Parkinsonism

Idiopathic Parkinson's disease

- There are many causes (Box 26.64) → most common is **Parkinson's disease (PD).**
- Genetic factors :
  - Having a first-degree relative with PD confers a 2–3 times increased risk .
- Prognosis :
  - It is a progressive and incurable condition, with a variable prognosis.
  - Whilst motor symptoms are the most common presenting features, non-motor symptoms (particularly cognitive impairment, depression and anxiety) become increasingly common as the disease progresses, and reduce quality of life

Pathophysiology

The pathological hallmarks of PD are:

1-depletion of the pigmented dopaminergic neurons in the substantia nigra and
2-Presence of α-synuclein and other protein inclusions in nigral cells (Lewy bodies).

- It is thought that environmental or genetic factors alter the α-synuclein protein, rendering it toxic and leading to Lewy body formation within the nigral cells.
- While interest has primarily focused on the dopamine system, : **neuronal degeneration with inclusion body formation** can also affect :
  - cholinergic neurons of the nucleus basalis of Meynert (NBM),
  - norepinephrine neurons of the locus coeruleus (LC),
  - serotonin neurons in the raphe nuclei of the brainstem,
  - neurons of the olfactory system,
  - cerebral hemispheres, spinal cord, and peripheral autonomic nervous system.
  - → **This "nondopaminergic" pathology is likely responsible for the nondopaminergic clinical features listed** → see Table 371-1.

- Striatum is **input region** of the basal ganglia.
- GPi and SNr RE **output regions** the basal ganglia.
  - The input and output regions are connected via direct and indirect pathways .
  - The output of the basal ganglia provides **inhibitory tone** to → thalamic & brainstem neurons → that in turn connect to motor systems in the cerebral cortex and spinal cord to regulate motor function.
- Dopaminergic projections from SNc neurons serve to modulate neuronal firing and to stabilize the basal ganglia network.

In Parkinson's disease

- **dopamine denervation** → leads to **increased firing of neurons in the STN and GPi** → resulting in :
  1- **Excessive inhibition** of the thalamus,
  2- **Reduced activation** of cortical motor systems,
  → Development of parkinsonian features .

Current role of surgery in treatment of PD is based upon this model, in which that : lesions or high-frequency stimulation of the STN or GPi
→ might reduce this neuronal overactivity and improve PD features.

Clinical Features

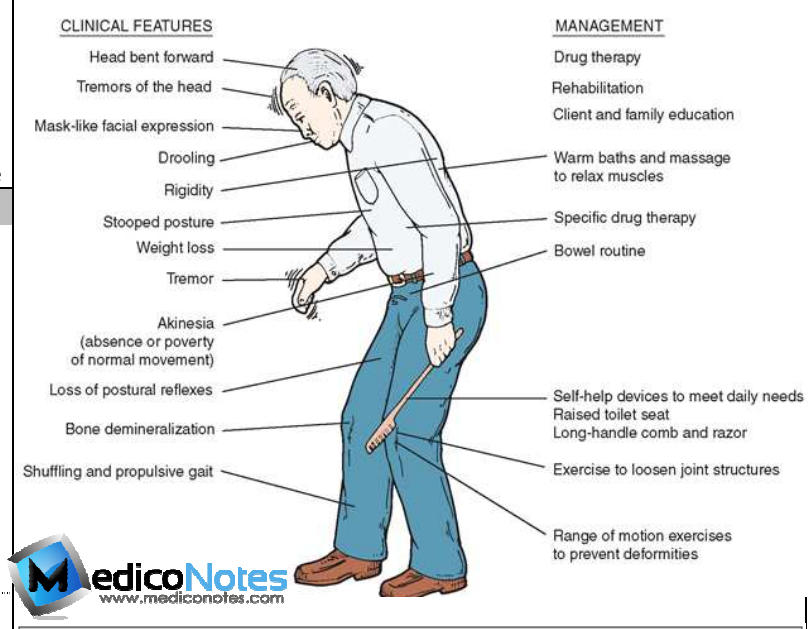

Table 372-1 Clinical Features of Parkinson's Disease

Cardinal Features	Other Motor Features	Nonmotor Features
Bradykinesia	Micrographia	Anosmia
Rest tremor	Masked facies (hypomimia)equalize	Sensory disturbances (e.g., pain)
Rigidity	Reduced eye blink	Mood disorders (e.g., depression)
Gait disturbance/postural instability	Soft voice (hypophonia)	Sleep disturbances
	Dysphagia	Autonomic disturbances
	Freezing	Orthostatic hypotension
		Gastrointestinal disturbances
		Genitourinal disturbances
		Sexual dysfunction
		Cognitive impairment/Dementia

