Parkinson’s disease
Therapeutic strategies

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Scope

• Modality of treatment
• Pathophysiology of PD and dopamine metabolism
• Drugs
• Are there guidelines for the treatment of Parkinson’s disease?
Modality of treatment

- Symptoms base treatment
  - Pharmacologic VS Non-pharmacologic
  - Motor VS Non-motor symptom
- Neuro-protective treatment
- Reversing pathology
- Prevention
Signs and Symptoms of PD

Motor symptoms (TRAP)

- *Tremor at rest*
  - "Pill rolling"
- *Rigidity* (stiffness)
  - "lead pipe" or like a "cogwheel"
- *Akinesia* (inability to move) or *Bradykinesia* (slow movement)
  - mask-like face, micrographia, freezing, impaired swallowing
- *Postural instability with gait problems*
Non-Motor Symptoms

- **Psychological**
  - depression, psychosis, anxiety, apathy, memory problems

- **Sleep**
  - RLS, REM behavior disorder

- **Autonomic Dysfunction**
  - constipation, drooling, decreased BP, temp regulation

- **Others**
  - fatigue, speech, swallowing, seborrhea, pain, weight loss
Pathophysiology of PD and dopamine metabolism
Neurotransmitters of the Basal Ganglia

Inhibitory
- Dopamine
- Norepinephrine
- Epinephrine
- GABA

Excitatory
- Acetylcholine
- Serotonin
- Histamine
- Glutamate
Symptoms of PD

Dopamine

Ach
Symptomatic Treatment

Enhance dopaminergic transmission

Drug manipulating neurotransmitter

Dopamine

Ach
Dopamine Metabolism

DDC = dopa decarboxylase; 3-OMD = 3-O-methyldopa; BBB = blood-brain barrier; COMT = catechol-o-methyl-transferase, MAO-B = monoamine oxidase-B; DOPAC = 3,4-dihydroxyphenyl acetic acid; HVA = homovanillic acid; 3-MT = 3-methoxytyramine.
Sites of action of common therapies for Parkinson’s disease

- **Tyrosine**
- **L-Dopa**
- **Dopamine (DA)**
- **Reuptake**
- **Degradation**
- **COMT**
- **DA Agonists** (bind to DA receptors)
- **Amantidine** (stimulates release of DA, inhibits reuptake)
- **Selegeline** (inhibits MAO-B)
- **Levodopa** (increases L-Dopa levels)
- **COMT Inhibitors** (block degradation of DA and L-Dopa)
- **Acetylcholine Inhibitors** (block action of ACh in striatum)

**Parkinson’s disease**
Enhance Dopaminergic transmission

- DA precursor
- Administer DA agonists
  - Ergolides
  - Non-ergolides
- Direct or indirect potentiate dopaminergic transmission
  - Enhance DA release
  - Block DA reuptake
  - Inhibit DA catabolism (degradation)
Increase DA synthesis

- Stimulate tyrosine hydroxylase (tetrahydrobiopterin)
- DA precursors (tyrosine, levodopoa)
- Modify levodopa pharmacokinetic
  - Dietary modification (minimize AA intake, administer antacids)
  - Block peripheral dopa decarboxylase (carbidopa, benserazide)
  - Slow-release levodopa (sinemet CR, Madopa HBS)
Enhance DA release
- Amantadine
- Methylphenidate
- Dextroamphetamine
- Pemoline
- Nicotine
- Electroconvulsive therapy

Block DA reuptake
- Amantadine
- Tricyclics
- Bupropion
- Mazidol
Inhibit DA catabolism (degradation)

- COMT inhibition (Tolcapone, Entacapone)
- MAO-B inhibitors
  Depreny (seligiline)

Administer DA agonist

- Bromocryptine
- Pergolide
- Lisuride
- Apomorphine
- Pramipexole
- Ropinirole
- Cabergolide
Drug manipulating other neurotransmitter

- **Anti-cholinergic drugs**
  - Trihexyphenidyl (Artane)
  - Benztropine (Cogentin)
  - Biperidine (Akineton)
  - Orphenadrine (Disipal)
  - Procyclidine (Kemadrine)
How to management?

