- Uses:
  - initial therapy, delaying use of levodopa.
  - adjunctive drug to levodopa, dopamine agonists in advanced PD.
  - ↓ dopa-induced dyskinesia (anti-glutamatergic effect).

## Parkinson Disease (Dopamine Agonists)

- Mediated through D2 receptor; bromocriptine weakest, cabergoline strongest (also has the longest T1/2).
- Uses:
  - initial therapy, delaying use of levodopa.
  - conjunctive to levodopa in advanced PD; ↓ dose of levodopa.
  - to overcome some adverse effects of long term levodopa use (↓ effects of off state).
- S.E.:
  - orthostatic hypotension (all).
  - red inflamed skin, retroperitoneal fibrosis (bromocriptine, pergolide, lisuride, cabergoline).
  - confusion, psychosis (bromocriptine); dyskinesia (pergolide, lisuride, cabergoline) though less likely than levodopa.
  - drowsiness, ankle edema, sleep attacks (pramipexole, ropinirole).

## Parkinson Disease (Dopamine Agonists - Doses)

- Bromocriptine (Parlodel)
  - come in 2.5 mg/tab.
  - start with 1.25 mg bd, and ↑ q2-4 wk by 2.5 mg/day.
  - 30-60 mg may be required after the first year.
  - S.E.: nausea, HT, confusion, hallucinations, leg edema, erythromelalgia, pulmonary or retroperitoneal fibrosis.
- Ropinirole (Requip)
  - newer D2, D3 dopamine agonists.
  - come in 1, 2, 5 mg/tab.
  - start with 0.25 mg tds, and ↑ 0.75 mg qwkly to 1 mg tds according to response; usual range is 3-9 mg daily.
  - S.E.: as above, drowsiness (including sudden onset of sleep).

## Parkinson Disease (Anticholinergics)

- Less effective antiparkinsonian agents than dopamine agonists; improve parkinsonisms by about 20%.
- Uses:
  - if tremor the predominant complaint can be the initial drug.
  - conjunctive with dopamine agonist or levodopa for tremor; an attempt to withdraw anticholinergic can be done if dopamine agonist or levodopa can control the tremor.
- S.E.:
  - forgetfulness, ↓ short term memory.
  - hallucination, psychosis.
  - dry mouth, urinary retention, constipation
 To be avoided in elderly > 70yr. Can use amitriptyline, diphenhydramine for anticholinergic effects instead.

## Parkinson Disease (Anticholinergics - Doses)

- Trihexyphenidyl (Artane)
  - come in 2, 5 mg/tab.
  - start with 1 mg daily, and ↑ by 2 mg q3-5 day; maintenance 6 – 15 mg tds.
  - S.E.:
    - forgetfulness, ↓ short term memory.
    - hallucination, psychosis.
    - dry mouth, urinary retention, constipation
- Amitriptyline
  - come in 10, 20, 25, 50 mg/tab
  - start with 25-50 mg bed time, gradual ↑ to 150 mg bed time.
  - S.E.: sedation, anti-cholinergic...

## Parkinson Disease (Pharmacotherapy)

- Moderate – multiple drugs, occupational and social activities affected.
  - Major decision is when to introduce levodopa:
    - *when other antiparkinsonian medications are no longer bringing about a satisfactory response.*
    - rule of thumb – use the lowest possible dose to bring about adequate symptoms reversal.
    - usually in combination with a peripheral dopa decarboxylase inhibitor, e.g. sinemet (levodopa-carbidopa), madopar (levodopa-benserazide).
      - each comes with different dosage and with standard or slow release form.

## Parkinson Disease (Sinemet - Doses)

- Comes in 25/100, 10/100, 25/250 (carbidopa/levodopa)
- The addition of carbidopa (DOPA decarboxylase inhibitor) at doses above 75 mg ↑ the CNS levodopa delivery by 4x, & substantially ↓ nausea & HT.
- Usual dose:
  - 50 – 100 mg of levodopa bd to tds.
  - ↑ by 1 tab q2d until therapeutic effects obtained.
  - max 600 mg.
 (Use the lowest possible dose)

## Parkinson Disease (Response to levodopa)

- Response to levodopa – the single most important piece of information to D/D PD or Parkinson-plus.
  - no or only minimal response → not PD.
  - adequate response → does not confirm PD, the following are also possible:
    - all presynaptic disorders (postencephalitic, MPTP-, reserpine-induced).
    - early stage of MSA.
  - bradykinesia, rigidity respond best, tremor can be resistant.
  - low dose levodopa producing dystonia → MSA; psychosis → diffuse lewy body disease or accompanying Alzheimer dz.

## Parkinsonism (Natural Course)

- The degenerative forms (PD included) worsen over time:
  - severe disability or death within 5 years – 25%, in next 5 years – 65%, 89% in 15 years.
  - 3x the mortality of that of general population.
- With advent of levodopa therapy:
  - no evidence that it alters the underlying pathologic process, but there is major impact on survival time and functional capacity.
  - mortality ↓ by 50%, and longevity extended by several years.

## Parkinson Disease (Pharmacotherapy)

Without functional disability

Selegiline ?