26.64 Causes of parkinsonism

Idiopathic Parkinson's disease (at least 80% of parkinsonism)

Cerebrovascular disease

Drugs and toxins
- Antipsychotic drugs (older and 'atypical')
- Metoclopramide, prochlorperazine
- Tetrabenazine
- Sodium valproate
- Lithium
- Manganese
- MPTP

Other degenerative diseases
- Dementia with Lewy bodies
- Progressive supranuclear palsy
- Multiple system atrophy
- Corticobasal degeneration
- Alzheimer's disease

Genetic
- Huntington's disease
- Fragile X tremor ataxia syndrome
- Dopa-responsive dystonia
- Spinocerebellar ataxias (particularly SCA 3)
- Wilson's disease

Anoxic brain injury

(MPTP = methyl-phenyl-tetrahydropyridine)

26.65 Physical signs in Parkinson's disease

General
- Expressionless face (hypomimia)
- Soft, rapid, indistinct speech (dysphonia)
- Flexed (stooped) posture
- Impaired postural reflexes

Gait
- Slow to start walking (failure of gait ignition)
- Rapid, short stride length, tendency to shorten (festination)
- Reduction of arm swing
- Impaired balance on turning

Tremor

Resting (3–4 Hz, moderate amplitude): most common
- Asymmetric, usually first in arm/hand ('pill rolling')
- May affect legs, jaw and chin, but not head
- Intermittent, present at rest, often briefly abolished by movement of the limb, exacerbated by walking

Postural (6–8 Hz, moderate amplitude)
- Present immediately on stretching out arms

Re-emergent tremor (3–4 Hz, moderate amplitude)
- Initially no tremor on stretching arms out, rest tremor re-emerges after a few seconds

Rigidity
- Cogwheel type, mostly upper limbs (due to tremor superimposed upon rigidity)
- Lead pipe type

Akinesia (fundamental feature)
- Slowness of movement
- Fatiguing and decrease in size of repetitive movements

Normal findings (if abnormal, consider other causes)
- Power, deep tendon reflexes, plantar responses
- Eye movements
- Sensory and cerebellar examination

Management

1- Drug therapy

→ Drug treatment for PD remains **symptomatic** rather than curative, and there is no evidence that any of the currently available drugs are neuroprotective.

Evidence-based statements regarding diagnosis and drug management of PD are listed in Box 26.66.

Levodopa (LD)

- **Failure of akinesia/rigidity to respond to LD 1000 mg/day should prompt reconsideration of the diagnosis.**
- **Most accept that the most effective, best-tolerated and cheapest drug is LD**

Mechanism of action :
- *Levodopa is* the precursor to dopamine.
- When administered orally, more than 90% is **decarboxylated to dopamine** peripherally in : GIT & Blood vessels, and ***only a small proportion reaches the brain.***
- This peripheral conversion is responsible for the high frequency of adverse effects, and to avoid this : **LD is combined with a dopa decarboxylase inhibitor (DDI) :**
  1- Carbidopa (compination with LD → Sinemet®)
  2- Benserazide (compination with LD → Madopar®)
  → Inhibitor does not cross the blood–brain barrier, thus avoiding unwanted decarboxylation-blocking in brain.

Effect :
- Most effective on relieving → **1- Akinesia 2- Rigidity;**
- Less satisfactory on relieving : Tremor
- No effect on relieving : 1- many motor (posture, freezing) 2- non-motor symptoms.

Adverse effects :

1- Postural hypotension, 2- Nausea and vomiting, (which may be offset by domperidone).
3- Exacerbate or trigger hallucinations,
4- Abnormal LD-seeking behaviour (dopamine dysregulation syndrome) in which the patient takes excessive doses of LD.
5- As PD progresses, the response to LD becomes less predictable in many patients , leading to **motor fluctuations .**
- Due to progressive loss of dopamine storage capacity by dwindling numbers of striatonigral neurons.
- LD-induced involuntary movements (dyskinesia) may occur as :
  - a peak-dose phenomenon or
  - a biphasic phenomenon (occurring during both the build-up and wearing-off phases).
- More complex fluctuations present as sudden, unpredictable changes in response, in which periods of parkinsonism ('off' phases) alternate with improved mobility but with dyskinesias ('on' phases).

Dopamine agonists

(Ropinirole→ monotherapy to delay L-dopa use in the early stages).

