Management in Parkinson’s Disease

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overview

- History of Parkinson’s Disease
- Clinical manifestation of PD
- Etiology and secondary cause of Parkinsonism
- Classification
- Treatment:
  - medical
  - surgical (new in Thailand)
- Late complications (motor VS non-motor)
overview

- **History of Parkinson’s Disease**
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History

1817: James Parkinson

“An Essay on the Shaking Palsy”

Almost 200 years ago

ในประเทศไทยเคยเรียกว่า “สันนิบาตลูกนก”
AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,
MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:
PRINTED BY WHITTINGHAM AND ROWLAND,
Goswell Street,
FOR SHERWOOD, NEELY, AND JONES,
PATERNOSTER ROW.
1817.
AN
ESSAY
ON THE
SHAKING Palsy.

CHAPTER I.
DEFINITION—HISTORY—ILLUSTRATIVE CASES.

SHAKING Palsy. (Paralysis Agitans.)

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.

The term Shaking Palsy has been vaguely employed by medical writers in general. By some it has been used to designate or-
- Parkinson ประย่ังค์ 44-014918.mpg
- 1961 using IV levodopa to treat PD patients
- 1966 combine with Decarboxylase inhibitor (benzerazide) less side effect and more potent
Pathology of Parkinson’s Disease
Normal Basal Ganglia Functional Anatomy

Cortex

Prefrontal Insular
Cingulate Sensory Motor
Suppl. Motor Premotor
Premotor Prefrontal

Striatum

STN
GPe
GPi

Thalamus VA/VL

Brainstem SC

D2 D1

Glu DA GABA subst P enk

+ = excitatory
- = inhibitory
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Signs and Symptoms

- **Cardinal Characteristics**
  - Resting tremor
  - Bradykinesia
  - Rigidity
  - Later; Postural instability (3-5 years after Dx)

- **Gait disturbance esp. dystonic posture of feet, fluctuation of symptoms (YOPD)**
Additional Signs and Symptoms

- Difficulty arising from a chair
- Difficulty turning in bed
- Hypophonic speech
- Sialorrhea
- Loss of the sense of smell
- Foot dystonia
- Other
  - Micrographia
  - Masked face
  - Slowing of ADLs
  - Stooped, shuffling gait
  - Decreased arm swing when walking
Clues Suggesting Atypical Parkinsonism

- Early onset “off”, or rapidly progressing dementia
- Rapidly progressive course
- Supranuclear gaze palsy
- Upper motor neuron signs
- Cerebellar signs—dysmetria, ataxia
- Urinary incontinence
- Early symptomatic postural hypotension
Criteria for Diagnosis

- At least two of three:
  - rest tremor, bradykinesia, rigidity
- Absence of a secondary cause; drugs, metabolic, etc.
- Definitive diagnosis can only be made by autopsy
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Cause of PD

Unknown in most cases

10% associated with genetic
Parkinson’s Disease
Risk Factors

- **Definite**: Old age
- **Highly likely**: MZ co-twin with early-onset PD
- **Probable**: Positive family history
- **Possible**: Herbicides, pesticides, heavy metals, proximity to industry, rural residence, well water, repeated head trauma, etc.
- **Possible protective effect**: Smoking
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**Classification**

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- Late complications (motor VS non-motor)
Parkinsonian syndrome

Classification

1. Idiopathic Parkinson’s Disease
2. Secondary Parkinsonism
3. Parkinson Plus syndrome
4. Associated disease
2. Secondary Parkinsonism

- Drug-induced
- Toxin-induced
- Metabolic
- Structural lesions
- Hydrocephalus
- Infection
Drug-Induced Parkinsonism

- **Antipsychotics**
  - haloperidol, chlorpromazine, thioridizine, perphenazine
  - risperidone, olanzapine

- **Antiemetics**
  - metoclopramide, prochlorperazine
Drug-Induced Parkinsonism

- Dopamine depletors
  - methyldopa, reserpine, tetrabenazine
- Antivertigo medications
  - Ca Channel blockers: flunarizine, cinnerizine

Treatment: Stop offending medications
Metabolic Causes of Parkinsonism

- Often reversible
- Hypo- or hyper-thyroidism
- Hypo- or hyper-parathyroidism
- Liver failure
- Central pontine myelinolysis
Infectious Causes of Parkinsonism

- Infectious
  - Post-encephalitic
  - Creutzfeldt-Jakob disease
  - Infectious masses
  - HIV
Toxin-induced Parkinsonism

- MPTP
- Carbon monoxide
- Manganese
- Cyanide
Structural Lesions Causing Parkinsonism

