AN OVERVIEW OF IDIOPATHIC PARKINSON’S DISEASE

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Outline of Presentation

- Definition and Historical Background
- Pathophysiology
- Epidemiology-Incidence and Prevalence
- Clinical Presentation and Diagnosis (including NICE guidelines)
- Motor features
- Non Motor Symptoms
- Differential Diagnoses
- Role of Investigations
- Management (including NICE guidelines)
  - Conventional Dopaminergic Treatment
  - Advanced (Continuous Dopaminergic Stimulation) therapies
- Homerton Parkinson’s Service
Definition of Idiopathic Parkinson’s Disease

- Clinical syndrome manifesting characteristically with Parkinsonism

- Parkinsonism is the term used to describe the complex of motor features originally described by James Parkinson in 1817

- The term Idiopathic Parkinson’s Disease (IPD) reserved for Parkinsonian patients without an overt cause of the disease and differentiates them from those who have a Parkinsonian syndrome as a consequence of identifiable aetiiological factors such as stroke, medication, encephalitis etc etc.
Historical Background - Milestones

- First described by Dr. James Parkinson in 1817

- In the 1867 Charcot named the condition “Maladie de Parkinson”
1817-James Parkinson
  - *Shaking Palsy*
    - Detailed analyses of the clinical effects

1867-Jean-Martin Charcot
  - Clinical classification and differential diagnosis
  - Proposes the eponymous label “Maladie de Parkinson”

1912 Friedrich Heinrich Lewy
  - Intracytoplasmic inclusions: the hallmark of Parkinson's disease

1919 Constantin Trétiakoff
  - Cell degeneration in the substantia nigra

1958-Arvid Carlsson and colleagues proposed that dopamine deficiency might be the neurochemical basis of Parkinson’s Disease

1960 Herbert Ehringer and Oleh Hornykiewicz
  - Dopamine deficiency in the striatum

1961 Hornykiewicz and Birkmayer
  - Use Dopa in injectable form in patients with PD with dramatic results

1968 George Cotzias
  - Reported dramatic effects with oral dopa by using a pure “levo-“ dopa form in NEJM and L-dopa becomes a therapeutic reality
Pathophysiology

- Parkinson’s disease is a progressive neurodegenerative disease

- Death of dopaminergic neurones in the pars compacta of the substantia nigra which project to the striatum (putamen and caudate) leads to striatal dopamine depletion (reduced by 80%) (as a consequence of 50% cell loss)
Normal Motor Control

- Dopamine increases the inhibitory activity of the direct pathway.
- Dopamine decreases the excitatory activity of the indirect pathway.
- Normal movement is maintained.

**Substantia Nigra (SN)**

- Dopamine increases the inhibitory activity of the direct pathway.

**Striatum**

- Inhibitory activity is reduced.

**GPI**

**Thalamus**

**Motor cortex**

- Excitatory (indirect)
- Inhibitory (direct)
Changes in the Basal Ganglia in Parkinson’s

Dopamine depletion results in decreased inhibitory activity of the direct pathway.

The motor cortex receives diminished excitatory output from the thalamus so movement is inhibited.

Dopamine depletion in the Substantia Nigra (SN) increases the excitatory activity of the indirect pathway.

Dopamine depletion decreases inhibitory activity of the direct pathway.

Excitatory (indirect) 

Inhibitory (direct)
Pathophysiology (factors involved in neuronal death)

**AETIOLOGY**
- Genetic factors
- Environmental factors
- Ageing

**PATHOGENESIS**
- Oxidative stress
- Mitochondrial dysfunction
- Excitotoxicity
- Inflammation
- Protein handling dysfunction with Lewy body formation

**Pathophysiology**
- Neuronal dysfunction
- Apoptosis
Primary vs Secondary Parkinsonism

Parkinsonism characteristically manifests as consequence of striatal dopaminergic denervation-induced dysfunction of basal ganglia irrespective of cause primary or secondary

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic Parkinsons Disease (IPD)</td>
<td>Iatrogenic-drug induced e.g neuroleptics</td>
</tr>
<tr>
<td>Genetic Parkinsonism</td>
<td>Toxic e.g MPTP, CO, manganese</td>
</tr>
<tr>
<td>Dementia with Lewy Bodys (DLB)</td>
<td>Infectious e.g encephalitis lethargica</td>
</tr>
<tr>
<td>Parkinson Plus Syndromes e.g PSP, MSA, CBD</td>
<td>Metabolic e.g Wilsons Disease</td>
</tr>
<tr>
<td>Fronto-temporal Dementia with Parkinsonism (FTDP)</td>
<td>Structural e.g NPH</td>
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Pathophysiology

