Medications in Parkinson’s disease

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Dr Jerome Ip
Neurologist and Geriatrician
VMO Neurologist, Hornsby and Ryde Hospitals
Staff Specialist in Neurology, Nepean Hospital
Honorary Associate, Brain and Mind Centre, Sydney University

jerome.ip@sydney.edu.au
Disclaimer

Nothing to declare
Outline

• Pathophysiology of PD and L-dopa metabolism
• Classes of anti-parkinsonian medications
• When and what drug to start as initial therapy
• Levodopa associated motor complications
• Paradigm shift in PD treatment
• (Advanced treatment options)
• Challenges and gems in PD medication management
Parkinson’s disease

• Relatively common neurological disorder in our community
  – 0.3% population
  – 100000 PD patients in Australia

• Age is single most important risk factor
  – Mean age of symptom onset 70 years old

• Incidence increases exponentially between 60 and 95 years old
  – 1 to 2% of 60 yo +

• Medication management poses dilemmas and challenges to clinicians
Parkinson’s disease: Pathogenesis

- Marked striatal dopamine depletion
  - Parkinsonian manifestations when >70% dopaminergic cell loss
  - At the time of death, more than 90% of dopaminergic cell loss
  - Degree dopaminergic cell loss best correlates with the severity of bradykinesia
α Synuclein accumulation in PD

α Synuclein accumulation in the SNC is relatively late development

α Synuclein accumulation induces cell death

Neurology 72 (Suppl 4) May 26, 2009
# Staging and natural history of PD

<table>
<thead>
<tr>
<th>Rating Scale and Symptomology</th>
<th>Premotor</th>
<th>Early</th>
<th>Moderate</th>
<th>Advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoehn and Yahr stage (approximate)(^a)</td>
<td>0</td>
<td>1, 2</td>
<td>2, 3, 4</td>
<td>4, 5</td>
</tr>
<tr>
<td>Presumed Braak stage (pathologic)</td>
<td>1, 2, 3</td>
<td>3, 4</td>
<td>4, 5</td>
<td>4, 5, 6</td>
</tr>
<tr>
<td>Typical UPDRS III score</td>
<td>0–5</td>
<td>10–35</td>
<td>20–50</td>
<td>30–60</td>
</tr>
</tbody>
</table>

### Motor
- None
- Subtle, such as stiff shoulder
- Restless legs syndrome
  - Very dopamine responsive: sustained, predictable
  - Some secondary features (stooped postures, hypomimia, hypophonia, micrographia)
- Motor complications: wearing off, dyskinesias, on/off phenomena
- Less consistent dopamine response
- More gait disturbance, some falls, increased axial symptoms
- Severe motor complications\(^b\)
  - Axial symptoms become most disabling feature (dysphagia, hypophonia, dysarthria, postural instability, balance, frequent falls, freezing of gait, etc)

### Autonomic
- Constipation
  - Urinary symptoms (mild)
  - Nausea\(^b\)
  - Sexual dysfunction
  - Sweating disturbance
- Urinary symptoms more common (urgency, frequency, nocturia)\(^b\)
- Orthostatic hypotension/ lightheadedness\(^b\)
- Worsening orthostatic hypotension\(^b\)
- Sialorrhea (drooling)

### Cognitive
- Subtle attention deficits, executive dysfunction
- More pronounced frontal executive dysfunction and decreased verbal fluency
- Psychosis including visual hallucinations, delusions, decreased attention, dementia

\(^a\) In patients with PD, the Yahr stage is the same as the Hoehn stage.
\(^b\) Common complications affecting patients who have PD.
### TABLE 1-5 Continued...

