Introduction

- Clinical features of Parkinson’s disease
- Differential diagnosis
- Management of the motor features
- Non-motor and neuropsychiatric aspects
Brain Regions Affected by Parkinson’s Disease

Motor Cortex

Globus pallidus

Thalamus

Striatum

Caudate Nucleus

Putamen

Substantia Nigra

Locus Ceruleus

Raphe Nuclei

Brainstem

Substantia Nigra (detail)

Pars Reticulata

Pars Compacta

Parkinson’s disease
Epidemiology

- 100-200 per 100,000 prevalence over 40 years
- Lifetime risk at 40 years 1:15 for men
- Mean age at diagnosis 70
Tremor
Reduced mobility and dexterity
Change in swallowing/speech
Anosmia
Constipation
REM Sleep Behaviour Disorder (RSBD)
Diagnosis - examination

- Tremor
- Bradykinesia
- Rigidity
- Impaired postural reflexes
Untreated Parkinson’s disease
Other features

- Hypomimia, dysarthria, hypophonia, dysphagia, sialorrhea
- Blepharospasm, reduced contrast sensitivity
- Micrographia, dystonia, camptocormia
- ‘Freezing of gait’, festination
- Seborrheic dermatitis
Diagnosis

- Rate of ‘expert’ misdiagnosis is quite high: (sensitivity = true positives 88% and specificity = true negatives 68%)
- Response to levodopa is not diagnostic
‘Red flags’

- Symmetry
- Absence of tremor
- Early falls / loss of independent mobility
- Early cognitive decline
- Poor response to levodopa
- Early bulbar dysfunction
- Breathing problems (stridor)
- Early autonomic failure
Differential diagnosis

- Lewy body disease
- Progressive supranuclear palsy
- Multiple system atrophy
- Cortico-basal degeneration
- Vascular parkinsonism
- Drug-induced parkinsonism
Drugs that frequently cause parkinsonism

- **Typical antipsychotics:**
  - Chlorpromazine
  - Promethazine
  - Perphenazine
  - Fluphazine
  - Haloperidol
  - Pimozide

- **Atypical antipsychotics:**
  - Risperidone
  - Olanzapine
  - Ziprasidone
  - Aripiprazole

- **Dopamine depleters:**
  - Reserpine
  - Tetrabenazine

- **Antiemetics:**
  - Metoclopramide
  - Prochlorperazine

- **Calcium channel blockers:**
  - Flunarizine
  - Cinnarizine
  - Verapamil
Drugs that infrequently cause parkinsonism

- **Atypical antipsychotics:**
  - Clozapine
  - Quetiapine

- **Mood stabilisers:**
  - Lithium

- **Antidepressants:**
  - SSRIs - citalopram, fluoxetine, paroxetine, sertraline

- **Antiepileptic drugs:**
  - Valproate
  - Phenytoin

- **Antiemetics:**
  - Domperidone
Risk factors for drug-induced parkinsonism

- Dementia
- Advanced age
- Female gender
- Family history PD
- High dose and rapid titration of agent
- Co-existent tardive dyskinesia
Features of drug-induced parkinsonism

- Symmetrical (mostly)
- Tremor not prominent
- Doesn’t progress
- Can take up to 18 months to recover
Management of Parkinson’s disease
Management of Parkinson’s disease

- Differs for different ages/goals
- Changes as disease evolves
- Multidisciplinary approach
Levo-DOPA → Dopamine

Levo-DOPA → DOPA decarboxylase

Anticholinergics:
- Benzotropine
- Orphenadrine
- Procyclidine
- Trihexyphenidyl

Dopamine:
- Apomorphine
- Rotigotine
- Bromocriptine
- Cabergoline
- Pergolide
- Pramipexole
- Ropinirole
- Rasagiline
- Selegiline

3,4-dihydroxy-phenylacetic acid

3-O-methyldopa

Catechol-O-methyl transferase

Amantadine

Entacapone

Tolcapone
Medications

- Levodopa
- Dopamine agonists
- Monoamine oxidase B inhibitors
- Anticholinergics
- Amantadine
- COMT inhibitors
- Apomorphine
All medications can induce or worsen:

- Confusion
- Hallucinations
- Postural hypotension
- Nausea
When to begin therapy

- Diagnostic role
- Timing of symptomatic therapy is individual
  - Degree of functional impairment
  - Handedness
  - Lifestyle of patient
  - BUT - no reason to delay initiation of treatment and harder to regain lost function
Case 1