• However the neurodegenerative process in PD is now considered to extend further than just the dopaminergic pathways in basal ganglia with diffuse degeneration affecting peripheral and central nervous system (manifesting with a multitude of Non Motor Symptoms)

• PD is now considered the clinical manifestation of a multi system synucleinopathic neurodegenerative process comprising not only the dopaminergic but also the other central neurotransmitter systems such as the noradrenergic, serotonergic and cholinergic systems

• Histological hallmark - Lewy Bodies - intracytoplasmic inclusion bodies containing protein alpha-synuclein
Braak Hypothesis (Braak et al. 2006)

The Braak staging system of Parkinson disease, showing the initiation sites in the olfactory bulb and the medulla oblongata, through to the later infiltration of Lewy body pathology into cortical regions.

Based on detailed pathological studies of patients at different disease stages, Braak suggests that neuronal damage in PD follows a predetermined sequence which begins in the medulla and ascends through the brain stem to cortical areas.
Epidemiology of Parkinson’s Disease – Incidence

• Idiopathic Parkinson’s disease is uncommon before the age of 50

• There is a sharp increase in incidence after the age of 60

Prospective population-based incidence studies of Parkinson’s disease

Epidemiology of Parkinson’s Disease – Prevalence

Idiopathic Parkinson’s disease is a common age-related condition.

Population-based prevalence studies of Parkinson’s disease

Incidence and Prevalence of Parkinson’s in UK

- Incidence: 18 per 100,000
- Prevalence: up to 200 per 100,000 = 1 per 500
- Approx - 120,000 in the UK
- Approx - 10,000 new cases per year
What does this mean locally? (i.e. City and Hackney)

- According to 2012 mid year estimate by Office for National Statistics, population of City and Hackney estimated to be 259,723

- Prevalence - 520 (approx) patients

- Incidence - 46 new patients (approx) diagnosed with PD per year
Burden of Parkinson’s Disease on patient

- Reduced quality of life\(^1\)
- Higher susceptibility to depression and cognitive impairment\(^2\)
- Increased risk for comorbidities such as pneumonia\(^2\)
- Increased medical expenses (physician visits and emergency care)\(^2\)
- Caregiver burden and risk of early nursing home placement\(^2,3\)

Burden of Parkinson’s Disease

• Economic impact includes:
  Direct cost to NHS
  Indirect cost to society
  Personal impact on individuals with Parkinson’s & their family / carers

• Parkinson’s chronic disabling condition likely to induce significant direct medical costs via service use
  In-patients stays (planned & unplanned)
  Outpatient visits (medication adjustment, counselling)
  Community visits (e.g. district nurses)
  GP consultations

• An average admission stay for someone with Parkinson’s for 7-10 days costs £4,529 - £6,470 (without any investigations included)
Burden on Resources: HES Data

Parkinson’s HES data 2009-10 (primary diagnosis code G20 in ICD-10):

- 55% of hospital admissions for Parkinson's are emergency admissions
- The average length of stay in hospital was 23 days
- Over two thirds of patients admitted to hospital for Parkinson's don't undergo procedures
Clinical Presentation

• Currently IPD is only diagnosed when the first symptoms and signs of motor parkinsonism become overt

• Currently non-motor symptoms (NMS) are not part of the diagnostic criteria for IPD
Cardinal Motor Features

- Bradykinesia
- Motor Parkinsonism
- Resting Tremor
- Rigidity
- Postural Instability
Bradykinesia

• **Bradykinesia** is a slowing down of voluntary movement with *progressive reduction in frequency and amplitude of sequential motor tasks*

• Specific manifestations include-delayed initiation, slowness of execution and inability to execute simultaneous and/or sequential actions

• **Hypokinesia** is poverty/scarcity of spontaneous movement

• **Akinesia** is absence of spontaneous movement
Clinical features reflecting bradykinesia/hypokinesia

- Loss of arm swing
- Increasingly small handwriting (micrographia)
- Difficulty with walking - tendency to drag a leg in early disease
- Difficulty with tasks involving fine hand movements - buttons, zips, cutting food
- Difficulty turning in bed
- Loss of facial expression (hypomimia)
- Reduced voice volume and modulation (hypophonia)
- Reduced blinking
- Reduced spontaneous swallowing with sialorrhea
Assessing for Bradykinesia

• Observation -
  - Gait-short steppage, dragging of one leg, reduced arm swing
  - Face and Voice-loss of expression (hypomimia), reduced voice modulation (hypophonia)

• Testing-
  - assessing repetitive hand movements - finger tapping test e.t.c
Bradykinesia- salient clinical features

- Bradykinesia
- Hypophonia
- Hypomimia
- Reduced arm swing
- Micrographia
Tremor (definitions)

- Tremor is an *involuntary rhythmic oscillatory movement of a body part*.