<table>
<thead>
<tr>
<th>Rating Scale and Symptomology</th>
<th>Premotor</th>
<th>Early</th>
<th>Moderate</th>
<th>Advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral</td>
<td>Anxiety</td>
<td></td>
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<tr>
<td></td>
<td>Depression</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Apathy</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Impulse control disorder(^b) (gambling, etc)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sleep</td>
<td>REM sleep behavior disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Excessive daytime sleepiness(^b)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Vivid dreams(^b)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Sleep maintenance</td>
<td></td>
</tr>
<tr>
<td>Other (sensory, pain, skin, systemic)</td>
<td>Olfactory loss</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Seborrhea</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Pain</td>
<td></td>
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<tr>
<td></td>
<td>Paresthesia</td>
<td></td>
<td>Change in vision/ bright lights</td>
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<td></td>
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<td>Weight loss(^b)</td>
</tr>
</tbody>
</table>

UPDRS = Unified Parkinson’s Disease Rating Scale.

\(^{a}\)Hoehn and Yahr staging:
Stage 1: Symptoms on one side of the body only.
Stage 2: Symptoms on both sides of the body. No impairment of balance.
Stage 4: Severe disability, but still able to walk or stand unassisted.
Stage 5: Needing a wheelchair or bedridden unless assisted.

\(^{b}\)Can be worsened, complicated by medications.
Parkinson’s disease: Management

• General principles
  – Supress symptoms
  – Keep patients functioning for as long as possible with minimal amount of medications
  – (Neuroprotection)
  – Individualised treatment

• Treatment options
  – Non-pharmacological management
  – Drug therapy
    • Preventative / protective
      – No definite preventative treatment at this stage
    • Symptomatic
      – Medical
      – Surgical
  – Restorative (experimental only)
    • Foetal or porcine cell transplantation
    • Neurotrophic factors eg GDNF
  – Management of non-motor manifestations
Non-pharmacological management

• Patient / carer education and support
  – Parkinson’s NSW (www.parkinsonsnsw.org.au)

• Multidisciplinary rehabilitation

• Physiotherapy
  – ‘Cued’ exercise regimen, treadmill, gait and balance training

• Occupational therapy
  – Home modifications

• Speech and language therapy

• Active music therapy

• Diet and nutrition
  – Increase dietary fibre and vegetable content
  – Manage protein load

• Psychosocial intervention
PD meds could be confusing!
Pharmacological management

Dopaminergic treatments:

- Levodopa plus a DDC inhibitor
  -- Levodopa plus a DDC inhibitor and a COMT Inhibitor
- Dopamine agonists

Others:
- MAO-B inhibitor
- Anticholinergics
- Amantadine

Sudden withdrawal or reduction in dosage of L-dopa or DA can induce the parkinsonism-hyperpyrexia syndrome.
Levodopa: peripheral and central metabolism

Levodopa → Dopamine

- Dopa Decarboxylase → Dopamine
- COMT → 3-OMD

Dopamine →
- COMT → DOPAC
- MAO → 3-MT

DOPAC → HVA

BBB = blood-brain barrier; COMT = catechol-O-methyltransferase; MAO = monoamine oxidase; 3-OMD = 3-O-methyldopa; DOPAC = dihydroxyphenylacetic acid; 3-MT = 3-methoxytyramine.
Medications for Parkinson’s disease

• **Levodopa** (+peripheral dopa-decarboxylase DDC inhibitor)
  – levodopa + carbidopa (Sinemet, Kinson)
  – levodopa + benserazide (Madopar)

• **COMT (catecho-o-methyltransferase) inhibitor**
  – entacapone (Comtan)
  – levodopa + carbidopa + entacapone (Stalevo)

• **Dopamine agonists**
  – Ergot: bromocriptine (Parlodel, Kripton), pergolide (Permax), cabergoline (Cabaser)
  – Non-ergot: pramipexole (Sifrol), rotigotine (Neupro), ropinirole (Repreve)
  – Apomorphine

• **Monoamine oxidase B inhibitors**
  – selegilene (Eldepryl, Selgene)
  – Rasagiline (Azilect)

• **Anticholinergics**
  – benzhexol (Artane)
  – benztropine (Cogentin)
  – biperiden (Akineton)