With mild functional disability

Amantadine

Dopamine agonist

Trihexyphenidyl

Tricyclics

With moderate functional disability

Carbidopa/levodopa

Dopamine agonist

COMT inhibitor

## Parkinson Disease (COMT Inhibitors)

- Entacapone (Comtan)
  - retards the enzymatic degradation of levodopa and dopamine, and improve kinetics.
  - dose: 100 mg~200 mg with levodopa.
  - ↑ action time by 15%.
  - S.E: may ↑ dyskinesia.
- Tolcapone (Tasmar)
  - more potent than entacapone, longer duration of action.
  - dose: 100~200 mg tds.
  - S.E: sudden hepatic failure.
- Uses:
  - extend the effects of levodopa in the setting of advanced PD with on-off phenomenon.

## Parkinson Disease (Major Outcomes after 5 years of Levodopa)

Smooth good response	25% (n = 83)
Troublesome fluctuations	43% (n = 142)
Troublesome dyskinesias	19% (n = 67)
Toxicity at therapeutic/ subtherapeutic dosages	4% (n = 14)
Total or subtotal loss of efficacy	8% (n = 27)

36 patients (11%) had both troublesome fluctuations & dyskinesias.

## Parkinson Disease Pharmacotherapy (Complications of Prolonged Levodopa)

### Fluctuations

- slow “wearing-off”
- sudden “off”
- random “off”
- yoyoing
- episodic failure to respond
- delayed “on”
- weak response at end of day
- varied response to meals
- sudden transient freezing

### Dyskinesias

- peak-dose chorea & dystonia
- diphasic chorea & dystonia
- “off” dystonia
- myoclonus

## Levodopa Related Complications (Mechanisms)

- In fluctuations thought to be due to:
  - potentiation of glutamate receptors on the striatal dopaminergic medium spiny neurons (GABAergic striatal efferents) because of peaks & valleys of brain dopamine levels.
  - oxyradicals formed from oxidation of dopamine attacking & altering dopamine receptors.
- In dyskinesias due to ↑ sensitivity and response of D1 receptor to dopamine.
  - dopamine agonists much less likely to cause dyskinesias because of lesser activation of the D1 receptor.

## Parkinson Disease Pharmacotherapy (Detection of “on-off” )

Wearing off (end-of-dose deterioration)  
(return of parkinsonism within 4 hours)

Duration of benefits ↓ & “off” state more profound

Fluctuation more abrupt in onset & random in timing

“On-off” effect; cannot be related to timing of levodopa intake.

*Once established not reversible.*

## Parkinson Disease (Handling Fluctuation)

- Available options:
  - Seligiline (wearing-off)
    - prolonging dopamine level at synapse.
  - Slow release form of Sinemet/Madopar (wearing-off)
    - or standard Sinemet with ↑ frequency and ↓ dose.
  - Liquefying levodopa for quicker predictable response (“on-off”).
  - Dopamine agonists with longer T<sub>1/2</sub> together with levodopa (standard/slow release) (wearing-off and “on-off”).
  - COMT (↓ off)      – High protein meal adjustment.
    - ↑ levodopa T<sub>1/2</sub>

## Parkinson Disease (Levodopa Related Dyskinesias)

- Include chorea, ballism, dystonia, or combinations of above, usually seen in patients having fluctuation.
- Yo-yo-ing (severe dyskinesia to severe “offs”).
- Incidence and severity ↑ with duration & dosage of levodopa.
- Three categories:
  - **peak-dose dyskinesia** (appearing at height of anti-parkinsonian benefit (20 min ~ 2 hours after a dose).
  - **diphasic dyskinesia** (usually affecting the legs, appear at beginning and end of the dosing interval).
  - **“off” dystonia** (can be painful sustained cramps, appearing during “off” states and may be seen at first as early-morning dystonia presenting as foot cramps).

## Parkinson Disease (Handling Dyskinesia)

- Available options:
  - Peak dose dyskinesias
    - ↓ dose but with ↑ frequency.
    - switching to the slow release form.
    - dopamine agonist added with reduced levodopa.
    - seligiline added with reduced levodopa.
  - Diphasic dyskinesias
    - ↑ levodopa dose.
    - switch to dopamine agonist with low dose levodopa.
  - “Off dystonia” (keep “on” most of the time)
    - switch to dopamine agonist with low dose levodopa.

## Parkinson Disease (Handling Freezing)

- “Off-freezing” & “on-freezing”
  - “off-freezing” a feature of parkinsonism.
  - “on-freezing” worsen by levodopa.
- “Off-freezing”
  - keep patient from getting “off”.
- “On-freezing”... an enigma.
- The last resort –
  - *subthalamic nucleus stimulation*

## Deep Brain Stimulation (DBS)

- High frequency, pulsatile electrical stimulation.
- Stereotactically placed into target nucleus
- Can be activated and deactivated by an external magnet.
- Exact physiology unknown, but higher frequencies mimic cellular ablation, not stimulation.

## Efficacy of DBS

- Thalamic DBS is a safe and effective. treatment for medically refractory ET and PD tremor.
- It can be performed bilaterally.
- The precise mechanism of action is unknown.
- DBS of GPi & STN seems to improve all aspects of PD motor symptoms.

## What Things You Do Not Want to Miss?

- D/D:
  - secondary parkinsonism
  - Parkinson-plus syndrome (different aetiology means different treatment, & prognosis).
- Anticipating the late complications of levodopa use early and adjust medication accordingly.

THE END  
THANK YOU