- *Rest tremor* is typical of PD and occurs when the body part is relaxed.

- *Postural tremor* occurs when a posture is sustained.

- *Action tremor* occurs when performing a task.
Parkinson’s Tremor

• Best recognised feature of PD (although only experienced by about 60-70% of patients)
• Classically tremor is at rest at a frequency of 4-6 Hz
• Characteristically described as “pill-rolling” - due to involvement of thumb and fingers and rotatory component
• Tremor can also occur in chin, jaw, tongue and eyelid but tremor of whole head is rare
Parkinsonian Tremor

- Resting Tremor 4-6 Hz
  - Worsens with mental distraction
  - Pill rolling characteristic
  - Diminished on action
  - Arms/legs/feet/jaw/tongue
Parkinson’s tremor is special

- Tremor does not increase at the same pace as other symptoms
- Tremor severity does not correlate with severity of other symptoms
- Tremor can be expressed mainly at the side contralateral to other symptoms (“wrong sided tremor”)
- Tremor does not respond as well to L-dopa as other symptoms
- Tremor dominance predicts a more benign disease progression
- Clinically and pathophysiologically different from other PD motor symptoms
Rigidity

- Involuntary increase in muscle tone and can affect all muscle groups

- Described as *lead pipe* as resistance to passive movement is independent of velocity (differentiating this from spasticity)

- **Cogwheeling** - is thought to be due to the superimposition of tremor on existing rigidity

- Patients describe rigidity as stiffness and tightness or sometimes pain

- Rigidity (in combination with bradykinesia) may manifest with a loss of dexterity (difficulty with tasks involving fine hand movements), difficulty turning in bed, and a shuffling small-stepped gait
Rigidity

“Cog wheel” nature

Flexed Posture

Mild rigidity detected by “activation”

“Lead pipe”
Postural Instability

• Results from failure/loss of postural reflexes (as well as axial rigidity and bradykinesia)

• Typically occurs later in the course of disease

• Least specific symptom though most disabling and leads to loss of balance and falls

• Assessed using pull (retropulsion test)

• Postural instability often accompanied by gait impairment ("axial motor" features)
Postural Instability

Loss of postural reflexes

Difficulty turning

Postural Instability

Assessed with retropulsion test

Occurs later in disease and associated with falls
Gait

Two types of gait disorder :

1) *Continuous*-consistently present

- Asymmetrically reduced or absent arm swing
- Step size becomes asymmetric starting in early PD
- Gently stooped posture
- Difficulties turning around in a standing position

- With disease progression-typical *parkinsonian gait* emerges with shuffling and short steps/bilaterally reduced arm swing and slow turns
Gait

2) Freezing of gait (FOG) - present in *paroxysms* triggered by *specific circumstances*

- During FOG - patients suddenly and mostly without warning feel as if their feet become *glued* to the floor

- FOG - frequently *asymmetrical* with freezing in just one leg

- Triggers - initiating or stopping gait, walking through a narrow passage, turning (most common) or executing a secondary task
Freezing of gait (FOG)

- FOG can present as *shuffling small steps with trembling* in an attempt to overcome block or being totally unable to start or continue walking (relatively rare).

- Most FOG episodes are brief, typically lasting only a few seconds/rarely >30 sec.

- “Festination” - taking increasingly rapid + small sequential steps during walking – seen in severely affected patients - may well reflect a form of FOG.
Freezing of gait (FOG)

• FOG - since episodic - patients find it hard to adapt behaviour – so frequently results in falling usually forwards

• FOG- usually regarded as “late “ feature of PD, however FOG may be less rare in early PD than previously thought and infact can occur in very early stages of IPD in some cases

• Early presence of FOG should therefore not be regarded as a red flag signalling atypical parkinsonism

• However is commonly present in PSP, VP and NPH- where tends to be more severe in early stages
Non Motor Symptoms (NMS)

MOTOR
PARKINSONISM

NMS
• Neuropsychiatric
• Sleep disorders
• Autonomic dysfunction
• GI problems
• Sensory problems
Non Motor Symptoms (NMS)

Neuropsychiatric symptoms
Cognitive Impairment / Dementia
Affective disturbance - Depression, Apathy, Anxiety, Panic attacks
Psychosis - Hallucinations, Illusions, Delusions

Sleep disorders
Insomnia and sleep fragmentation
Excessive daytime somnolence
Vivid dreaming
Rapid eye movement (REM) sleep behaviour disorder and REM loss of atonia
Restless legs and periodic limb movements
Sleep-disordered breathing

Sensory Symptoms
Pain
Paraesthesia
Olfactory dysfunction (Hyposmia)
Non Motor Symptoms (NMS)