• When to started?
• Drug choice?
• Disease progression, management and complication of treatment
Management of Parkinson’s Disease

Stage

0
Considerations
- Age
- Cognitive function
- Comorbidity

1-4

Nonpharmacologic
- Education
- Support
- Exercise
- Nutrition

Pharmacologic
- Neuroprotection
- ?Selegiline

Functional impairment
Yes
- Dopamine agonists

No
- Levodopa
  (+/- COMT inhibitor)

1
Dopamine agonists

2
Dopamine agonist
+ Levodopa
  (+/-COMT inhibitor)

Add COMT inhibitor

Motor complications
- See section on control of motor complications

3
Unacceptable control with medical therapies

3-4
Consider surgery

The Natural History of Response to Levodopa in Patients With Parkinson's Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>very early</td>
<td>refractory period</td>
<td>days – weeks</td>
</tr>
<tr>
<td>Initial (levodopa-honeymoon)</td>
<td>excellent, stable and smooth response</td>
<td>2-5 years</td>
</tr>
<tr>
<td>response fluctuations, Initial, transition phase</td>
<td>response to single doses; feel onset and termination of dose effect; ±dyskinesias</td>
<td>months – years</td>
</tr>
<tr>
<td>response fluctuations, final complex phase</td>
<td>“wearing off”, “on off”, “delayed on”, no-on”, severe dyskinesias; dystonias</td>
<td>forever</td>
</tr>
</tbody>
</table>
When to started?

- Interfering with activities of daily living
- Patient to patient
- Job to job
Management of Parkinson’s Disease

Considerations
- Age
- Cognitive function
- Comorbidity

Nonpharmacologic
- Education
- Support
- Exercise
- Nutrition

Pharmacologic
- Neuroprotection
- Selegiline
- Functional impairment

Dopamine agonists

Dopamine agonist + Levodopa (+/- COMT inhibitor)
- Add COMT inhibitor
- Motor complications

Levodopa (+/- COMT inhibitor)
- Unacceptable control with medical therapies
- See section on control of motor complications
- Consider surgery

Continue to monitor

Early-anti-PD therapy

L-dopa

VS

Dopamine agonist
Levodopa

**Benefit**
- Marked improvement in the major motor signs and symptoms
- Virtually all PD patients respond
- May improve mortality rate

**Disadvantage**
- Cause side effect
  - Dyskinesia and dystonia
  - Motor fluctuation
  - Parkinsonian psychosis
- Do not treat all features of PD
- Do not stop disease progression
- Theoretically: oxidative metabolites may accelerate disease progression
Dopamine agonist

**Benefit**
- Anti parkinson effect when use as mono Rx or adjunctive Rx
- Reduced risk for developing L-dopa related motor complication
- Do not generate oxidative metabolite
- Levodopa sparing effect
- Potential neuropotential effect

**Disadvantage**
- Neuropsychiatric side effect
- Agonist specific side effect
- Sedative side effect
- Do not treat all feature of PD
- Do not stop disease progression
Elderly

- long-term complications of L-dopa therapy minimal: short live
- short-term side-effects of dopamine agonists high: comorbid

*L-dopa as the first-line*

Young patient

- risks VS benefits: L-dopa VS dopamine agonist drugs discuss
- age < 65, or age > 65 with no other co-morbidity are started on