- Acute or subacute onset
- Other signs—hemiparesis, hyperreflexia, aphasia, sensory loss, seizures
- Brain tumor
- Infectious mass
- Aneurysm
Vascular Parkinsonism

- Abrupt onset, usually unilateral
- Step-wise or no progression
- Other signs—hemiparesis, aphasia, hyperreflexia
- Infarcts on neuroimaging helpful in confirming diagnosis
Hydrocephalus-induced Parkinsonism

- Can be communicating or obstructive
- Normal pressure hydrocephalus—idiopathic
- Clinical triad:
  - parkinsonism/gait disorder
  - urinary/fecal incontinence
  - dementia
3. Parkinson Plus Syndrome

- Progressive supranuclear palsy
- Multiple system atrophy
- Corticobasal ganglia degeneration
- Diffused Lewy body disease
- Parkinson-dementia complex syndrome
4 Associated disease

- Essential tremor
- Alzheimer’s disease
Classification by age of onset

- **Juvenile-onset**
  - Age of onset less than 21 years old

- **Young-onset**
  - Age onset less than 40 years old
  - but more than 21 years old
- Mean age of onset 60 to 65 yr.
- 5-10% start below age of 40 yr.
- Incidence about 200-250 : 100,000 in normal population in developed country
- Estimate >100,000 PD patients in Thailand
242 medical records were enrolled

- 224 were reviewed
- 18 were excluded due to incomplete data

174 medical records of IPD

Statistical analysis and reported

50 medical records of other diagnosis
Demographic data

- **Sex:** 98 males (56.3%)  
  76 females (43.7%)  
  \[ M : F = 1.29 : 1 \]

- **Age of onset:** 12-90 y (mean 55.6 y)  
  - age $> 40$ yr $= 82.3\%$  
  - age 20-40 yr $= 15.9\%$  
  - age $< 20$ yr $= 1.8\%$  
  - (age $< 40$ yr $= 17.7\%$)
Modified Hoehn and Yahr
Clinical staging of PD

Stage
0  no signs of disease
1  Unilateral disease
1.5  Unilateral plus axial involvement
2  Bilateral disease, without impairment of balance
2.5  Mild Bilateral disease, with recovery on pull test
3  Mild to moderate bilateral disease: some postural instability: physical independent
4  Severe disability: still able to walk or stand unassisted
5  Wheelchair bound or bedridden unless aided
The Course of Parkinson's Disease

Early symptoms

Diagnosis

“honeymoon period”

“Lost Paradise”

Complications during treatment and disease progression
Current concept in treating PD (continuous dopaminergic stimulation)

Tonic and continuous dopaminergic stimulation occurs in normal circumstances
Pulsatile dopaminergic stimulation promote more dopaminergic cell lost (post synaptic change) resulting in development of motor fluctuation and dyskinesia

(Mouradian MM. pathogenesis of dyskinesia in Parkinson’s Disease. Ann neurol 1989)
Lost of striatal dopamine receptor that occurs with disease progression results in a diminished capacity of these terminal to buffer in fluctuation in plasma levodopa

Continuous delivery of dopaminergic agents can prevent or attenuate the development of dyskinesia
Motor complications associated with levodopa therapy include motor fluctuations and dyskinesia are particular problems in younger patients. Less likely to occur in those whose symptoms begin after the age of 70 years.

(Golbe LI, Neurology 1991, Quinn N, Mov Disord 1987)
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**Treatment:**

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When to start treatment

Determine whether the patients have functional impairment or not

1. Whether the symptoms effect the dominant or non-dominant hand
2. Whether the patient is employed or employable
3. The type of parkinsonian symptoms that are present (e.g. bradykinesia tends to be more disabling than tremor)
4. Individual patient sentiment
5. The philosophy of treating physician
Symptomatic treatment

1. Levodopa
2. Dopamine agonist
3. COMT inhibitor
4. MAO$_B$ inhibitor
5. Anticholinergic
6. Amantadine
Sites of action for two types of medical therapies to treat PD

Presynaptic Therapies
- SUBSTANTIA NIGRA
  - Levodopa
  - Amantadine
  - Selegiline

Blood-brain barrier

Dopa Decarboxylase inhibitors
- Carbidopa
- Benserazide

COMT inhibitors
- Tolcapone
- Entacapone

Nigrostriatal neuron

Postsynaptic Therapies
- Dopamine Agonists
  - Bromocriptine
  - Pergolide
  - Pramipexole
  - Ropinirole

Acetylcholine

Amitriptyline

GABA

STRIATUM
Decision tree for early management of PD
American Academy of Neurology, 2001

Levodopa

- Most effective symptomatically antiparkinsonian drug
- All PD patients respond
- Improves disability and prolongs capacity to maintain employment and independent activities of daily living
- Improves mortality rate
Levodopa prolongs life expectancy and non-toxic to substantia nigra

Adapt from A.H. Rajput/ Parkinson and related Disorders 8 (2001) 95-100
Is Levodopa Toxic?