**Autonomic symptoms**
- Cardiac sympathetic denervation
  - Orthostatic hypotension
  - Orthostatic intolerance
  - Post prandial hypotension
- GU-Bladder dysfunction
  - Nocturia
  - Urgency
  - Frequency
- Thermoregulatory
  - Excessive Sweating (Hyperhydrosis)
- Sexual dysfunction
  - Loss of libido
  - Erectile dysfunction
  - Premature ejaculation
  - Secondary Dyspareunia
  - Failure of orgasm

**Gastrointestinal symptoms**
(overlap with autonomic symptoms)
- Sialorrhoea-Excessive Drooling
- Dysphagia (and choking)
- Ageusia
- Constipation
- Unsatisfactory voiding of bowel
- Faecal incontinence (rare)

**Other symptoms**
- Fatigue
- Weight loss
- Weight gain (possibly drug-induced)
- Visual problems
  - Loss of acuity
  - Blurred vision
  - Abnormal Colour discrimination
Diagnosing Parkinson’s Disease (NICE guidance 2006)

- People with suspected PD should be referred quickly (6 weeks for mild PD and 2 weeks for complex later stage PD)

- Refer untreated to a specialist with expertise in the differential diagnosis of the condition (either neurologist or geriatrician with special interest in PD)

- PD diagnosis should be made clinically based on UK PD Society Brain Bank Criteria

- Diagnosis should be reviewed regularly at 6-12 month intervals
Diagnosing IPD-UK Brain Bank Criteria

• Developed from an autopsy study of 100 cases who were clinically diagnosed with PD (1992)

• At autopsy 24/100 cases had alternative diagnosis including PSP, MSA and lacunar cerebrovascular disease

• Subsequent updated study (2001) showed improvement in accuracy to 90% with MSA being the commonest error (6 out of the 10 cases)
Diagnosing Parkinson's disease
United Kingdom PD Society Brain Bank Criteria

Step 1-establishing parkinsonism

- Bradykinesia
  At least 1…
  - Rigidity
  - 4-6 Hz rest tremor
  - Postural instability
    - Not visual
    - Not vestibular
    - Not cerebellar
    - Not sensory
Diagnosing Parkinson's disease
United Kingdom PD Society Brain Bank Criteria

Step 2—exclusions

- Stepwise progression
- Head injuries
- Encephalitis
- Oculogyric crises
- Neuroleptics
- Familial
- Sustained Remission
- Strictly unilateral after 3 y
- Supranuclear gaze palsy

- Cerebellar signs
- Early, severe autonomic involvement
- Early, severe dementia
- Babinski sign
- Tumour/hydrocephalus
- L-Dopa unresponsive
- MPTP exposure
Diagnosing Parkinson's disease
United Kingdom PD Society Brain Bank Criteria

• **Step 3—supportive features**
  • Unilateral onset
  • Persistent asymmetry, worse on onset side
  • Rest tremor
  • Progressive disorder
  • 70-100% response to levodopa
  • Severe levodopa-induced dyskinesias
  • > 5 year history levodopa-responsiveness
  • Disease course ≥ 10 years
Main Differential Diagnoses for Parkinson’s Disease in clinical practice

- Other conditions causing *Parkinsonism*
- Essential Tremor
- Dystonic Tremor (*tremor produced dystonic muscle contraction*)
Essential Tremor

• In early disease this is the main differential
• ET is 10x more common than IPD
• Tremor is usually bilateral and typically involves hands, head/neck, voice but rarely involves legs
• FH in approx 50% of cases (AD inheritance)
• No other neurological features apart from occasional instability
• Improves with alcoholic beverages
• Rx is with B-blockers-1st line, primadone and topiramate -2nd line, DBS in severe intractable cases
## Differential Diagnoses for Parkinsonism

