Parkinsonism

- 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 function of SNc neurons.

- Dopaminergic projections from SNc neurons serve as a basal input region to the basal ganglia.
- Some of these projections connect to motor systems in the cerebral cortex and spinal cord to regulate motor function.
- The basal ganglia are a balanced network of inhibitory and excitatory neurons, whose activity is controlled by the thalamus.
- The basal ganglia control motor function through a feedback mechanism that involves the thalamus.

In Parkinson’s disease:

- Dopamine denervation leads to increased inhibition from the STN and Gpi, resulting in:
  - Excessive inhibition of the thalamus.
  - Reduced activation of cortical motor systems.

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 inactivity and improve PD features.

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 excretion/absorption to respond to LD 1000 mg daily should prompt reconsideration of the diagnosis.
- Levodopa is the most effective, best-tolerated and cheapest drug in PD.

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:

1. Carbidopa (combination with LD = Sinemet®)
2. Benserazide (combination with LD = Madopar®)

- Inhibitor does not cross the blood-brain barrier, thus avoiding undeserved 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. Exacerate or trigger hallucinations.
- 4. Abnormal LD-seeking behaviour (dopamine dysregulation syndrome) in which the patient takes excessive doses of LD.
- 5. 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 wear-off phases).
  - More complex fluctuations present as sudden, unpredictable changes in response, in which periods of 1. motor suppression ("off" phases) alternate with improvements despite dyskinesias ("on" phases).

- The non-ergot agonists are preferable to the ergot agonists.
- With the exception of amantadine, 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.

- These were the main treatment for PD prior to the introduction of LD. 2. Help tremors.

- Their role is now limited to:
  - 1. Lack of efficacy (apart from an effect on tremor sometimes)
  - 2. Adverse effects:
    - dry mouth, blurred vision, constipation, urinary retention, confusion and hallucinations.

- Several anticholinergics are available, including:
  - 1. Trihexyphenidyl (benzhexol)
  - 2. Orphenadrine.

- 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.

- This has a mild, usually short-lived effect on bradykinesia and is rarely used unless patients are unable to tolerate side effects of carbidopa.

- It is more commonly used as a treatment for LD-induced dyskinesia, although again benefit is modest and short-lived.

2. Surgery

- Destructive neurosurgery was commonly used before the introduction of LD.
- 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.

- 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 improve the ability to understand and produce language.

- As with many complex neurological disorders, patients with PD should ideally be managed by a multidisciplinary team, including PD specialist nurses.