- Early patients develop motor fluctuations, but may be a function of neuronal cell loss
- Increased life expectancy with LD introduction
- LD-naive advanced PD patients develop fluctuations almost immediately with LD induction
- No LD neuronal dropout in laboratory animals
- Recent data suggest possible neuroprotection
- Some believe continuous infusion may be safer than pulsatile therapy
ELLDOPA study

- 360 never-treated PD patients randomized to placebo or carbidopa/levodopa (37.5/150, 75/300, 150/600 mg/day)

- No evidence that levodopa had any deleterious effect on disease progression and failed to support the notion of levodopa toxicity

Levodopa is not harmful to SNc neuron in PD
Levodopa-Induced Dyskinesias

- Manifestation of excessive dopaminergic stimulation
- Typically late effect, and with higher doses
- Narrowing of therapeutic window
- Rare in LD-naive patients on DA monotherapy
- Most common is “peak dose” dyskinesia
  - disappears with dose reduction
- Choreiform, ballistic and dystonic movements
- Most patients prefer some dyskinesias over the alternative of akinesia and rigidity
### Levodopa/Carbidopa Formulations

<table>
<thead>
<tr>
<th>Type</th>
<th>Onset</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Release</td>
<td>20-40 min</td>
<td>2-4 hr</td>
</tr>
<tr>
<td>10/100, 25/100, 25/250</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled Release</td>
<td>30-60 min</td>
<td>3-6 hr</td>
</tr>
<tr>
<td>25/100, 50/200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Fast acting”</td>
<td>10-20 min</td>
<td>0.5-1 hr</td>
</tr>
<tr>
<td>(dissolved tablets)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
- Levodopa taking alone without DDC inh. only 1% reach the brain
- With DDC inh. 10% reach the brain
Prospective, double blind trial in 618 levodopa-naïve patients

sustained-release Sinemet
intermediate-release Sinemet

After 5 years there is no difference in the prevalence of motor complications between two groups

Similar result with Madopar HBS

(Block G. Multicenter 5 years study. Eur Neurol 1997)
Control-released levodopa

Indication
- Early morning akinesia
- Night time wearing off
Fast acting levodopa

- Madopar DT 125
  - Early morning dystonia or akinesia
  - End of dose wearing off
  - Dysphagia
  - Faster onset, better absorption
DB RANDOMIZED DA-AGONIST MONOTHERAPY-TRIALS
- Drop-outs resulting from AEs-

<table>
<thead>
<tr>
<th>Study</th>
<th>Agonist-Arm</th>
<th>L-Dopa-Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabergoline vs. L-Dopa*</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>Ropinirole vs. L-Dopa</td>
<td>27%</td>
<td>33%</td>
</tr>
<tr>
<td>Ropinirole vs</td>
<td>20%</td>
<td>-</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>20%</td>
<td>-</td>
</tr>
<tr>
<td>Pergolide vs. L-Dopa</td>
<td>18%</td>
<td>10%</td>
</tr>
<tr>
<td>Pramipexole vs. L-Dopa</td>
<td>15%</td>
<td>13%</td>
</tr>
</tbody>
</table>

*Calculated from published figure
# DB RANDOMIZED DA-AGONIST MONOTHERAPY-TRIALS

- Incidence of Hallucinosis-

<table>
<thead>
<tr>
<th>Study</th>
<th>Agonist-Arm</th>
<th>L-Dopa-Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabergoline vs. L-Dopa*</td>
<td>1.4%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Ropinirole vs. L-Dopa</td>
<td>17.3%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Ropinirole vs.</td>
<td>9.0%</td>
<td>-</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>7.7%</td>
<td>-</td>
</tr>
<tr>
<td>Pergolide vs. L-Dopa</td>
<td>3.4%</td>
<td>0%</td>
</tr>
<tr>
<td>Pramipexole vs. L-Dopa</td>
<td>9.3%</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

*2 – months-analysis
Motor fluctuations and dyskinesias related to levodopa therapy