- February 2010
- 72 year-old woman
- 6 months tremor
- Positive family history for ET and PD
- On prochlorperazine
- Action and postural tremor both hands
- Rest tremor left hand, minimal bradykinesia, mildly impaired postural reflexes
Case 1

- Did nothing for a year (turned out to be 2 ½)
- Mid 2012 had worsening rest tremor, problems with balance, bradykinetic and very anxious
- Decided not to be treated
Case 1

- Mid 2013 returned with worsening tremor and bradykinesia
- Started Sinemet (levodopa and carbidopa) to good effect (one 25/100 tds)
Dopamine-related

Pre-symptomatic

Treatment

Fluctuations, Involuntary movements, Neuropsychiatric

Motor Disability
Reduced “on” & “off”

6 1-2 2 6-8 10 10+

‘Honeymoon’

Balance
Gait
Swallowing
Speech
Mood
Sleep
Cognitive
Autonomic

Non Dopamine-related

Reduced Quality of Life
Non-motor features

- Cognitive decline
- Psychosis and hallucinations
- Mood disorders – depression, anxiety and apathy
- Sleep problems, fatigue, sleepiness
- Autonomic dysfunction (postural hypotension, bladder dysfunction)
- Gastrointestinal dysfunction – constipation
- Pain and sensory disturbances
- Seborrhoeic dermatitis
- Olfactory disturbance
Case 2

- 69 year-old retired businessman PD for 11 years
- Followed from 2009
- Fluctuating mobility with poor balance and falls
- Severe dyskinesia
- Behavioural changes – impulsivity, hypersexuality, gambling, punding, ACE-R 95/100
- Bladder dysynergia with incontinence – SPC put in 2011
- Anxiety and depression
- Residential care 2011
- Died 2016
Sydney Multicenter Study of Parkinson’s Disease:
Non-L-Dopa–Responsive Problems Dominate at 15 Years

Mariese A. Hely, MBBS,¹{*} John G.L. Morris, MD,¹ Wayne G.J. Reid, PhD,¹ and
Robert Trafficante, BAppScMaths²

¹Department of Neurology, Westmead Hospital, Westmead New South Wales, Australia
²Covance Pty Ltd, Ainslie, Australian Capital Territory, Australia
At 15 years of follow up:
  1/3 of the original cohort of 136 still alive
Major disability:
  Dementia 48% (cognitive decline in 84%)
  Loss of balance and falls (81%; #23%)
  Autonomic failure (postural hypotension 35%; urinary incontinence 41%)
  Dysphagia 50%
  Hallucinations 50%
  Depression 50%
  40% in residential care
The Sydney Multicenter Study of Parkinson’s Disease: The Inevitability of Dementia at 20 years

Mariese A. Hely, MBBS, Wayne G.J. Reid, PhD, Michael A. Adena, PhD, ASTAT, Glenda M. Halliday, PhD, and John G.L. Morris, MD

1Department of Neurology, Westmead Hospital, Westmead, New South Wales, Australia
2Covance Pty Ltd, Braddon, Australian Capital Territory, Australia
3Prince of Wales Medical Research Institute, Randwick, New South Wales, Australia
At 20 years of follow up:
26% of the original cohort of 136 still alive

Major disability:
Dementia 83% (mean duration at onset 10.9 years)
Falls (87%; #35%)
Autonomic failure (postural hypotension 48%; urinary incontinence 71%)
Dysarthria 81%
Dysphagia 50%
Hallucinations 74%
Depression 50% (at least)
48% in residential care
Neuropsychiatric disorders in Parkinson’s disease

- Depression
- Anxiety
- Apathy
- Cognitive impairment / dementia
- Psychosis
- Impulse control disorders (ICDs)
- Disorders of sleep and wakefulness
Depression

- Common - 40-50%
- Makes everything worse (UPDRS motor)
- Symptoms overlap those of the disease
- Dopamine agonists can make depression better
- Watch for cyclical mood variation
- GDS best screen
Depression

- Younger patients more at risk
- Patients dislike drugs
- CBT shown to help
- Psycho-geriatric opinion invaluable
Anxiety

- Common - 20-50%
- Often with depression
- Can be an ‘off’ period symptom
- Generalised anxiety disorder, panic disorder, social phobia, situational anxiety all described
- Treatment similar to the general population
Apathy

- Commonly associated with depression and/or cognitive decline
- Mood is blunted rather than sad
- Distressing for caregivers
Mild cognitive impairment in 20% of newly diagnosed PD