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<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Distinguishing Features</th>
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<tbody>
<tr>
<td>Multi system atrophy</td>
<td>- Autonomic dysfunction</td>
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<tr>
<td></td>
<td>- Cerebellar involvement</td>
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<tr>
<td></td>
<td>- Pyramidal tract degeneration</td>
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<td></td>
<td>- OH</td>
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<tr>
<td></td>
<td>- Bladder dysfunction</td>
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<tr>
<td></td>
<td>- Cerebellar signs</td>
</tr>
<tr>
<td></td>
<td>- Pyramidal tract signs</td>
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<tr>
<td>Progressive supranuclear palsy</td>
<td>- Supranuclear paralysis of eye movements</td>
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<tr>
<td></td>
<td>- Pyramidal signs</td>
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<tr>
<td></td>
<td>- Cognitive impairment</td>
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<tr>
<td></td>
<td>- Axial rigidity</td>
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<tr>
<td></td>
<td>- Failure of vertical gaze</td>
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<tr>
<td></td>
<td>- Early falls (backwards)</td>
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<tr>
<td>Lewy body dementia</td>
<td>- Early progressive dementia</td>
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<tr>
<td></td>
<td>- Fluctuating Cognition and Marked Visual Hallucinations</td>
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<tr>
<td>Drug-induced parkinsonism</td>
<td>- Symmetrical disease</td>
</tr>
<tr>
<td></td>
<td>- Younger patient</td>
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<tr>
<td></td>
<td>- Taking dopamine antagonists/lithium/valproate/venlafaxine</td>
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<tr>
<td>Vascular parkinsonism</td>
<td>- Sudden onset</td>
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<tr>
<td></td>
<td>- Stuttering progression</td>
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<tr>
<td></td>
<td>- Minimal tremor</td>
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<tr>
<td></td>
<td>- Lower limbs affected &gt; upper limbs</td>
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<tr>
<td></td>
<td>- MRI diagnosis</td>
</tr>
<tr>
<td></td>
<td>- basal ganglia infarct</td>
</tr>
<tr>
<td></td>
<td>- subcortical ischaemia</td>
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<tr>
<td></td>
<td>- diffuse small vessel changes</td>
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## Typical vs Atypical Parkinsonism

<table>
<thead>
<tr>
<th>Typical Parkinsonism</th>
<th>Atypical Parkinsonism (MSA PSP+CBD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>asymmetric</td>
<td>symmetric</td>
</tr>
<tr>
<td>resting tremor</td>
<td>no tremor (or action tremor)</td>
</tr>
<tr>
<td>limb &gt; trunk &gt; midline</td>
<td>midline</td>
</tr>
<tr>
<td>appendicular involvement</td>
<td>axial involvement</td>
</tr>
<tr>
<td>later instability</td>
<td>early instability</td>
</tr>
<tr>
<td>L-dopa responsive</td>
<td>poor response to L-dopa</td>
</tr>
<tr>
<td>slowly progressive</td>
<td>Aggressive progression</td>
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</tbody>
</table>
Diagnosing Parkinson’s Disease-role of investigations (NICE guidance 2006)

- Consider SPECT (*functional neuroimaging*) where essential tremor (ET) cannot be clinically differentiated from PD

- *Structural MRI* (*Structural neuroimaging*) may be considered in the differential diagnosis of parkinsonian syndromes (such as vascular parkinsonism)

- Acute levodopa and apomorphine challenge tests should NOT be used (but do have a limited role in determining responsiveness to dopaminergic therapy)
Imaging of the presynaptic dopamine system-Single photon emission CT (SPECT)

- Dopamine transporter activity (i.e., reuptake of dopamine from synaptic cleft into presynaptic neurones) in presynaptic neurones in the substantia nigra is measured by isotope (ioflupane /FP-CIT used in DatSCAN)

- SPECT reliably distinguishes between degenerative Parkinsonism and non-degenerative Parkinsonism such as ET
Imaging of the presynaptic dopamine system - DatSCAN

Tyrosine → L-Dopa → Dopamine

\[ \text{Dopamine Transporter} \]

\[ \text{DaTSCAN} \]

\[ D_3 \quad D_2 \quad D_4 \quad D_1A \]

cellular response
Imaging of the presynaptic dopamine system - DatSCAN

- Essential Tremor
- Drug-induced Parkinsonism
- Vascular Parkinsonism (except if focal basal ganglia infarct)

- Parkinson’s disease
- Progressive Supranuclear Palsy
- Multiple System Atrophy
Management of Parkinson’s Disease (key priorities according to NICE guidelines 2006)

- **Patient-centred care** (based on good communication and education-) taking into account each patient's individual needs and preferences

- **Access to Multidisciplinary Care** (OT/Physio/SLT)

- **Regular Access to specialist care** (usually through PDNS)

- **Access to palliative care** (throughout all phases of the condition)

- **Identification and treatment of NMS**
Multidisciplinary Approach across primary and secondary care

**Primary care**
- GP
- Community Matron
- District Nurse
- Social Services
- Voluntary Sector

**Secondary care**
- Geriatrician
- Neurologist
- Psychiatrist
- Psychologist
- Neurosurgeon

**Primary and Secondary Care**
- PD Nurse Specialist
- Physio
- OT
- SLT
- Dietician
- Pharmacist
Conventional Dopaminergic treatment

- Aims to correct *dopamine deficiency* and provides *symptomatic benefit of motor impairment* (none is proven as having neuroprotective effect)

- Treatment is initiated when required from a functional point of view to maintain function and quality of life

- Of the motor symptoms, bradykinesia and rigidity are most responsive to treatment, postural instability is the least responsive and pharmacological response to tremor is variable
Current Conventional Dopaminergic-treatment options

- Levodopa
- Dopamine Agonists
- MAO-B inhibitors
- COMT inhibitors
- Amantadine

- Currently NICE recommends
  - Initial treatment with Levodopa, Dopamine agonists or MAO-B inhibitors
  - Adjuvant treatment with Dopamine agonists, COMT inhibitors, MAO-B inhibitors
Levodopa

- Levodopa is currently the most effective treatment and still remains the “gold standard” (after its initial introduction in the early 1970s) and eventually all PD patients require L-dopa treatment.