On-period Dyskinesia

Off-period

6 - 8 Hours
Early

3 - 5 Hours
Moderate

0.5 - 2 Hours
Advanced

Parkinson's Disease
Motor Complication During Long-term L-Dopa Therapy

<table>
<thead>
<tr>
<th>Dose</th>
<th>400-800 mg/d&lt;sup&gt;a&lt;/sup&gt;</th>
<th>&gt;950 mg/d&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor fluctuations</td>
<td>35-58%</td>
<td>65-80%</td>
</tr>
<tr>
<td>Peak-dose dyskinesias</td>
<td>41-64%</td>
<td>23-88%</td>
</tr>
</tbody>
</table>

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<sup>a</sup> Lee et all 1971, Barbeau and Roy 1976, Battistin et al 1978, Rajput et al 1984, power et al 1986

Levodopa Overview (cont’d)

- Levodopa induces motor complications\(^1-4\)
  - Up to 80% of Parkinson’s disease patients suffer from motor fluctuations and dyskinesias after approximately 5 to 10 years of treatment with levodopa\(^4\)
  - 50% to 75% of patients develop motor fluctuations 3 to 6 years after initiating therapy\(^1-3\)

Dykinesias and motor fluctuations in a community-based study of PD

Schrag et al, 2000

- Dykinesias in 28% of the patients
- Motor fluctuations in 40% of the patients
- Predictors for the evolution of motor fluctuation:
  - Disease duration
  - LD dose
- Predictors for the evolution of dyskinesias:
  - Duration of treatment
# Mortality of Parkinson’s Disease

## - Role of L-Dopa Therapy -

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Follow-up</th>
<th>Death Rate</th>
<th>Mortality Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Hoehn &amp; Yahr, 1967</em></td>
<td>241</td>
<td>9 years</td>
<td>38%</td>
<td>2.90</td>
</tr>
<tr>
<td>Yahr, 1976</td>
<td>597</td>
<td>12 years</td>
<td>12%</td>
<td>1.46</td>
</tr>
<tr>
<td>Shaw et al. 1980</td>
<td>178</td>
<td>13 years</td>
<td>27%</td>
<td>1.46</td>
</tr>
<tr>
<td>Diamond et al. 1987</td>
<td>359</td>
<td>15 years</td>
<td>34-63%</td>
<td>1.43-2.66</td>
</tr>
<tr>
<td>DATATOP, 1988</td>
<td>800</td>
<td>8 years</td>
<td>17%</td>
<td>0.8</td>
</tr>
<tr>
<td>Hely et al., 1999</td>
<td>130</td>
<td>13 years</td>
<td>48%</td>
<td>1.58</td>
</tr>
<tr>
<td>* pre-L-Dopa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mechanism of developing dyskinesia

Risk factors

1. Chronic exogenous exposure to dopaminergic drugs (mainly when given intermittently); dopamine receptor supersensitivity
2. Severe dopamine depletion resulting from nigrostriatal denervation
3. The required presence of anatomically intact striatal neurons
Dopamine Receptor Subtypes

- D1, D2 subcortical
- D3, D4, D5 cortical
- Differentiated biochemically & pharmacologically into two families:
  - D1 family: D1, D5
  - D2 family: D2, D3, D4
Dopamine agonist (1)

- Ergotamine
  - Bromocriptine
  - Pergolide
  - Lisuride
  - * Apomorphine
  - Carbergoline
Dopamine agonist (2)

- Non ergotamine
  - Ropinirole
  - Pramipexole
  - Piribedil
Dopamine agonist (3)

- Reduced motor complication compared with levodopa
- Antiparkinsonian effect superior to placebo in early-stage PD
- Antiparkinsonian effect comparable to levodopa in early-stage PD
- Can use as monotherapy up to several years
Dopamine agonist (4)

- Supplementation with levodopa provides clinical benefits comparable to levodopa alone but with reduced motor complications
- ? Neuroprotective effects
CALM-PD: Pramipexole vs Levodopa

Motor Function (UPDRS Motor) Score

\[ P < .0001 \]

Mean Score

Pramipexole

Levodopa

Weeks From Randomization
DAs: Common Adverse Effects

- Nausea, vomiting
- Dizziness, postural hypotension
- Headache
- Dizziness
Association of effusions and fibrosis with ergot vs. non-ergot dopamine agonists

<table>
<thead>
<tr>
<th></th>
<th>Bromocriptine</th>
<th>Cabergoline</th>
<th>DHEC</th>
<th>Lisuride</th>
<th>Pergolide</th>
<th>Pramipexole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural</td>
<td>215</td>
<td>12</td>
<td>1</td>
<td>6</td>
<td>104</td>
<td>0</td>
</tr>
<tr>
<td>Pericardial</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>29</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>244</td>
<td>13</td>
<td>2</td>
<td>7</td>
<td>131</td>
<td>0</td>
</tr>
</tbody>
</table>
DAs: Common Adverse Effects

- Drowsiness & somnolence
- Dyskinesias (less than Levodopa)
- Confusion, hallucinations, paranoid
- Erythromelalgia
DAs: Common Adverse Effects (2)

- Pulmonary & retroperitoneal fibrosis, pleural effusion & pleural thickening, Raynaud’s phenomena.