*dopamine agonist as initial monotherapy*
## Dopamine agonist

<table>
<thead>
<tr>
<th>Dopamine agonist</th>
<th>Bromocriptine</th>
<th>Pergolide</th>
<th>Cabergoline†</th>
<th>Lisuride†</th>
<th>Ropinirole</th>
<th>Pramipexole</th>
<th>Apomorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ergot-derived</td>
<td>30 to 40 mg/day</td>
<td>3 to 5 mg/day</td>
<td>2 to 6 mg/day</td>
<td>2 to 5 mg/day</td>
<td>Up to 24 mg/day in 3 divided doses</td>
<td>Up to 4.5 mg/day in 3 divided doses</td>
<td>Parenteral agent as needed or given as continuous infusion</td>
</tr>
<tr>
<td></td>
<td>Peripheral and central dopaminergic side effects; pedal edema</td>
<td></td>
<td></td>
<td></td>
<td>Similar peripheral and central dopaminergic side effects to those of ergot-derived dopamine agonists, with the probable exceptions of pleuropulmonary reaction, retroperitoneal fibrosis, and erythromelalgia</td>
<td>As for ropinirole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pleuropulmonary reaction, retroperitoneal fibrosis, erythromelalgia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Peripheral and central dopaminergic side effects</td>
<td>Concomitant antiemetic (e.g., domperidone†, trimethobenzamide) needed</td>
</tr>
<tr>
<td></td>
<td>Peripheral side effects often well controlled with domperidone†</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>Rare pulmonary, retroperitoneal, and skin effects possibly due to ergot derivation (drug withdrawal usually required)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>As for bromocriptine</td>
<td></td>
<td></td>
<td></td>
<td>As for bromocriptine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>As for bromocriptine</td>
<td></td>
<td></td>
<td></td>
<td>Long half-life allows once-daily dosage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Effective as first-line and adjunctive therapy; dopamine D3-agonist effects could contribute to efficacy</td>
<td></td>
<td></td>
<td></td>
<td>As for bromocriptine</td>
<td></td>
<td></td>
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<tr>
<td>Non-ergot-derived</td>
<td>As for bromocriptine</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>As for bromocriptine</td>
<td></td>
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</table>
# Dopamine agonist

<table>
<thead>
<tr>
<th>Drug</th>
<th>Structure</th>
<th>Actions</th>
<th>Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromocriptine</td>
<td>Ergot</td>
<td>D₂ agonist, D₁ antagonist</td>
<td>Hypotensive reactions</td>
</tr>
<tr>
<td>Lisuride</td>
<td>Ergot</td>
<td>D₂ agonist, D₁ antagonist</td>
<td>Severe peripheral vascular disease, coronary disease</td>
</tr>
<tr>
<td>Pergolide</td>
<td>Ergot</td>
<td>D₁ and D₂ agonist</td>
<td>History of cardiac disease, or confusion</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>Non-ergot</td>
<td>D₂ agonist</td>
<td>Cardiac disease, major psychoses, hepatic and renal impairment</td>
</tr>
<tr>
<td>Cabergoline</td>
<td>Ergot</td>
<td>D₂ agonist</td>
<td>Hypotensive reactions</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>Non-ergot</td>
<td>D₂ and D₃ agonist</td>
<td>Renal impairment, psychoses</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>Non-ergot</td>
<td>D₁ and D₂ agonist</td>
<td>Postural hypotension, cognitive impairment</td>
</tr>
<tr>
<td>Drug</td>
<td>Formulation, mg</td>
<td>Starting dose, mg</td>
<td>Target dose mg/d</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>2.5, 5.0</td>
<td>1.25 daily</td>
<td>15-30</td>
</tr>
<tr>
<td>Pergolide</td>
<td>0.05, 0.25, 1.0</td>
<td>0.05 daily</td>
<td>1.5-30</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>0.125, 0.25, 0.5, 1.0, 1.5</td>
<td>0.125 twice daily</td>
<td>3.0-4.5</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>0.25, 0.5, 1.0, 2.0, 5.0</td>
<td>0.25 twice daily</td>
<td>6-24</td>
</tr>
</tbody>
</table>
## Dopamine agonist