- Levodopa is the precursor to the neurotransmitter-dopamine and is given with a peripheral decarboxylase inhibitor (carbidopa or benserazide) to alleviate peripheral dopaminergic effects.

  - L-dopa + carbidopa = co-careldopa (Sinemet)
  - L-dopa + benserazide = co-beneldopa (Madopar)
Levodopa

- Levodopa has short half life (90 min) and therefore administered 3x day to cover waking period usually at least 1 hour before meals (to aid absorption)

- recommended maximum dose per day is 2000mg
Levodopa-short term side effects

- nausea and vomiting
- postural hypotension
- confusion/agitation
- psychoses (with visual hallucinations and/or delusions)

- Cautions with L-dopa can exacerbate
  - melanoma
  - glaucoma
  - psychoses
Levodopa-motor complications

• L-dopa is effective throughout the course of the disease but as a consequence of disease progression and the constant loss of dopaminergic neurones its effects are changed

• Long term treatment is associated with motor complications

• 50% of patients will experience motor complications within 4-6 years according to analysis of the published literature
Response to Levodopa and Progression of Parkinson’s Disease

- Long duration motor response
- Low incidence of dyskinesias

- Shorter duration motor response
- Increased incidence of dyskinesias

- Short duration motor response
- “On” time consistently associated with dyskinesias

# Levodopa-subtypes of motor complications

<table>
<thead>
<tr>
<th>Motor fluctuations/predictable</th>
<th>Motor fluctuations/unpredictable</th>
<th>Dyskinesias-chorea-like and/or dystonic movements</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Wearing off”</td>
<td>random “on-of” fluctuations</td>
<td>peak-dose-occurring at peak plasma L-dopa levels</td>
</tr>
<tr>
<td>Nocturnal akinesia</td>
<td></td>
<td>biphasic-beginning of dose or end of dose</td>
</tr>
<tr>
<td>Early Morning akinesia</td>
<td></td>
<td>“off” period dystonic posturing-usually painful</td>
</tr>
<tr>
<td>Delayed “on” or no “on” phenomena</td>
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Dopamine agonists

• Dopamine receptors are divided into 5 subtypes, D1-D5

• D1 and D2 receptors are heavily concentrated in the striatum (while D3 receptors are primarily located in mesolimbic structures)

• DAs primarily stimulate D2 and D3 receptors

• DAs have much longer half lives than L-dopa and less likely to induce dyskinesias (possibly because of less pulsatile dopamine receptor stimulation)

• However less effective at alleviating the motor impairment in PD
Dopamine Receptor Nomenclature/Subtypes

D1 family
- receptor subtypes
  - $D_1$, $D_5$

D2 family
- receptor subtypes
  - $D_2$, $D_3$, $D_4$

Localisation

- $D_1$, $D_2$: striatum and substantial nigra
- $D_3$, $D_4$: limbic brain areas (emotional, cognitive + some endocrine function)
- $D_5$: hippocampus, hypothalamus, parafascicular nucleus of the thalamus
Dopaminergic Pathways

- Caudate nucleus
- Nucleus accumbens
- Amygdala
- Putamen
- Ventral tegmental area
- Substantia nigra

- **mesolimbic pathway**: Red
- **nigrostriatal pathway**: Green
- **D3 receptor**: Yellow
- **D2 receptor**: Blue
Dopamine agonists

- Currently most widely used DAs are pramipexole and ropinirole (available in both immediate release and prolonged release oral formulations).

- Rotigotine is available as a long acting transdermal patch and recent study (RECOVER 2013) indicated that rotigotine may ameliorate NMS including fatigue, nighttime problems and depression.

- Pramipexole has been found to have beneficial effect on depression.