  (May be more common with ergotamine DAs)
## Dopamine agonist dose ranges

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initiating dose (mg)</th>
<th>Usual dose range (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromocriptine</td>
<td>1.25 bid-tid</td>
<td>7.5-40</td>
</tr>
<tr>
<td>Pergolide</td>
<td>0.05 qd</td>
<td>0.75-6</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>0.125 tid</td>
<td>0.75-3</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>0.25 tid</td>
<td>9-24</td>
</tr>
<tr>
<td>Cabergoline</td>
<td>0.25 qd</td>
<td>0.5-5</td>
</tr>
<tr>
<td>Peribedil</td>
<td>50 qd</td>
<td>50-250</td>
</tr>
</tbody>
</table>
## Dopamine agonist

<table>
<thead>
<tr>
<th>Drug</th>
<th>T $\frac{1}{2}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbidopa/levodopa</td>
<td>1-1.5</td>
</tr>
<tr>
<td>Pergolide</td>
<td>12-27</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>8-12</td>
</tr>
<tr>
<td>Cabergoline</td>
<td>65+</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>4</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>6</td>
</tr>
</tbody>
</table>
## Dopamine Agonists in Comparison

<table>
<thead>
<tr>
<th></th>
<th>Pramipexole</th>
<th>Piribedil</th>
<th>Pergolide</th>
<th>Bromocriptine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual daily dosage (mg)</td>
<td>1.5-4.5 mg/d</td>
<td>150-250 mg/d</td>
<td>1-4 mg/d</td>
<td>10-40 mg/d</td>
</tr>
<tr>
<td></td>
<td>divided t.i.d.</td>
<td>divided 3-5</td>
<td>divided t.i.d.</td>
<td>divided t.i.d.</td>
</tr>
<tr>
<td>Presentation</td>
<td>Tab 0.25, 1 mg/Tab</td>
<td>Tab SR 50 mg/Tab</td>
<td>Tab 0.05, 0.25</td>
<td>Tab 2.5 mg/Tab</td>
</tr>
<tr>
<td></td>
<td>0.25, 1 mg.</td>
<td>mg.</td>
<td>mg.</td>
<td>mg.</td>
</tr>
<tr>
<td>Price/tab</td>
<td>$26.00-90.00</td>
<td>$14.56</td>
<td>$15.00-34.40</td>
<td>$18.60</td>
</tr>
<tr>
<td>Daily cost (min. maint. dose)</td>
<td>$135.00 (1.5 mg/d)</td>
<td>$43.68 (150 mg/d)</td>
<td>$137.60 (1 mg/d)</td>
<td>$74.40 (10 mg/d)</td>
</tr>
<tr>
<td>US FDA approval (<a href="http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm">http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm</a>)</td>
<td>As monotherapy and adjunctive to levodopa</td>
<td>Not being approved</td>
<td>As adjunctive to levodopa</td>
<td>As monotherapy and adjunctive to levodopa</td>
</tr>
</tbody>
</table>
Assessment of Dopamine Agonists for the treatment of PD according to *Evidence Based Medicine*^*

<table>
<thead>
<tr>
<th>Category</th>
<th>Bromocriptine</th>
<th>Cabergoline</th>
<th>Lisuride</th>
<th>Pergolide</th>
<th>Piribedil</th>
<th>Pramipexole</th>
<th>Ropinirole</th>
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<td>Monotherapy in early PD</td>
<td>±</td>
<td>?</td>
<td>±</td>
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<td>?</td>
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<tr>
<td>Combination therapy with L-Dopa in late PD</td>
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<td>✓</td>
<td>±</td>
<td>✓</td>
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<tr>
<td>Treatment of motor fluctuations</td>
<td>±</td>
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<td>?</td>
<td>✓</td>
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<tr>
<td>Prevention of motor complications</td>
<td>±</td>
<td>✓</td>
<td>?</td>
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<td>Imaging indicates slowed loss of</td>
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Dopamine agonist

- Start low, go slow
  (gradually titrated over several weeks or months)
- Improved motor and ADL scores
- Decreases “off” time
- provided a levodopa sparing effect
Apomorphine (1)

- D1/D2 agonist
- Parenteral delivery (s.c., i.v., sublingual, intranasal, rectal)
- Rapid “off” period rescue
  - 2-5 mg s.c.; pen injection systems
Apomorphine (2)

