Parkinson’s Disease

- **Parkinson’s Disease** is a common (lifetime risk 1 in 40) neurodegenerative disease characterised by asymmetrical onset of movement disorder secondary to diminished activity of dopaminergic neurons in the substantia nigra.

- **Causes:**
  - 15% have first degree relative → hereditary component
  - Most cases appear to have idiopathic trigger mechanism
  - MPTP (a neurotoxin) is found in pesticides and used to cut heroin
  - Possible role of heavy metals, head trauma, Lewy Body dementia
  - Drug-induced Parkinsonism may be secondary to prochlorperazine, antipsychotics, methyldopa, amiodarone, lithium and metoclopramide
  - Nicotine is protective (also protects against Alzheimer’s, UC, sarcoidosis, EAA)

- **Symptoms are usually unilateral at onset:**
  - Bradykinesia:
    - Slowness when initiating movements
    - Shuffling, festinating gait with poor turning and ↓ arm swing
    - “Frozen” facial expression
    - Small spidery handwriting
    - Dysphonia and monotony, slurring dysarthria
    - **TEST:** fast finger tap
  - Muscular rigidity: “stiffness equal in opposing muscle groups”
    - Increased tone more noticeable with distraction
    - “Cog-wheeling” jerks break up rigidity
  - Resting tremor:
    - “pill-rolling” at 4-6Hz
    - ↑ with anxiety, ↓ with movement/concentration
  - Postural instability:
    - Gait changes, loss of righting reflexes → risk of falls
    - **TEST:** pull test
  - Other symptoms
    - REM sleep disorder: have tone in sleep → act out their dreams whilst asleep
    - Restless leg syndrome
    - Autonomic: constipation, urinary incontinence, impotence, OH + dizziness, greasy sweaty skin, aching joints, dysphagia + dribbling, heartburn
    - Neuropsychiatric: anxiety, depression, sleep disturbance, vivid dreams, florid hallucinations, delirium, dementia (80% cumulative incidence)

- **Differential diagnoses**
  - Movement disorder: PD, Alzheimer’s/DLB, stroke (sudden), PSP (impaired vertical gaze), MSA (mainly autonomic), Wilson’s (early cognitive deterioration, family history)
  - Resting tremor: physiological, benign essential, anxiety, thyrotoxicosis, salbutamol, asterixis (CO₂/hepatic) cerebellar/intention tremor

- **Investigations:**
  - Detailed history and examination for upper limb neurology, festinating gait, poor finger tap, poor righting reflexes, resting pill-rolling tremor, vertical gaze (ΔPSP)
  - MRI +/- DATscan to assess dopamine absorption in brain
  - Best test is to see if they respond to levodopa – if they do it’s definitely PD

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**Drugs used to treat Parkinson’s Disease**

1) **Co-careldopa or Sinemet: Levodopa + Carbidopa**
   - Levodopa is broken down into dopamine by dopa-decarboxylase in the substantia nigra, and as a result boosts dopaminergic transmission in the brain to reduce symptoms
   - Only 5-10% of levodopa crosses the BBB; the rest is usually metabolised to dopamine peripherally resulting in side effects and reduced effective concentrations in the brain
   - Carbidopa is a peripheral dopa-decarboxylase inhibitor which stops the peripheral breakdown of levodopa to reduce side effects and increase the dopamine reaching the brain
   - The combined preparation is expressed for example as co-careldopa 10/100, which contains 10mg carbidopa and 100mg levodopa (other preparations 25/100 and 25/250)

2) **Co-Beneldopa or Madopar** is an immediate release preparation containing benserazide and MPTP (a neurotoxin) is found in pesticides and used to cut heroin
   - Levodopa, usually used for breakthrough symptoms or “wearing off”
   - Possible role of heavy metals, head trauma, Lewy Body dementia
   - Causes: very uncommon
   - Postural instability: history of fibrotic disorders/valve disease for ergot-derived drugs+
   - **Side effects:** are many and complex:
     - nausea, vomiting (give domperidone), taste disturbance, dry mouth, anorexia
     - postural hypotension, dizziness, syncope, sleepiness, fatigue, narcolepsy
     - arrhythmias
     - dementia, psychosis (incidence increases with age and worsening cognitive decline), hallucinations, confusion, euphoria, insomnia, depression, anxiety
     - dystonia, dyskinesia, chorea (motor complications are a major problem)

