Medical Management of Parkinson’s Disease

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Management of PD
Multiple clinical problems

Multiple pharmacological treatments

- 1951 apomorphine injections improved PD
- 1960 striatum dopamine deficiency
- 1961 1st use of levodopa
- 1967 Cotzias et al (single blind, placebo-controlled)
- 1974 bromocriptine
- 1975 Sinemet® and Madopar®
- 1982 pergolide
- 1990 cabergoline
- 1991 ropinirole
- 1992 pramipexole
- 2000 entacapone
- 2004 rasagiline
- 2005 duodopa
- 2006 rotigotine

50 yrs
Case 1

- ♀, 65 years-old, farmer
- Began complaints of rest tremor in the left arm 1 yr ago and more recently began tremor in the right arm
- Referred to a movement disorders clinic
- No family history of PD

Neurological examination:
- video
- PD assumed as diagnosis
- Patient completely independent. Aware of intermittent tremor. But no difficulties or impairment

Question 1

- How and when would you start treatment?
Possible answers

1. No specific treatment, schedule follow-up
2. Start on levodopa SD/CR
3. Start on levodopa + entacapone
4. Start on dopamine agonist
5. Start on MAO-B: rasagiline/selegiline
6. Start on amantadine
7. Start on anticholinergic
8. Propose a “neuroprotective trial” or “early symptomatic trial”
9. Other options

It depends on the target objectives of the therapeutic intervention

1. Prevent clinical progression?
2. Improve parkinsonism?
   1. Slight to moderate improvement
   2. Best benefit possible
3. Prevent motor complications?
4. Maintain compliance!

Recommendations for the treatment of early PD

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Prevention of clinical progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>EFNS</td>
<td>No definitive evidence for pharmacological neuroprotection</td>
</tr>
<tr>
<td>AAN</td>
<td>Insufficient evidence to recommend any drug for neuroprotection</td>
</tr>
<tr>
<td>NICE</td>
<td>No drug recommended</td>
</tr>
</tbody>
</table>

Recent positive data with rasagiline (Adagio trial)!

Effect due to rasagiline or early symptomatic effect? Clinical relevance of the magnitude of effect?

STRIDE-PD (Stalevo) – neg
PROUD (pramipexole delayed start design) - neg
Recommendations for the treatment of early PD

Symptomatic control of parkinsonism

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Highest level of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS</td>
<td>Levodopa, levodopa CR, pergolide, pramipexole, ropinirole, DHEC, selegiline, rasagiline</td>
</tr>
<tr>
<td>EFNS</td>
<td>Levodopa, levodopa CR, pramipexole, ropinirole, ropinirole CR, rotigotine, DHEC, pergolide, selegiline, rasagiline</td>
</tr>
<tr>
<td>AAN</td>
<td>No data</td>
</tr>
<tr>
<td>NICE</td>
<td>Levodopa, non-ergot dopamine agonists, MAO-I</td>
</tr>
</tbody>
</table>

No evidence of no efficacy, but no data limits knowledge
Duration of commercialization produces safety data
Is there a pharmacological class effect? Are dopamine agonists all alike?
Levodopa is the most potent antiparkinsonian drug

Recommendations for the treatment of early PD

Prevention of motor complications

<table>
<thead>
<tr>
<th>Guideline</th>
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</tr>
</thead>
<tbody>
<tr>
<td>MDS</td>
<td>Cabergoline, ropinirole, pramipexole</td>
</tr>
<tr>
<td>EFNS</td>
<td>Pramipexole, ropinirole, cabergoline (ineffective levodopa CR)</td>
</tr>
<tr>
<td>AAN</td>
<td>No data</td>
</tr>
<tr>
<td>NICE</td>
<td>No data</td>
</tr>
</tbody>
</table>

What is the clinical relevancy of delaying the onset of non-troublesome dyskinesia up to 5 yrs of treatment?