• **Amantadine (Symmetrel)**
<table>
<thead>
<tr>
<th>Class</th>
<th>Medications</th>
<th>Typical Initial Dose</th>
<th>Maximal Recommended Doses</th>
<th>Important Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa preparations</td>
<td>Carbidopa/levodopa</td>
<td>25 mg/100 mg 3 times/d</td>
<td>~1200 mg levodopa/d</td>
<td>Short-term: nausea, vomiting, lightheadedness, orthostasis</td>
</tr>
<tr>
<td></td>
<td>Benserazide/levodopa&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25 mg/100 mg 3 times/d</td>
<td>(selected cases may require up to 2500 mg/d divided in 5 or 6 doses)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carbidopa/levodopa/entacapone</td>
<td>25 mg/100 mg/200 mg 3 times/d</td>
<td>200 mg with each dose of levodopa</td>
<td></td>
</tr>
<tr>
<td>Catechol-O-methyltransferase inhibitors&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Entacapone</td>
<td>200 mg 3 times/d</td>
<td>200 mg with each dose of levodopa</td>
<td>Same as for levodopa preparations (maximize levodopa effects)</td>
</tr>
<tr>
<td></td>
<td>Tolcapone</td>
<td>100 mg 3 times/d</td>
<td>200 mg 3 times/d</td>
<td>Entacapone: diarrhea, brownish-orange discoloration of urine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tolcapone: risk of potentially fatal fulminant hepatic toxicity, which requires close monitoring of liver function tests; diarrhea; brownish-orange discoloration of urine</td>
</tr>
<tr>
<td>Dopamine agonists</td>
<td>Pramipexole</td>
<td>IR: 0.125 mg 3 times/d</td>
<td>IR: 1.5 mg 3 times/d</td>
<td>Excessive sleepiness, impulse control disorders, leg edema, hallucinations, orthostasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>XR: 0.375 mg/d</td>
<td>XR: 4.5 mg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ropinirole</td>
<td>IR: 0.25 mg 3 times/d</td>
<td>IR: 8 mg 3 times/d</td>
<td>Cabergoline is associated with pulmonary fibrosis and cardiac valvulopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>XR: 2 mg/d</td>
<td>XR: 24 mg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rotigotine patch</td>
<td>2 mg/24hrs</td>
<td>8 mg/24hrs</td>
<td>Apomorphine is associated with orthostatic hypotension, nausea, lightheadedness, sedation</td>
</tr>
<tr>
<td></td>
<td>Cabergoline&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 mg/d</td>
<td>6 mg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Apomorphine</td>
<td>0.2 mL (2 mg)</td>
<td>0.6 mL (6 mg)</td>
<td></td>
</tr>
<tr>
<td>Monoamine oxidase-B inhibitors</td>
<td>Rasagiline</td>
<td>1 mg/d</td>
<td>1 mg/d</td>
<td>Nausea, lightheadedness, dyskinesia, hallucinations</td>
</tr>
<tr>
<td></td>
<td>Selegiline</td>
<td>5 mg/d</td>
<td>5 mg 2 times/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Selegiline orally disintegrating</td>
<td>1.25 mg every morning</td>
<td>2.5 mg every morning</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Amantadine</td>
<td>100 mg/d</td>
<td>100 mg 3 times/d</td>
<td>Cognitive impairment, hallucinations, dry mouth, myoclonus, livedo reticularis, leg edema</td>
</tr>
</tbody>
</table>

<sup>a</sup> Immediate release; <sup>b</sup> Formulation not available in the United States.
<sup>c</sup> Catechol-O-methyltransferase inhibitors are used as adjunct to carbidopa/levodopa therapy.