- Treatment of unpredictable, frequent motor fluctuations
  - continuous s.c. infusion via mini-pump
- SE: nausea, vomiting, hypotension
  - trimethobenzamide 250 mg t.i.d.
  - domperidone 20 mg t.i.d.; not available in U.S.
COMT inhibitor

- No titration easy to administer
- Decreased “off” time, increased “on” time and enhanced motor responses in patients with levodopa motor fluctuation
- Improved motor and ADL scores in stable levodopa responders
- May reduce risk for motor complications if used from onset of levodopa therapy
COMT inhibitor

- Entacapone 200 mg with each dose of levodopa
- Talcapone 100-200 mg tid
- Side effect: discoloration of urine, increase dyskinesia, diarrhea
COMT inhibitor

- Increase plasma levodopa elimination half life by 50% and area under the curve by 75% without rising of either the maximal plasma concentration ($C_{max}$) or the time to reach maximal plasma concentration ($T_{max}$).
Anticholinergics

- **Dopaminergic depletion** → **cholinergic overactivity**
- Initially used in the 1950s
- Effective mainly for tremor (rigidity)
- Common agents *(Start low, go slow)*:
  - Trihexyphenidyl: 2-15 mg/day
  - Benztropine: 1-8 mg/day
Anticholinergics

- **Side effects:**
  - Dry mouth, sedation, delirium, confusion, hallucinations, constipation, urinary retention, impaired cognition
Selegiline

- Irreversible MAO-B inhibitor
- Clinically active by inhibiting dopamine metabolism in brain
- May be neuroprotective (DATATOP, SINDEPAR)
- Dosage: 5 mg at breakfast and lunch
Selegiline

- Side effects: insomnia, hallucinations, nausea (rarely), dyskinesia
- Potential interactions with tricyclics and SSRI antidepressants
- As adjunct to levodopa, provides reduced motor fluctuations and increased “on” time
DATATOP Follow-Up

- DATATOP: 3 year follow-up studies (Ann Neurol 1996)
  - subjects requiring levodopa (n=352)
    - selegiline made no difference with regard to disease severity, wearing-off or dyskinesias
  - subjects not requiring levodopa (n=162)
    - No difference in parkinsonian disability between the two groups
- 8 year follow-up (Ann Neurol 1998)
  - No increase in mortality

- No increase in mortality
overview

- History of Parkinson’s Disease
- Clinical manifestation of PD
- Etiology and secondary cause of Parkinsonism
- Classification
- Treatment:
  - medical
  - surgical (new in Thailand)
- Late complications:
  - motor VS non-motor
Stages in Decline of Response to LD

- I: Patient not aware of effect of individual dose
- II: Mid-afternoon loss of benefit
- III: Loss of sleep benefit; early-morning akinesia, possible foot dystonia
- IV: Regular “wearing off” every 4 hours at first, shortens with time
- V: Frequent wearing off, abrupt on-off, unpredictable dose response
Late Complications

- **Motor**
  - response fluctuations, dyskinesias, dystonia, freezing, falls

- **Non-motor (Behavioral/neuropsychological)**
  - depression, sleep disorders, psychosis

- **Autonomic**
  - orthostatic hypotension; hyperhidrosis, constipation, impotence, urinary incontinence or retention
LD Response Fluctuations

- **Peripheral causes:**
  - delayed gastric emptying
  - dietary protein
  - short plasma half-life

- **Central causes:**
  - pulsatile delivery to striatal receptors
  - impaired storage capacity
  - alteration of DA receptors
Response Fluctuations: Treatment

- Increase LD dose
- Increase DCI dose
- Add dopamine agonist
- Add COMT inhibitor
  - reduce LD
  - liver function monitoring
- Apomorphine rescue
Peak Dose Dyskinesia or Dystonia

- Chorea more common than dystonia
- May be worse on more affected side
- May not be as disabling as akinesia/rigidity
- Dose adjustments, add-ons:
  - reduce LD dose, increase dose frequency
  - reduce LD, add DA, COMT inhibitor
**Off-period Dystonia**

- Appears when LD level is low, especially early AM
- w/ or w/o parkinsonism
- **Dose adjustments, add-ons:**
  - more frequent LD dosing to avoid low plasma levels
  - add DA, COMT inhibitor, MAO-B inhibitor
Wearing Off

- Regular and predictable decline in response 2-4 hours after LD dose
- Most common motor fluctuation
- Dose adjustments, add-ons:
  - change to LD-CR, or increase LD frequency
  - reduce LD, add DA or COMT inhibitor
On-off Response