3) **MAO-B inhibitors: rasagiline, selegiline**
   - These irreversibly inhibit monoamine oxidase enzymes involved in dopamine breakdown
   - May be used alone or as adjuncts to levodopa to manage “wearing off”
   - Rasagiline: newer and more expensive, ↑↑ effects with ↓↓ side effects
   - Selegiline: is generally well tolerated, delays need for levodopa and may be neuroprotective
   - Metabolised by CYP450 therefore avoid giving with enzyme inhibitors
   - Cautions: hepatic impairment, postural hypotension, history of ulcer disease, CV risk, ↓BP
   - **Side effects:** nausea, constipation, dizziness, dry mouth, postural hypotension, dyskinesia, vertigo, sleep disturbance, confusion, hallucinations, arthralgia, myalgia, ↑ increased CV risk

4) **COMT inhibitors: entacapone, tolcapone**
   - Similar action to carbidopa: inhibit peripheral levodopa breakdown by COMT so that more can cross the BBB and have an effect in the brain
   - Used as adjuncts to levodopa in patients experiencing “wearing off”
   - Tolcapone can cause hepatotoxicity; entacapone is preferred
   - Metabolised by CYP450 and may interfere with metabolism of other drugs e.g. warfarin
   - **Side effects:** GI upset, urine turns reddish-brown, withdrawal, other dopaminergic side effects

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5) Apomorphine
   • This is a potent dopamine receptor agonist which provides rapid but short-lived relief
   • May be helpful in advanced disease for patients experiencing unpredictable “wearing off”
   • It is usually given by SC infusion under specialist supervision: apomorphine is highly emetogenic so patients must receive domperidone for at least 2 days before starting Tx
   • Cautions: as for levodopa
   • Contraindications: respiratory depression, opioid hypersensitivity, hepatic impairment
   • Side effects: nausea and vomiting, drowsiness, narcolepsy, confusion, hallucinations, injection site reactions

6) Amantadine
   • This is a weak dopamine agonist with modest anti-Parkinsonian effects which may also delay the need to commence levodopa treatment if used as monotherapy in early disease
   • Its effects are, however, short-lived and its efficacy in more advanced disease is poor
   • Cautions: hepatic and renal impairment, heart failure, elderly patients
   • Contraindications: epilepsy, history of peptic ulceration
   • Side effects: GI upset, anxiety, inability to concentrate, insomnia, dizziness, convulsions, other dopaminergic side effects, withdrawal

7) Antimuscarinic drugs: orphenadrine, procyclidine, trihexyphenidyl
   • Act by reducing the effects of the relative central cholinergic excess that occurs as a result of dopamine deficiency
   • Often used in drug-induced Parkinsonism, used less in idiopathic PD because other drugs are better: antimuscarinics reduce tremor, rigidity and sialorrhoea but have little effect on bradykinesia
   • Cautions: CV disease, TBP, psychosis, BPH, fever, glaucoma risk, elderly, hepatic/renal D.
   • Contraindications: GI obstruction, myasthenia gravis
   • Side effects: anticholinergic side effects e.g. constipation, dry mouth, N+V, tachycardia, dizziness, confusion, hallucinations, memory, anxiety, urinary retention, blurred vision

8) Cholinesterase inhibitors used in Parkinsonian dementia
   • These act to boost cholinergic neurotransmission in the brain by inhibiting acetylcholinesterase enzymes involved in postsynaptic ACh breakdown
   • Examples include rivastigmine, donepezil, galantamine
   • Memantine has a similar action but is in fact an NMDA antagonist
   • Unfortunately these drugs have only limited efficacy in mild to moderate dementia