Table 1-1 Medications Used in Parkinson Disease

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**Parkinsonian Syndromes**

Williams, David R.; Litvan, Irene
doi: 10.1212/01.CON.0000436152.24038.e0
Levodopa

• Precursor of dopamine

• Most effective medications to improve motor features of PD
  – Bradykinesia, rigidity > tremor; max benefit in 4 – 8/52

• Fewest short-term side effects
  – N+V (20%), postural hypotension

• Combined with a peripheral DDC inhibitor to reduce nausea and to increase L-dopa delivery to the brain
  – L-dopa / carbidopa = Sinemet, Kinson, L-dopa / benserazide = Madopar

• Gets to the brain in 30-45 mins; Half life (with DDCI) – 90 mins

• Competition with amino acids for transport across GIT and BBB: food slows absorption and lowers peak plasma level

• **Sinemet CR (200/50)** – controlled release over 8-12 hrs
  – More convenient, fewer dosing; bioavailability 30% less than regular L-dopa -> dose increased 20-60%
  – Not found to reduce development of motor fluctuation / dyskinesia

• **Madopar Rapid 62.5 or 125 Dispersible tablet**
  – Orally disintegrates. ‘liquid’ levodopa
  – Useful as a ‘kick-start’ therapy and in those with swallowing difficulties
  – Same clinical benefit and side effects
Monoamine oxidase type B inhibitor

- Selegiline (Eldepryl), Rasagiline (Azilect)
- Relatively selective, irreversible MAO-B inhibitor
- Decrease catabolism and increase half life of dopamine

Monotherapy:
- Modest symptomatic benefit
- Delay need for L-dopa
- Selegiline (DATATOP), Rasagiline (ADAGIO)

Adjunctive to levodopa
- Smooth out early wearing-off (Zydis selegiline) for patients with motor fluctuations
- Rasagiline reduces OFF time in L-dopa treated patients with motor fluctuations (PRESTO, LARGO study)

SE: dyskinesia, mood elevation, hallucinations, bruxism, confusion, insomnia, increased risk of tyramine induced hypertensive crisis at higher dose

Used with caution with SSRI or MAO A inhibitor – precipitate serotonin syndrome (MAO also metabolises serotonin)

No evidence to support earlier claims of neuroprotective / disease modifying benefits of MAOBI (DATATOP study, DATATOP 3yrs f/u)
Amantadine

- **Symmetrel**

  - Anti-viral. Anti-parkinsonian mechanism uncertain? Direct stimulation of dopamine receptors and by inhibiting dopamine reuptake
  - Symptomatically reduces levodopa-induced peak-dose dyskinesia; minor benefits on reversing motor symptoms
  - Benefits short-lived, may last less than a year
  - Used with caution in elderly and in those with dementia; reduce dose in renal impairment
  - **SE:** anti-cholinergic, hallucinations and confusion, delirium, livedo reticularis (50%), ankle oedema (5-10%)
  - Abrupt withdrawal may substantially worsen PD motor symptoms and signs
Dopamine agonists

- Act on post-synaptic dopamine receptors (D2) in the striatum
- Does not compete with amino acid for uptake from the GIT
- Longer half-life: 4-8 hours or longer
- As monotherapy (vs L-dopa as initial therapy)
  - Equally effective in early disease to improve motor symptoms (ropinirole 056 study)
  - Delay need for L-dopa
  - Delay or less likely to develop dyskinesias or motor complications than L-dopa (ropinirole 056 study group; pramipexole CALM Cohort)
  - No long term difference in mortality, disability or disease modifying effects
- As adjunctive therapy to L-dopa
  - Reduces OFF time
  - Reduce motor fluctuations
- Neuroprotective benefit on functional imaging studies but clinical significance?

- **SE:** N+V, postural hypotension, sleep attacks, hallucinations, peripheral oedema
- Impulse control disorder (at risk: male, younger, hx of substance abuse, bipolar disorder, previous impulsivity)
- **Ergot based DAs:** pleuropulmonary or retroperitoneal fibrosis, cardiac valvular fibrosis
  - Baseline CXR, ECHO, ESR, renal function
**COMT** (catechol-O-methyltransferase) **inhibitor**

- **Entacapone (COMTAN)** – selective, reversible, peripherally acting COMT inhibitor