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bromocriptine</th>
<th>Lisuride</th>
<th>Pramipexole</th>
<th>Cabergoline</th>
<th>Pergolide</th>
<th>Ropinirole</th>
<th>Apomorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Novartis (Parlodel)</td>
<td>Non-proprietary</td>
<td>Pharmacia (Mirapexin)</td>
<td>Pharmacia (Cabaser)</td>
<td>Lilly (Celance)</td>
<td>Glaxo-SmithKline (Requip)</td>
<td>Britannia (Britaject)</td>
</tr>
<tr>
<td>Maintenance dose range</td>
<td>10–40 mg</td>
<td>0.6–5 mg</td>
<td>1.5–4.5 mg</td>
<td>2–6 mg</td>
<td>1–5 mg</td>
<td>6–18 mg</td>
<td>3–100 mg</td>
</tr>
<tr>
<td>Typical daily dose</td>
<td>20 mg</td>
<td>1.2 mg</td>
<td>1.5 mg</td>
<td>4 mg</td>
<td>3 mg</td>
<td>12 mg</td>
<td>25 mg (s.c. infusion)</td>
</tr>
<tr>
<td>Annual cost of typical daily dose</td>
<td>£463.77</td>
<td>£918.05</td>
<td>£1162.01</td>
<td>£1376.96</td>
<td>£1611.29</td>
<td>£2409.00</td>
<td>£2910.88</td>
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### Levodopa

<table>
<thead>
<tr>
<th>Dopamine precursor</th>
<th>Levodopa</th>
<th>Levodopa + DDI</th>
<th>Variations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Given with peripheral dopa decarboxylase inhibitor (carbidopa [4:1 and 10:1 ratios] or benzerazide [4:1]†) or controlled-release formulations (with carbidopa [4:1] or benzerazide [4:1]†)</td>
<td>Varied; begin with 3-times-daily schedule (controlled-release levodopa–carbidopa may be given twice daily at first); late in disease patients may require multiple doses/day (sometimes &gt;2 g/day), with meals avoided in order to improve absorption</td>
<td>Peripheral and central dopaminergic side effects: peripheral (e.g., nausea, vomiting, and orthostatic hypotension); central (i.e., motor fluctuations, dyskinesias, psychiatric disturbances)</td>
<td>Peripheral side effects often controlled by additional carbidopa or the peripheral dopamine-receptor blocker domperidone†</td>
</tr>
</tbody>
</table>

**Levodopa + DDI**

- Madopar (levodopa+benserazide)
- Sinemet (levodopa+carbidopa)
- Madopar HBS
- Sinemet CR
Doses of the preparations of Sinemet and Madopar

<table>
<thead>
<tr>
<th></th>
<th>L-dopa (mg)</th>
<th>Decarboxylase inhibitor (mg)</th>
<th>Colour of tablets</th>
<th>Cost per 100 tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madopar capsules</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>62.5</td>
<td>50</td>
<td>12.5</td>
<td>Blue/grey</td>
<td>£6.67</td>
</tr>
<tr>
<td>125</td>
<td>100</td>
<td>25</td>
<td>Blue/pink</td>
<td>£9.29</td>
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<tr>
<td>250</td>
<td>200</td>
<td>50</td>
<td>Blue/caramel</td>
<td>£15.84</td>
</tr>
<tr>
<td>Madopar tablets – dispersible</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>62.5</td>
<td>50</td>
<td>12.5</td>
<td>White scored</td>
<td>£7.92</td>
</tr>
<tr>
<td>125</td>
<td>100</td>
<td>25</td>
<td>White scored</td>
<td>£14.04</td>
</tr>
<tr>
<td>Madopar CR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>125</td>
<td>100</td>
<td>25</td>
<td>Dark green/ light blue</td>
<td>£17.06</td>
</tr>
<tr>
<td>Sinemet tablets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>62.5</td>
<td>50</td>
<td>12.5</td>
<td>Yellow scored</td>
<td>£7.81</td>
</tr>
<tr>
<td>110</td>
<td>100</td>
<td>10</td>
<td>Blue scored</td>
<td>£8.17</td>
</tr>
<tr>
<td>Plus – 25/100</td>
<td>100</td>
<td>25</td>
<td>Yellow scored</td>
<td>£12.01</td>
</tr>
<tr>
<td>275</td>
<td>250</td>
<td>25</td>
<td>Blue scored</td>
<td>£17.07</td>
</tr>
<tr>
<td>Sinemet CR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25/100</td>
<td>100</td>
<td>25</td>
<td>Pink</td>
<td>£31.65</td>
</tr>
<tr>
<td>50/200</td>
<td>200</td>
<td>50</td>
<td>Peach</td>
<td>£37.25</td>
</tr>
</tbody>
</table>
How should L-dopa be started?