- Sudden and unpredictable off periods unrelated to dosing schedule
- One of the hardest features to manage
- Dose adjustments, add-ons:
  - reduce LD, add DA
Other Motor Complications

- **Diphasic dyskinesia**
  - dyskinesia at beginning and end of dose
  - Dose adjustments, add-ons: add DA

- **Drug failure**
  - late afternoon, probably related to poor gastric emptying or absorption
  - liquid preparations; increase gastric motility; decrease dietary protein
  - apomorphine rescue
Freezing and Falls

- **Freezing**
  - motoric block; at initiation of gait, turning, narrow spaces
  - use auditory, visual, proprioceptive cues

- **Falls**
  - physical therapy evaluation
  - cane, scooter, wheelchair may be necessary
Psychosis

- **Features**
  - Vivid dreams/nightmares, disorientation, hallucinations, delusional thought

- **Simplify medical regimen**
  - Stop unnecessary non-PD meds
  - Stop: anticholinergic drugs, amantadine, selegiline, dopamine agonists, COMT inhibitors

- **Change from CR to standard carbidopa/levodopa**

- **Try atypical antipsychotic agents**

- **Try low-potency traditional antipsychotic agents**
Depression

- Reported in 30-90% of PD patients
- Difficult to discern from vegetative symptoms
- Requires inquiry into depression symptoms
- Usually responds quickly to medications
  - Tricyclic agents
  - Selective serotonin re-uptake inhibitors
- If ECT needed, will transiently improve PD symptoms
Anxiety/Restlessness

- **Primary anxiety disorder**: treat with benzodiazepines
  - Associated with “off-periods” or low-levodopa levels: adjust levodopa dosing
- **Restless Leg Syndrome**: benzodiazepines, narcotics, levodopa, dopamine agonists
Insomnia

- careful history
- difficulty with sleep initiation: tricyclic agents, benzodiazepines, diphenhydramine, chloral hydrate
- treat depression
- REM-behavioral disorder: clonazepam
Sleep Disorders (2)

- Excessive daytime sleepiness
  - Correct poor sleep at night
  - Discontinue anticholinergics, amantadine
  - Reduce dopamine agonist, levodopa dosages if possible
  - selegiline; caffeine; methylphenidate 5-20 mgs/d
Orthostatic Hypotension

- Light-headedness, dizziness, fatigue, shoulder or neck pain, blood pressure drops when standing
- Taper anti-hypertensive agents
- Taper non-PD drugs
- Increase salt intake
- Compression stockings
- Fludrocortisone (0.1-0.4 mg/d)
- Midodrine (2.5 - 20 mg/d)
Urinary Incontinence/Frequency

- Rule out urinary tract infection

- Bladder evaluation for
  - detrusor hyperactivity
    - oxybutinin 5-30 mg/d; propantheline 7.5 - 15 mg/d
  - detrusor hypoactivity
    - phenoxybenzamine; prazosin

- Urinary frequency
  - avoid fluid pooling in feet
  - DDAVP inhaler; tolterodine tartrate 2mg hs to 2mg tid
Sexual Dysfunction

- Medical screening
  - depression, anxiety, iatrogenic causes

- Endocrinologic evaluation
  - prolactin, testosterone, lutenizing hormone, thyroid screen

- Urologic evaluation
  - yohimbine, sildenafil
Nausea

- Levodopa-related: take with meals, add carbidopa, add domperidone
- Other anti-PD medications: same.
  - If no improvement: withdraw newest agent, re-initiate at minimal doses, slowly increase
Excessive Sweating

- Usually levodopa related, and may be seen at peak or trough dose drug levels
  - reduce levodopa
  - add dopamine agonist or COMT inhibitor
  - add carbidopa
  - add Beta-blocker
Surgical Treatment in Parkinson’s Disease
Surgical Treatments for Parkinson’s Disease

- **Ablative**
  - thalamotomy
  - pallidotomy

- **Electrical stimulation**
  - VIM thalamus, globus pallidus internus, subthalamic nucleus

- **Transplant**
  - autologous adrenal, human fetal, xenotransplants, genetically engineered transplants
Thalamotomy

- Significant improvement in contralateral tremor
  - depends on correct placement
- Minimal improvement in other PD signs
- Bilateral procedures poorly tolerated
- AEs: bulbar, sensory and motor deficits, gait, surgical complications
- Gradually being replaced by thalamic DBS
Deep Brain Stimulation (DBS)

- High frequency, pulsatile, bipolar electrical stimulation
- Stereotactically placed into target nucleus
- Can be activated and deactivated with an external magnet
- Exact physiology unknown, but higher frequencies mimic cellular ablation, not stimulation
Movement Disorder Surgery