- Used in conjunction with L-dopa/DDCI
  - Extend L-dopa T1/2 30-50%; ↑ duration of L-dopa 0.5 to 1 hr
  - Allow more L-dopa delivered to the brain over longer time
    - 30-50% reduction in plasma variability
  - Reduces ‘off’ time and add ‘on’ time (90 mins) each day in patients with motor fluctuations on L-dopa

- Side-effect: dopaminergic S/E; orange or brown discoloration of saliva, urine or sweat, diarrhoea (4-10%); hepatotoxicity not reported (cf tolcapone)

- **STALEVO** = L-dopa / carbidopa + entacapone
  - May need to reduce L-dopa dose 10-30% if increased dyskinesia

- STRIDE-PD study: Stalevo 100 v L-dopa 100 3.5 hrly QID
  - Stalevo not delay the onset of dyskinesia
When should treatment be started?

• FUNCTION, FUNCTION, FUNCTION

• Initiate treatment when interfering occupational, social and recreational function

• Patient’s subjective impression of functional impairment

• Individualised
Which drug should be started with?

- L-dopa “phobia” postpones L-dopa treatment, due to
- L-dopa associated motor complications
- Neurotoxic effect of L-dopa on dopamine neurons
L-dopa as initial therapy

• **PD MED 2014 (Lancet 2014)**
  – Pragmatic open-label randomised control trial
  – L-dopa vs L-dopa sparing therapy (DA or MAOBI) as initial therapy
  – Primary end-point: patient-rated QoL mobility scale (PDQ-39)
  – Very small but persistent (7 years) benefits for patients randomised to L-dopa
  – No difference in rates of dementia, admissions to institutions and death
  – More dyskinesias years 3 to 5 but not at 7 years
  – In the L-dopa sparing groups, MAOBI better than DA, less discontinuation due to side effects

• **ELLDOPA (NEJM 2004)**
  – Compare L-Dopa 37.5/150 vs 75/300 vs 150/600 vs placebo 40 weeks followed by wash-out period of 2 weeks, on progression of PD (UPDRS)
  – Severity of parkinsonism increased more in the placebo group
  – Motor benefits were dose-dependent, as were dyskinesias (17% in highest dose group)
  – Detrimental effects on dopamine neurons with early L-dopa therapy not proven

• **STRIDE-ED (Ann Neurol 2010)**
  – L-dopa+carbidopa+entacapone (LCE) vs LC as initial therapy
  – More frequent dyskinesias more frequent and shorter time to dyskinesias in the LCE group
Initial therapy

- L-dopa (+DDCI), DA (non-ergot), MAOBI are all reasonable options

- Probably not L-Dopa+DDCI+COMTI (entacapone)

- Aim for optimal quality of life in the present

- Adequate doses of antiparkinsonian medication is probably more important than choice of a particular drug
Main issue to consider when to start medication is functional disabilities experienced by patients during everyday life activities.

Early PD = ‘Honeymoon’: reliable good control

L-dopa is a good option to start in older patients (greatest benefit least SE; shorter disease horizon)

It may be more suitable to start younger patient (60yo) with mild symptoms on DA due to tendency to develop early dyskinesias

Monotherapy with MAOBI or amantadine for mildly affected de novo patients

Vlaar A et al. Pract Neuro 2011; 11: 145-152
## Prevalence of levodopa-associated motor complications