Prevention of motor complications

Long term controlled cohorts

PDRG-UK trial - fourteen-year report

- Benefit of bromocriptine monotherapy in reducing motor complications reported at 5 years, diminished by 10 years and disappeared at 14 yrs

Sydney Multicenter Study of Parkinson’s Disease - 15 Years

- Bromocriptine treatment group: delayed dyskinesia onset
- No significant difference for predictable offs, unpredictable offs, sudden offs and duration of off between the groups
Correct answer(s)?
Treatments with better supportive data

1. No specific treatment, schedule follow-up
2. Start on levodopa S/D/CR
3. Start on levodopa + entacapone
4. Start on dopamine agonist
5. Start on MAO-B: rasagiline/selegiline
6. Start on amantadine
7. Start on anticholinergic
8. Propose a “neuroprotective trial” or “early symptomatic trial”
9. Other options

Case 2

- 75 years old, 14 years of PD duration, referred to the movement disorders outpatient clinic due to the aggravation of parkinsonism and frequent falls
- Patient main concern were the falls. Falls occurred more frequently in early afternoon
- Patient described also the occurrence of wearing-off and On-Off phenomena. He did not mention involuntary movements, but his daughter clearly mentioned the presence of occasional slight dyskinesias

Antiparkinsonian treatment

<table>
<thead>
<tr>
<th>Time</th>
<th>Sinemet 25/100</th>
<th>Ropinirole</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:00</td>
<td>1.5</td>
<td>2 mg</td>
</tr>
<tr>
<td>12:00</td>
<td>1.5</td>
<td>2 mg</td>
</tr>
<tr>
<td>16:00</td>
<td>1.5</td>
<td>2 mg</td>
</tr>
<tr>
<td>20:00</td>
<td>1.5</td>
<td>2 mg</td>
</tr>
</tbody>
</table>

To better characterise motor fluctuations and the cause of falls ...
Motor fluctuation patient diaries
Question 1

• Which therapeutic objectives to define?

Possible answers

1. Improve parkinsonism
2. Reduce OFF time
3. Increase ON time
4. Improve postural instability/freezing
5. Reduce intensity & frequency of dyskinesias
Question 2

• How would you adjust treatment?

Antiparkinsonian treatment

<table>
<thead>
<tr>
<th>Time</th>
<th>Sinemet 25/100</th>
<th>Ropinirole 2 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakfast</td>
<td>1mg</td>
<td>1 mg</td>
</tr>
<tr>
<td>Lunch</td>
<td>1mg</td>
<td>1 mg</td>
</tr>
<tr>
<td>Mid-afternoon</td>
<td>1mg</td>
<td>1 mg</td>
</tr>
<tr>
<td>Dinner</td>
<td>1mg</td>
<td>1 mg</td>
</tr>
</tbody>
</table>

Possible answers

1. Increase ropinirole dose
2. Switch to another dopamine agonist
3. Switch to equivalent dose of slow release levodopa
4. Increase levodopa dose and/or frequency of intakes
5. Add COMT-inhibitor (entacapone)
6. Switch to Stalevo
7. Add MAO-B inhibitor: rasagiline or selegiline
8. Others

Recommendations for the symptomatic control of motor complications

Wearing-off

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Highest level of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS</td>
<td>Pergolide, Pramipexole, Ropinirole, Apomorphine, Selegiline, Entacapone, Tolcapone</td>
</tr>
<tr>
<td>EFNS</td>
<td>Entacapone, MAD-I, non-ergot DA</td>
</tr>
<tr>
<td>AAN</td>
<td>Entacapone, rasagiline</td>
</tr>
<tr>
<td>NICE</td>
<td>Levodopa, non-ergot dopamine agonists, entacapone, MAD-I</td>
</tr>
</tbody>
</table>
Entacapone for motor LD-induced motor complications