- DAs are slowly uptitrated to minimise side effects.
Dopamine Agonists - side effects

- Nausea and vomiting
- Orthostatic Hypotension
- Excessive Daytime sleepiness (including “sleep attacks”)
- Pedal oedema

- Neuropsychiatric
  - Visual hallucinations and psychosis (more common in elderly)
  - Impulse Control Disorders
Impulse Control Disorders

- A person’s inability to resist a temptation or impulse

- More likely to happen in those with a previous history of novelty seeking or risk-taking behaviours

- Compulsive behaviours have been reported as a side effect with dopaminergic treatment particularly dopamine agonists

- Behaviours can include:
  - Pathological gambling
  - Hypersexuality
  - Compulsive eating
  - Compulsive shopping
  - Punding (aimless, repetitive activity or manipulations along with a peculiar fascination with certain objects)

- It is important that this is discussed with the patient and changes in behaviour closely monitored and adjustments in medication made if necessary as the effect is usually reversible on reduction of dose or discontinuation
MAO-B (monoamine oxidase type B) inhibitors

- Block enzymatic metabolism of dopamine in the brain, therefore increasing dopamine concentrations in striatum

- Role as initial monotherapy in patients with mild motor impairment in early PD particularly to delay the introduction of other dopaminergic agent such as L-dopa

- Selegilene delays the need for additional dopaminergic treatment by 9-12 months in early PD and Rasagiline by 6 months
MAO-B inhibitors

- When used as mono therapy are strikingly less effective than L-dopa or even DAs

- Also role as *adjunct* to L-dopa to reduce “off” time in patients with later stage PD with motor fluctuations

- Relatively *well tolerated* with few SE and indeed rasigiline when used as monotherapy has an adverse effect profile similar to that of placebo

- Selegiline is metabolised to amphetamine-like metabolites and therefore can cause sleep disturbances (so avoid later in the day)
COMT-inhibitors

- Majority of L-dopa is metabolised peripherally by catechol-O-methyl transferase (COMT).

- Therefore only a low percentage of orally administered L-dopa enters the brain (even when combined with decarboxylase inhibitor)

- Entacapone and tolcapone when given with L-dopa increase the half life of L-dopa by 30-50% and pharmokokinetically decrease the low trough levels seen with regular L-dopa resulting in more stable plasma levels
COMT-inhibitors

• Main role is in fluctuating PD patients where they increase “on” time with corresponding reduction in “off” time

• Associated with increased dyskinesia (can respond to reduction of L-dopa dose)

• Tolcapone acts both peripherally and centrally and therefore more effective

• However as a consequence of SE profile of potentially fatal hepatic toxicity, its use is restricted and regular liver function monitoring required
**COMT-inhibitors**

- Entacapone acts only peripherally and is used as first line COMT inhibitor

- SE-diarrhoea, discolouration of urine and other bodily fluids

- Entacapone is available in a formulation together with L-dopa and carbidopa as single tablet (*Stalevo*) with different L-dopa dosages available
Amantadine

• Initially developed to treat influenza and found by chance to improve motor symptoms of PD albeit modestly

• Currently its primary role is in the treatment of L-dopa induced dyskinesias (thought to stem from inhibition of glutamate receptors of NMDA subtype)

• Antidyskinetic effect typically observed within 3 weeks but usually transient and often lost within 1 year
Amantadine-side effects

- confusion and agitation, visual hallucinations especially in older patient
- ankle oedema
- livedo reticularis (mottled colour to legs)
- stimulating effect which can help with sleepiness/tiredness but should be avoided later in day as can cause insomnia
# NICE Guidance- Initial Therapy

<table>
<thead>
<tr>
<th>Initial therapy for early PD</th>
<th>First-choice option</th>
<th>Symptom control</th>
<th>Risk of side effects</th>
<th>Other adverse events</th>
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<tbody>
<tr>
<td>Levodopa</td>
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<td>Good degree of symptom control</td>
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<td>Evidence of increased other adverse events</td>
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<td>Moderate degree of symptom control</td>
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<td>MAO-B inhibitors</td>
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<td>Lack of evidence</td>
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<td>Adjuvant therapy for later PD</td>
<td>First-choice option</td>
<td>Symptom control</td>
<td>Risk of side effects</td>
<td>Other adverse events</td>
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<tr>
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<td>Evidence of increased other adverse events</td>
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<tr>
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<td>No</td>
<td>Limited degree of symptom control</td>
<td>Evidence of reduced motor complications</td>
<td>Evidence of increased other adverse events</td>
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</table>
Therapies for reducing motor complications in advanced PD refractory to optimal conventional treatment

APO-go

LCIG

DBS
Prerequisites for L-Dopa induced Motor Response Fluctuations

• peripheral pharmacokinetic of oral L-dopa
  - short half life
  - erratic gastric emptying
  - dietary amino acids

• worsening dopaminergic denervation of striatum-with striatal dopamine buffered in early PD but fluctuate widely in late PD-impaired storage presynaptic/impaired reuptake