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Prevalence of complication</th>
<th>Length of study (years)</th>
<th>Method of evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poewe et al. 1986</td>
<td>52% wearing off</td>
<td>6</td>
<td>Webster scale</td>
</tr>
<tr>
<td></td>
<td>54% dyskinesias</td>
<td></td>
<td>Modified Columbia Scale</td>
</tr>
<tr>
<td>Hely et al. 1994</td>
<td>41% wearing off</td>
<td>5</td>
<td>Modified Columbia Scale</td>
</tr>
<tr>
<td>Montastruc et al. 1994</td>
<td>34% wearing off</td>
<td>5</td>
<td>Physician evaluation</td>
</tr>
<tr>
<td></td>
<td>48% dyskinesias</td>
<td></td>
<td>Columbia Scale, UPDRS</td>
</tr>
<tr>
<td>Dupont et al. 1996</td>
<td>59% fluctuations</td>
<td>5</td>
<td>UPDRS, part IV</td>
</tr>
<tr>
<td></td>
<td>41% dyskinesias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DATATOP. 1996</td>
<td>50% wearing off</td>
<td>2</td>
<td>Physician evaluation</td>
</tr>
<tr>
<td></td>
<td>30% dyskinesias</td>
<td></td>
<td>UPDRS, part IV</td>
</tr>
<tr>
<td>Rascol et al. 2000</td>
<td>45% dyskinesias</td>
<td>5</td>
<td>UPDRS, dyskinesia scale</td>
</tr>
<tr>
<td>PSG. 2000</td>
<td>30% dyskinesias</td>
<td>2</td>
<td>Physician evaluation</td>
</tr>
<tr>
<td>Rajput et al. 2002</td>
<td>15% dyskinesias</td>
<td>2.6</td>
<td>Physician evaluation</td>
</tr>
<tr>
<td></td>
<td>31% dyskinesias</td>
<td>6.4</td>
<td></td>
</tr>
</tbody>
</table>

Predictors: intrinsic dopa responsiveness; age of onset (<40yo); duration of dopamine depletion (severity of disease at time of L dopa initiation)
Changes in levodopa response in mid and late-stage disease

Pulsatile stimulation of dopamine receptors
- contributes to the development of motor fluctuations and dyskinesia
- associated with disease severity and the use of dopaminergic agents with short T1/2
- L-dopa has a short T1/2 (60–90 min)

Obeso et al. 2000

MOTOR FLUCTUATIONS
Reappearance of parkinsonism
Dyskinesias
Wearing-off

- End-of-dose failure, nocturnal and early morning akinesia, delayed onsets or dose failures (no ON), ON/OFF fluctuations

- Early symptoms can be subtle

- Can also be non-motor: anxiety, fatigue, mood lowering, restlessness, autonomic dysfunction

- May occur suddenly

- ~40% of patients affected within 2 years
- Affect 10% of patients with each year of L-dopa treatment; higher rate in young onset PD
Dyskinesias

• Manifestation of excessive dopaminergic stimulation
• Seen later in the disease and at higher dose of L-dopa; approx 10%/year
• DA alone usually no or mild dyskinesia

• Mixture of choreiform, ballistic and dystonic movements

• Types
  – Peak-dose dyskinesia: the commonest, 1 – 2 hours after dose
  – Biphasic (intermediate-dose) dyskinesia: both dose onset and offset
  – End-of-dose dystonia: late in dose cycle, can cause pain, need increased dose

• Concept of “disabling dyskinesias”: most patients don’t mind some dyskinesia for remaining at the ‘on’ state; can be mild or asymptomatic

• If disabling,
  – Reduce each dose of L-dopa (or other meds entacapone, MAOBI, DA)
  – Smaller dose of dopamine in shortened dosing interval (fractionate)
  – Amantadine (short-lived benefits 6/12)
Figure 1  Simplified and schematic representation of motor complications in Parkinson’s disease in relation to disease progression. Upper panels (A,B,C) the red bar indicates stage of disease. For a given extracellular or plasma level of dopaminergic therapy, the chances of the patient being in a satisfactory ON state decrease as the condition advances. (A) In early Parkinson’s disease treated with levodopa, the optimal therapeutic window (mid-blue shading) is wide with no wearing-OFF (dark blue) or dyskinesia (light blue). (B) As the disease progresses, owing, in large part, to ongoing loss of nigrostriatal neurones and postsynaptic receptor and neuronal changes, the therapeutic window narrows and wearing-off and dyskinesias emerge. (C) In advanced disease, with further narrowing of the therapeutic window, it becomes increasingly difficult to maintain the patient in the satisfactory ON state, with OFF periods and dyskinesias often predominating. Lower panels (D,E,F). Early management strategies to treat motor complications. Note x-axis is now time of day. (D) The patient treated with standard three times daily levodopa experiences sequential OFF periods, ON without dyskinesia, and peak dose dyskinesia. (E) Fractionating levodopa into larger numbers of smaller doses may result in some improvements but is increasingly inconvenient for patients. (F) Use of a longer-acting dopamine agonist may allow more consistent control of motor symptoms, reducing OFF time and time with dyskinesia. Courtesy R Genever.
Strategies to improve motor fluctuations