Siriraj Movement Disorder Group

อภิชาติ พิศาลพงษ์
กนภกรรณ บุญญพิศิษฐ์
วรพรณ เสนนรัตน์
นิพนธ์ พวงวรินทร์

อรสา ชาวลาดภูทิ้ง
ไพรวัช สายวิรุณพร

ศรันย์ นันทอวีย์
นันทสกัด ทิศาวิกากร
VIM Thalamic DBS

- 80% reduction in contralateral arm and leg tremor
- Possible mild improvement in bradykinesia and rigidity
- No functional improvement (UPDRS part II), but significant improvement based upon global scores
- No effect: gait and bulbar symptoms
- AEs: bulbar, gait, paresthesia, surgical
Globus Pallidus internus DBS

- Effects tend to mimic those of pallidotomy
- Significant improvement in dyskinesia
- Moderate improvement in cardinal “off” signs
- No comparison between unilateral and bilateral
- Bilateral DBS may be better tolerated than bilateral pallidotomy
- AE: surgical complications
Bilateral Subthalamic DBS

- Bilateral placement appears to be superior to unilateral placement
- Theorized neuroprotective mechanism, but no clinical evidence supporting this
- AE: confusion and hallucinations, increased dyskinesia before medication adjustments, eyelid opening apraxia, weight gain, surgical complications
Clinical Results

Patient Diary Data
Subthalamic Nucleus

Pre-Implant
n = 39
L-dopa equiv. = 1325 mg

6 Months
n = 25
L-dopa equiv. = 1016 mg

12 Months
n = 12
L-dopa equiv. = 988 mg

Asleep
27%
“on” time
23%
“off” time
35%
“on” with Dyskinesia
14%

Asleep
33%
“on” time
53%
“off” time
11%
“on” with Dyskinesia
3%

Asleep
33%
“on” time
53%
“off” time
12%
“on” with Dyskinesia
2%
Subthalamic DBS

- All cardinal features of PD noted to improve in open label trials
- “Off” UPDRS improved 60%
- “On” UPDRS improved 10%
- Dyskinesia tends to improve but this is probably due to decreased levodopa dose
Activa® Parkinson’s Control System
Implanted Components

Activa® System
STN

T2W FSE

axial

coronal
Stimulation-induced effects (sagittal and frontal sections)

- Tremor reduction, akinesia remains
- Sweating, mydriasis, dysesthessias
- "Dystonia," tetanic muscle contractions, dysarthria
- Inhibition of L-Dopa effect, increased akinesia

Thalamus

dorsal
posterior
ventral
anterior

Mf
Vo.m
Vo.i
Zs
V.L
V.P.M
Thalamus
V.O

GPi

STN

Subst.

nigra

H1+2

H2

capsula

interna

dyskinesia, reduction of
rigidity, tremor, akinesia

"Dystonia," tetanic muscle
contractions, dysarthria

Inhibition of L-Dopa effect,
increased akinesia

Dorsal
Medial
Ventral
Lateral

Tremor reduction,
akinesia remains
Double vision,
ocular deviation,
fusion disturbances,
mydriasis,
postural disturbances
Cell Transplants

- Autologous adrenal transplants
  - No efficacy
- Allogenic human fetal transplants
  - Initial encouraging clinical results
- Xenogenic fetal transplant (porcine and bovine)
  - Preliminary results pending
- Genetically engineered cells
  - Research ongoing
Human Fetal Transplants

- **Efficacy**
  - Encouraging preliminary results in young PD pts
  - PET studies consistent with cell functioning
  - Autopsies (2) show cell survival

- **Problems**
  - 4-10 embryos < 10 weeks gestation needed
  - Immunosuppression requirements unknown
  - Numerous technical problems
Nonpharmacologic Treatments (1)

- Patient/caregiver education
- Physical therapy
- Exercise
- Occupational therapy
Nonpharmacologic Treatments (2)

- Speech/language therapy
- Diet and nutrition
- Psychosocial interventions
Current management in Young –onset Parkinson’s Disease patients

- Start with Dopamine agonist
- Add levodopa when disability can not overcome by DA
- Add COMT inhibitor when developing motor fluctuations
- Consider start with anticholinergic or amantadine if tremor is the prominent symptom
Current management in Late-onset Parkinson’s Disease patients

- Start with dopamine agonist if no contraindication and add on levodopa later
- Or start with levodopa when reaching dosage of 400-600 mg add on dopamine agonist
- Considering COMT inhibitor when developing motor fluctuations
- ? Start with triple combinations (L-dopa+DDC+COMT inhibitor)