- Gradually introduced
  - L-dopa 100 mg/day is the traditional starting dose
  - Madopar 62.5 twice daily, or Sinemet 62.5 twice daily. (Both of these tablet formulations contain 50 mg of L-dopa.)
- The daily dose of L-dopa should be increased by
  - 100 mg after 1 week
  - same amount after 2 weeks
- If tolerated, further increases should be reviewed after 6–12 weeks on this dose.
L-dopa side effect

BOX 5.1 Cautions and common side-effects associated with using L-dopa

Cautions
L-dopa can exacerbate:
- Cardiac disease
- Pulmonary disease
- Peptic ulceration
- Melanoma
- Diabetes mellitus control
- Glaucoma
- Psychoses.

Side-effects
Frequently reported following L-dopa use:
- Nausea, vomiting
- Postural hypotension
- Insomnia
- Psychoses
- Depression
- Confusion, agitation
- Arrhythmias.
Management of Parkinson’s Disease

Considerations
- Age
- Cognitive function
- Comorbidity

Nonpharmacologic
- Education
- Support
- Exercise
- Nutrition

Pharmacologic
- Neuroprotection
  - Selegiline
- Functional impairment
  - Yes
  - Dopamine agonists
  - Add COMT inhibitor
    - Motor complications
      - See section on control of motor complications
      - Unacceptable control with medical therapies
        - Consider surgery
  - No
    - Levodopa (+/- COMT inhibitor)
      - Continue to monitor
COMT: early or late

**Advantages**
- No titration: easy to administer
- Decrease off time, increase on time
- Enhanced motor responses in motor fluctuation patient
- Reduce risk of motor complication if used from onset of levodopa therapy

**Disadvantage**
- Dopaminergic side effect, esp dyskinesia
- Discoloration of urine

Tolcapone (peripheral + central COMT)
Entacapone (peripheral COMT)
Suspected diagnosis of PD

Consider in patients over 75 years

Loss of function/compromise of lifestyle

Considered choice of first line of therapy

Introduce L-dopa

Add COMT inhibitor

Add DA agonist

Introduce DA agonist. Increase to maximal dose if tolerated

Add L-dopa

Add COMT inhibitor

Expert advice re availability of apomorphine or surgery
Anticholinergic drugs

**Advantage**
- Some antiparkinsonian efficacy
- Peripheral acting agent may be useful to treating sialorrhea

**Disadvantage**
- Relatively ineffective for the more disabling feature of PD
- Cognitive side effect
- Troublesome muscarinic side effect
MAO-B inhibitor (selegiline)

- Enhance the L-dopa effect
- May be neuroprotective property
- Start 5 mg twist daily
As the disease progress, the Therapeutic window narrow

symptoms and side effects occur as the levodopa therapeutic window diminishes

- Smooth, extend response
- Absent or infrequent dyskinesia

- Diminished duration
- Increased incidence of dyskinesia

- Short, unpredictable response
- ‘on’ time is associated with dyskinesia
Proposed Mechanisms of Dopaminergic Neuron Death in Parkinson’s Disease

Overactive Microglial Cell

Glu

Unknown substance releases iron from storage molecules

Glu

Overactive Glutamate-Producing Cell

Fe + Dopamine

Dopamine-Producing Cell

Fe

Mitochondrial “complex I” inhibited

Mutation in mitochondrial gene

Unknown toxin acts on mitochondrial protein

Loss of mitochondrial function

Free radicals cause cell damage

Cell Death

NO

Superoxide Free Radicals

More Free Radicals

[Ca^{2+}]↑

Loss of mitochondrial function

Overactive Glutamate-Producing Cell

NO ↑

Superoxide ↑

Fe ↑

Fe + Dopamine

Dopamine-Producing Cell

Glu

Proposed Mechanisms of Dopaminergic Neuron Death in Parkinson’s Disease