- **Levodopa dose manipulations**
  - increase size of levodopa dose
  - smaller, more frequent doses
  - IPX066 L-dopa formulation (long acting) under trial

- Add DA with longer T1/2 than L-dopa

- Add COMT inhibitor

- Add MAOB-I

- Sustained-release levodopa
  - at bed time, improve nocturnal mobility

- Apomorphine: rescue Rx for sudden ‘off’s or s/c infusion

- Enteral infusion of levodopa (Duodopa)

- Surgery

Worth PF. Pract Neurol 2013; 13: 140-152
## Choice of advanced therapy

### Table 1
Illustrating how specific complications of the disease process and documented adverse effects of previous drug therapy may influence the decision to use device-aided therapy

<table>
<thead>
<tr>
<th></th>
<th>Apomorphine</th>
<th>Levodopa/carbidopa intestinal gel</th>
<th>Deep brain stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age over 70 years</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Presence of comorbidities</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Severe speech disturbance</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Postural instability, falls</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Hallucinations/psychosis</td>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Impulse control disorders</td>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Excessive daytime sleepiness</td>
<td>–</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mild dementia</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Moderate–severe dementia</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Moderate–severe depression</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Previous suicide attempts</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Weight gain</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Restless legs</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

+=Presence of side effect/complication strengthens the decision to select the device-aided therapy.
0=Presence of side effect/complication does not influence the decision.
-=Presence of side effect/complication argues against selecting the device-aided therapy.

The table is based largely upon clinical experience and expert opinion in the absence of published robust comparative evidence.
New treatment paradigm in PD

• Aiming for optimal quality of life is more important than fear of possible long term complications of drug therapy

• L-dopa phobia probably not justified

• Adequate doses of antiparkinsonian medication more important than choice of a particular type of drug

• Earlier consideration of advanced therapy for suitable patients
Challenges in medication management in hospital PD patients

- Concurrent acute medical illnesses and co-morbidities; delirium
- Polypharmacy including medications for other non-motor manifestations
- Administration and dispensing issues
  - Different meals, wake-up / sleep times
  - Frequent dosing regimen (and resource implication)
  - Patient autonomy vs medication safety
- Swallowing difficulties / NBM / tube feeding – L-dopa absorption issue
- Different formulations /dosage eg Sinemet IR vs CR; Madopar IR vs HBS vs rapid
- Motor fluctuations and recognise non-motor OFF symptoms
- Parkinsonism made worse by concurrent medical illnesses or treatment
  - Anti-emetics, anti-psychotics
- Risk of deconditioning, falls, delirium, etc
Gems in PD medication management

• Balancing management priorities: motor vs cognitive

• Reducing or withholding may be necessary (DA, amantadine, MAOBI, late night dose in delirium), but should avoid stopping all PD meds

• Clarify PD disease and treatment history. Liaise with usual treating clinicians

• Encourage use of “PD chart”, particularly when titrating medications

• Treat acute precipitants rather than dose escalation of PD

• Caution about prolonged use of anti-emetics, anti-psychotics

• Early multi-disciplinary team involvement, rehabilitation
References

• Lees, A. Parkinson’s disease. JNNP 2010; 10:240-246
• Vlaar et al. The treatment of early Parkinson’s disease: levodopa rehabilitated. Pract Neurol 2011; 11:145-152
• Worth PF. When the going gets tough: how to select patients with Parkinson’s disease for advanced therapies. Pract Neurol 2013; 13:140-152