- The **non-ergot agonists** are preferable to the ergot agonists.
- **With the exception of apomorphine**, all the agonists are :
  - considerably less powerful than LD in relieving parkinsonism,
  - have more adverse effects (nausea, vomiting, confusion and hallucinations, impulse control disorders)
  - more expensive.

Anticholinergics

- These were the main treatment for PD prior to the introduction of LD. → help **tremors.**
- Their role now is limited by :
  1- Lack of efficacy (apart from an effect on tremor sometimes)
  2- Adverse effects : dry mouth, blurred vision, constipation, urinary retention, confusion and hallucinosis.
- Several anticholinergics are available, including : **1- Trihexyphenidyl (benzhexol) 2- Orphenadrine.**

Inhibitors of (MAOI)-B

- Monoamine oxidase type B facilitates breakdown of excess dopamine in the synapse.
- Alternate to Dopamine agonists in treatment of early PDs.
- Two inhibitors are used in PD: **1- Selegiline 2- Rasagiline**.

Catechol-O-methyl-transferase (COMT) inhibitors

- Catechol-O-methyl-transferase (along with dopa decarboxylase) is involved in peripheral breakdown of LD.
- Two inhibitors are available: **1- Entacapone 2- Tolcapone**
  - Entacapone has a modest effect and is most useful for **early wearing-off**.
  - It is available either as a single tablet taken with each LD/DDI dose, or as a combination tablet with LD and DDI.

Amantadine

Weak DA agonists

- This has a mild, usually short-lived effect on **bradykinesia** and is rarely used unless patients are unable to tolerate other drugs.
- It is more **commonly used as a treatment for LD-induced dyskinesias**, although again benefit is modest and short-lived.

2- Surgery

1- **Destructive neurosurgery** , was commonly used before the introduction of LD.
2- **Stereotactic surgery** has emerged and most commonly involves : **Deep Brain Stimulation (DBS)** :
- Various targets have been identified, including the thalamus (though this is only effective for tremor), globus pallidus and subthalamic nucleus.
- DBS is usually reserved for patients with medically refractory tremor or motor fluctuations
3- **Intracranial delivery of fetal grafts** or specific growth factors remains experimental.

3- Physiotherapy, occupational therapy and speech therapy :

- Patients at all stages of PD benefit from physiotherapy, which helps reduce rigidity and corrects abnormal posture.
- Occupational therapists can provide equipment to help overcome functional limitations, such as toilet, and bathing equipment.
- Speech therapy can help where dysarthria and dysphonia interfere with communication
- As with many complex neurological disorders, patients with PD should ideally be managed by a **multidisciplinary team,** including PD specialist nurses.

EBM 26.66 Management of Parkinson's disease

Early treatment

'Patients with early PD may be considered for treatment with:
- levodopa plus dopa decarboxylase inhibitor *or*
- oral or transdermal dopamine agonists *or*
- monoamine oxidase B inhibitors.'

'Ergot-derived dopamine agonists should not be used as first-line treatment.'

'Anticholinergic drugs should not be used as first-line treatment.'

Motor fluctuations

'Motor fluctuations may be treated with either monoamine oxidase B inhibitors or dopamine agonists.'

'Dopamine agonists may be used to manage motor complications in patients with advanced PD. The non-ergot agonists are preferable to the ergot agonists.'

'Intermittent or infusions of subcutaneous apomorphine may be used to manage advanced PD.'

'Catechol-O-methyl-transferase (COMT) inhibitors may be used to reduce off-time in patients with advanced PD.'

- SIGN 113. Diagnosis and pharmacological management of Parkinson's disease, 2010.

For further information: www.sign.ac.uk

Differential Diagnosis of Parkinsonism

Parkinson's Disease:
1- Genetic
2- Sporadic

Atypical Parkinsonisms:
1- Multiple-system atrophy
- Cerebellar type (MSA-c)
- Parkinson type (MSA-p)

2- Progressive supranuclear palsy
3- Corticobasal ganglionic degeneration
4- Frontotemporal dementia

Secondary Parkinsonism:
1- Drug-induced 2-Tumor 3- Infection
4- Vascular 5-Trauma 6- Liver failure
7- Normal-pressure hydrocephalus
8- Toxins (e.g., carbon monoxide, , MPTP, cyanide)

Other Neurodegenerative Disorders:
1- Wilson's disease
2- Huntington's disease
3- Neurodegeneration with brain iron accumulation
4- Alzheimer's disease with parkinsonis