Dementia related to disease duration – 83% by 10.9 years – risk increases with age

Deficits in attention, working memory, executive function, memory and visuo-spatial skills
# Montreal Cognitive Assessment (MOCA)

**Version 7.1 Original Version**

## Visuospatial / Executive
- Copy cube
- Draw clock: (Ten past eleven) (3 points)

## Naming
- Contour [ ] Numbers [ ] Hands [ ]

## Memory
- Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

<table>
<thead>
<tr>
<th>1st trial</th>
<th>2nd trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACE</td>
<td>VELVET</td>
</tr>
<tr>
<td>CHURCH</td>
<td>DAISY</td>
</tr>
<tr>
<td>RED</td>
<td>[ ] 2 1 8 5 4 [ ] 7 4 2</td>
</tr>
</tbody>
</table>

## Attention
- Read list of digits (1 digit/sec):
  - Subject has to repeat them in the forward order [ ] 2 1 8 5 4 [ ] 7 4 2
  - Subject has to repeat them in the backward order [ ] 7 4 2 [ ] 2 1 8 5 4
- Read list of letters. The subject must tap with his hand at each letter A. No points if ≥2 errors.
- Serial 7 subtraction starting at 100: [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
  - 4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt

## Language
- Repeat: I only know that John is the one to help today.
- The cat always hid under the couch when dogs were in the room.
- Fluency / Name maximum number of words in one minute that begin with the letter F [ ]
  - (N ≥ 11 words) [ ]

## Abstraction
- Similarity between e.g. banana – orange = fruit [ ] train – bicycle [ ] watch – ruler [ ]

## Delayed Recall
- Has to recall words WITH NO CUE
- Points for UNCUED recall only [ ]/5

## Optional
- Category cue
- Multiple-choice cue

## Orientation
- Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City [ ]

Total [ ]/30

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Administered by: ____________________________________________________________

Normal ≥ 26 / 30

Add 1 point if ≤ 12 yr edu
Rule out delirium due to intercurrent illness and/or medication

Review medications

Consider cholinesterase inhibitors (some evidence for rivastigmine and donepezil)

Think ahead – social/legal implications, ACP, driving
Rivastigmine for Dementia Associated with Parkinson’s Disease

Murat Emre, M.D., Dag Aarsland, M.D., Ph.D., Alberto Albanese, M.D., E. Jane Byrne, F.R.C.Psych., M.B., Ch.B., Günther Deuschl, M.D., Peter P. De Deyn, M.D., Ph.D., Franck Durif, M.D., Ph.D., Jaime Kulisevsky, M.D., Ph.D., Teus van Laar, M.D., Ph.D., Andrew Lees, M.D., Werner Poewe, M.D., Alain Robillard, M.D., F.R.C.P.C., Mario M. Rosa, M.D., Erik Wolters, M.D., Ph.D., Peter Quarg, M.Sc., Sibel Tekin, M.D., and Roger Lane, M.D.

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Figure 2. Results of the Primary Efficacy Analysis in the Efficacy Population.

Panel A shows the changes from baseline in the score for the cognitive subscale of the Alzheimer’s Disease Assessment Scale (ADAS-cog). Scores can range from 0 to 70, with higher scores indicating more severe impairment and decreases in scores indicating improvement. Panel B shows the scores for the Alzheimer’s Disease Cooperative Study–Clinician’s Global Impression of Change (ADCS-CGIC) at 24 weeks. Minimal changes were predefined as those that were clinically detectable but that did not affect a patient’s clinical status; moderate changes were defined as definite, detectable changes that had a corresponding effect on clinical status; and marked changes were defined as those that had a dramatic effect on clinical status. P=0.007 for the overall difference between groups at 24 weeks. A few patients in the efficacy analysis had missing data on either of the two primary end points at week 24.
Psychosis

- Experienced by 60% of patients by 12 years
- More likely if older, on more levodopa, history of RSBD
- Predicts carer stress, mortality and residential care
A 12-Year Population-Based Study of Psychosis in Parkinson Disease

Elin B. Forsaa, MD; Jan Petter Larsen, MD, PhD; Tore Wentzel-Larsen, MSc; Christopher G. Goetz, MD; Glenn T. Stebbins, PhD; Dag Aarsland, MD, PhD; Guido Alves, MD, PhD