Surgery for Parkinson’s Disease

• Thalamotomy for drug-resistant unilateral tremor (no effect on bradykinesia)
• Pallidotomy for drug-induced dyskinesia, severe “on-off” fluctuations and drug failure
• Sub-thalamotomy for tremor, bradykinesia and rigidity (may provoke dyskinesia/hemiballismus)
• Bilateral brain stimulation: electrodes placed in basal ganglia with stimulator below clavicle
   ➢ Thalamic for tremor
   ➢ Bilateral subthalamic nucleus for most symptoms
   ➢ Pallidal for dyskinesia
   ➢ Significant risk of intracerebral haemorrhage and permanent confusion: NICE recommends only using this therapy after drug treatment has failed
   ➢ Other recent advances include gene therapy, nanotechnology and neural stem cell transplantation

Management Strategies

There is no single first-line choice of therapy: depends on patient’s age, clinical features, lifestyle and personal preferences.

Choices for initial drug treatments include:

• Co-careldopa: excellent symptom control, but risk of motor complications and other adverse events. Useful in the elderly or frail, in patients with significant comorbidities, and in those with more severe symptoms. Start low and go slow to minimise risk of dyskinesias.
• Dopamine agonists: moderately good symptom control, with fewer motor complications but other significant adverse effects e.g. hypersexuality, compulsive gambling. Especially useful in younger patients (age <50) with early disease to reduce the dose of levodopa required.
• MAO-B inhibitors: these also provide moderately good symptom control with fewer motor complications, but there are other side effects and adverse events e.g. hypotension, CV risk. Useful in delaying need for levodopa if younger patients respond tolerably.

Problems with long-term levodopa treatment

As disease progresses, levodopa can begin to cause adverse motor effects which limit its use. These occur in 50-90% of people who have been on levodopa for 5-10 years, usually younger patients.

• “Wearing off phenomenon”: end of effective levodopa dose leads to return of Parkinsonian symptoms e.g. tremor, bradykinesia, stiffness/freeze/ing. Variable timing, not with every dose. Duration of dose effectiveness will inevitably decrease over time.
   ➢ Smaller, more frequent doses of levodopa or prolonged-release preparations, try taking them 30 minutes before food
   ➢ Use of carbidopa to cover time until next dose
   ➢ Add in dopamine agonist, MAO-B-I or COMT-I to prolong levodopa effects (NB the levodopa dose needs to be decreased slightly when you start these drugs)
• “On-off fluctuations”: usually occur in more advanced disease. Rapid and unpredictable fluctuations between good motor function, dyskinesia secondary to excess levodopa activity, and poor motor function with Parkinsonism.
   ➢ Add in dopamine agonist to reduce levodopa dose
   ➢ Use fewer doses of levodopa and start SC apomorphine infusion
• Dyskinesias: these may occur at the beginning or end of a dose, or at its peak. Usually choreoathetoid, always hyperkinetic, may include dystonia, tics, stereotyped movements, myoclonus or hemiballismus. Theories suggest these may develop as the substantia nigra progressively deteriorates, resulting in inability of medication to compensate and reduced dopamine storage capacity, all released at once.
   ➢ If at peak of dose: make doses smaller and more frequent or try modified slow release levodopa, add dopamine agonist, consider surgery
   ➢ If at beginning/end of dose: try soluble levodopa before meals, add COMT-I

Adding in adjuvants

• First choice: dopamine agonists, MAO-Bs, COMT-I (entacapone first) +/- modified release levodopa
• Then try: antimuscarinics (if tremor/rigidity predominate), amantadine, apomorphine infusions (intermittent injections to ↓ off time, continuous infusion to ↓ off time and dyskinesias)
• Other problems: Depression and anxiety: TCAs e.g. nortriptyline, SSRIIs (not with selegiline), support
• Compulsive behaviours: behavioural therapy, family involvement, review drug regime
• Hallucinations and psychosis: may be due to drugs, delirium or dementia. Use atypical antipsychotics preferentially (careful in dementia). Clozapine (D4 antagonist) is useful.
• Dementia: poor prognostic indicator – high mortality within 1-2 years. Difficult to manage and often necessitates nursing home admission. Screening may help early detection.

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