• intermittent dopaminergic treatment -leads to intermittent stimulation of striatal dopaminergic neurones
  - motor response complications correlate with L-dopa dose and duration
Progressive denegeneration of dopamine neurons lead to reduced dopamine storage capacity in the striatum

Fluctuations in plasma levodopa levels because of drugs short half life can no longer be buffered

Pulsatile stimulation of striatal dopamine receptors

Downstream dysregulation of genes, proteins, and second messenger systems

Altered Basal Ganglia firing patterns

MOTOR COMPLICATIONS
Rationale for Continuous Dopaminergic stimulation

- Intermittent stimulation of striatal dopaminergic neurons is non-physiologic
- L-Dopa induced pharmacodynamic changes are reversible to an extent - Plasticity
- Basal ganglia undergo plastic changes with denervation and long-term intermittent L-dopa exposure
- These changes are at least partly reversible by switching from intermittent to continuous therapy
- These findings provide the rationale for CDS both at:
  - outset of PD therapy
  - potential to delay or prevent complications
  - advanced PD with established motor complications
  - reverse complications
Levodopa-Carbidopa Intestinal Gel (LCIG) pump infusion therapy

- An intestinal infusion of LCIG requires insertion of a percutaneous gastrostomy tube with tip placed at junction of duodenum and jejunum

- Infusion is typically given during the waking period (16 hours) and this smooths out fluctuations inherent in oral therapy in advanced disease
Apomorphine Infusion Pump Therapy

• Apomorphine is a potent dopamine agonist with extensive first pass metabolism and therefore has to be given subcutaneously by injection or pump infusion

• As pump therapy is usually given during waking period (16 hours)
Deep Brain Stimulation-STN

- DBS device consists of implanted pulse generator (IPG), connecting wire and lead which has 4 electrode contacts which are planted in the subthalamic nucleus.

- Electrical impulses from IPG interfere with neural activity in the target site, in this case STN causing functional blockade, STN hyperactivity leads to motor features in PD.
# Indications

<table>
<thead>
<tr>
<th>Apomorphine injections</th>
<th>Apomorphine infusion</th>
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<tbody>
<tr>
<td>“off” fluctuations in spite of optimised peroral Rx</td>
<td>Severe disease</td>
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<td>Pronounced motor fluctuations</td>
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<tr>
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<td>Dyskinesias</td>
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<tr>
<td></td>
<td>Nocturnal akinesia</td>
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<th>STN-DBS</th>
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<td>Dyskinesias</td>
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</tr>
<tr>
<td>Nocturnal akinesia</td>
<td>Severe tremor not responding to medication</td>
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<tr>
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<td>Apomorphine injections</td>
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<tr>
<td>---------------------</td>
<td>------------------------</td>
</tr>
<tr>
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<tr>
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<td>• No dementia</td>
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<td>Troublesome “off”</td>
<td>• Troublesome “off”</td>
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<td>periods</td>
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<tr>
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<td>• No Dementia</td>
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<tr>
<td>Troublesome fluctuations</td>
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<td>Troublesome fluctuations or tremor</td>
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### Contraindications

<table>
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<th>STN-DBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Severe Dementia</td>
<td>• Severe Dementia</td>
<td>• Severe Dementia</td>
<td>• Age&gt;70 years</td>
</tr>
<tr>
<td>• Severe orthostatic</td>
<td>• Strong tendency to</td>
<td>• Contraindications for</td>
<td>• Dementia</td>
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<tr>
<td>hypotension</td>
<td>hallucinations</td>
<td>abdominal surgery</td>
<td>• Depression/Anxiety</td>
</tr>
<tr>
<td>• Severe Dyskinesia</td>
<td>• No compliance /No</td>
<td>• No compliance /No Support</td>
<td>• Contraindications for brain surgery</td>
</tr>
</tbody>
</table>

- LCIG: Contraindications for abdominal surgery
- STN-DBS: Contraindications for brain surgery
Stages of Parkinson’s adapted from:
5. H&Y addition - Data on File
Homerton Parkinson’s Service

• Consultant led Multidisciplinary clinics held twice weekly in Bryning Unit at HUH reviewing new patients with suspected Parkinson’s and regular review of known patients with Parkinson’s

• Adult Community Rehabilitation Team (ACRT) based at St Leonards Hospital provide in reach service screening all new patients from City & Hackney for therapy needs and providing ongoing community input

• As part of multidisciplinary team input - regular educational forum held for patients and care givers, PD exercise classes, Lee Silverman Voice Therapy.

• PD Nurse Specialist (PDNS) - Sandra Glynn reviewing patients in both acute trust and community

• Referral direct by Choose @Book or by paper correspondence to Bryning Unit or email to soumit.singhai@nhs.net
THANKYOU....!

Any Questions......?