Arch Neurol. 2010;67(8):996-1001
- 230 PD patients followed up for 12 years
- 137 of 230 patients (59.5%) developed psychosis
- Onset on average 13.0 years after motor onset, (2.2-25.1 years)
The Changing Face of Parkinson’s Disease-Associated Psychosis: A Cross-Sectional Study Based on the New NINDS-NIMH Criteria

Gilles Fénelon, MD, PhD,¹,²* Thierry Soulas, MA,³ Franck Zenasni, PhD,⁴ and Laurent Cleret de Langavant, MD¹,²

Movement Disorders, Vol. 25, No. 6, 2010
FIG. 1. Distribution of psychotic symptoms in 116 consecutive PD outpatients. Psychotic symptoms include hallucinations and delusions (white bars) and minor phenomena (gray bars). The proportion of patients with psychosis (black bars) is shown, based on the usual definitions (hallucinations or delusions) and the new NINDS-NIMH criteria (hallucinations, delusions, sense of presence, or visual illusions). Values are given in percentages.
Hallucinations

- Unformed visual hallucinations common
- Auditory and tactile can occur
- Older patients with sensory deficits and cognitive impairment more vulnerable
- Associated with depression and daytime sleepiness
Delusions

- Relatively uncommon 4-10%
- Common themes – infidelity, abandonment
Case 3

- 71 year-old woman PD since 2004
- Admitted with falls, hallucinations, collapses
- Hallucinating, dyskinetic, hypotensive
- Levodopa changed from CR to straight and dose reduced; rehydrated and given fludrocortisone; amantadine stopped
- Quetiapine sedated, donepezil caused diarrhoea, rivastigmine patch resulted in resolution of hallucinations
Management of psychosis

- Exclude/treat intercurrent illness
- Review medications
Management of psychosis

- Stop drugs in the following order:
  - Anticholinergics
  - MAO-B inhibitors all gradually
  - Amantadine
  - Dopamine agonists
  - Levodopa – reduce to the minimum needed
Benzodiazepines (short term)
Atypical antipsychotics
Best evidence for clozapine
Quetiapine sedates and causes postural hypotension
Clozapine causes agranulocytosis (0.7%), severe constipation, myocarditis
Original Investigation

Association of Antipsychotic Use With Mortality Risk in Patients With Parkinson Disease

Daniel Weintraub, MD; Claire Chiang, PhD; Hyungjin Myra Kim, ScD; Jayne Wilkinson, MD, MSCE; Connie Marras, MD, PhD; Barbara Stanislawski, MPH, MSW; Eugenia Mamikonyan, MS; Helen C. Kales, MD

*JAMA Neurol.* doi:10.1001/jamaneurol.2016.0031
Published online March 21, 2016.
Gambling, shopping, hypersexuality, eating
Punding, hobbyism, hoarding, pacing
Dopamine dysregulation syndrome
Impulse Control Disorders in Parkinson Disease

A Cross-Sectional Study of 3090 Patients

Daniel Weintraub, MD; Juergen Koester, PhD; Marc N. Potenza, MD, PhD; Andrew D. Siderowf, MD, MSCE; Mark Stacy, MD; Valerie Voon, MD; Jacqueline Whetteckey, MD; Glen R. Wunderlich, PhD; Anthony E. Lang, MD, FRCPC

Arch Neurol. 2010;67(5):589-595
DOMINION study

- 3090 patients with PD screened for ICD
- 66% on dopamine agonists and 87% on levodopa
- 14% had an ICD, and 29% of these had ≥ 2:
  - Gambling 5%
  - Hypersexuality 3.5%
  - Compulsive buying 5.7%
  - Binge-eating 4.3%
Impulse control disorders

- Patients rarely reveal spontaneously.
- More likely with DA than levodopa
- Premorbid personality traits increase risk
- Young males, single, smokers
- Executive dysfunction
Management

- Warn patients and partners
- Identify the problem
- Stop, reduce or change dopamine agonists
- Antidepressants, antipsychotics etc
Conclusions:

- Motor deficit responds best to levodopa
- PD is much more than dopamine deficiency
- Non-dopa responsive symptoms cause most of the long term disability in PD
- Non-dopa responsive symptoms can be treated
- PD is a multi-system disease that requires multi-disciplinary management
Effects of coffee/caffeine on brain health and disease: What should I tell my patients?

Astrid Nehlig

Caffeine

- Safe up to 200mg (2 1/2 cups coffee) per sitting or 400mg per day
- Improves mood, alertness, attention and concentration
- Potentiates analgesics in headache and migraine
- Reduces risk of dementia, stroke and Parkinson’s disease
Thank you