**COCHRANE SYSTEMATIC REVIEW**

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Mean Difference (95% CI)</th>
<th>Weighted Mean Difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post DBS + Entacapone</td>
<td>31</td>
<td>1.3 (0.4, 2.3)</td>
<td>0.9 (0.4, 1.5)</td>
<td>0.047</td>
</tr>
<tr>
<td>Post DBS</td>
<td>30</td>
<td>0.6 (0.3, 0.8)</td>
<td>0.3 (0.1, 0.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>Post DBS + Entacapone</td>
<td>31</td>
<td>1.0 (0.2, 1.8)</td>
<td>0.6 (0.1, 1.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>Post DBS + Entacapone</td>
<td>31</td>
<td>1.0 (0.2, 1.8)</td>
<td>0.6 (0.1, 1.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>Post DBS + Entacapone</td>
<td>31</td>
<td>1.0 (0.2, 1.8)</td>
<td>0.6 (0.1, 1.1)</td>
<td>0.005</td>
</tr>
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</table>

41 minutes!
95% CI: 13 min, 1 hour 8 min, P=0.004

**How strong is the evidence?**
Beneficial

**How big is the effect?**
41 min

**Does the effect matter to patients?**
?

Deane KH, Cochrane Database Syst Rev 2006

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**STN DBS vs BEST MEDICAL TREATMENT**

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Mean Difference (95% CI)</th>
<th>Weighted Mean Difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deuschl G, N Engl J Med 2006</td>
<td>-4.2 h</td>
<td>Improves Health Related QoL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**How strong is the evidence?**
Beneficial (replicated)

**How big is the effect?**
-4.2 h

**Does the effect matter to patients?**
Improves Health Related QoL


---

**Recommendations for the symptomatic control of motor complications**

**Severe motor fluctuations**

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Highest level of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS</td>
<td>No data</td>
</tr>
<tr>
<td>EFNS</td>
<td>Predictable ON-OFF: DBS (STN); subcutaneous apomorphine (perhex) Unpredictable ON-OFF: DBS (STN)</td>
</tr>
<tr>
<td>AAN</td>
<td>No data</td>
</tr>
<tr>
<td>NICE</td>
<td>Unpredictable ON-OFF: intermittent apomorphine</td>
</tr>
</tbody>
</table>

Patients with unpredictable ON-OFF excluded from "oral" RCT
Case

- It was decided to increase the ropinirole dose (9 mg daily)
- After adjusting treatment, there was an increase of dyskinesias, including troublesome dyskinesias

Video

Recommendations for the symptomatic control of motor complications

Peak-dose dyskinesias

<table>
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<tr>
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<th>Highest level of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS</td>
<td>Amantadine</td>
</tr>
<tr>
<td>EFNS</td>
<td>Amantadine, DBS (STN)</td>
</tr>
<tr>
<td>AAN</td>
<td>Amantadine</td>
</tr>
<tr>
<td>NICE</td>
<td>Amantadine, continuous subcutaneous apomorphine</td>
</tr>
</tbody>
</table>
Treatment of non-motor symptoms

• Neuropsychiatric manifestations
• Cognitive impairment
• Sleep disorders
• Autonomic dysfunctions
• Sensory disorders (pain)

NEUROPSYCHIATRIC MANIFESTATIONS

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>FREQUENCY %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>66</td>
</tr>
<tr>
<td>Fatigue</td>
<td>56</td>
</tr>
<tr>
<td>Irritability</td>
<td>52</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>49</td>
</tr>
<tr>
<td>Self-withdrawal</td>
<td>44</td>
</tr>
<tr>
<td>Euphoria</td>
<td>42</td>
</tr>
<tr>
<td>Lassitude/weariness</td>
<td>42</td>
</tr>
<tr>
<td>Sadness</td>
<td>38</td>
</tr>
</tbody>
</table>

Witas T. Neurology, 2002

Treatment of depression

• Highest evidence-based recommendations:
  • Desipramine
  • Nortriptyline
  • Pramipexole

• General practice points:
  • Optimise dopaminergic treatment
    (fluctuating mood, suicidal ideation accompanying ‘off’ periods)
  • Alert on sub-diagnosis
Recommendations for the treatment of psychosis

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Highest level of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS</td>
<td>Clozapine</td>
</tr>
<tr>
<td>EFNS</td>
<td>Clozapine</td>
</tr>
<tr>
<td>AAN</td>
<td>Clozapine</td>
</tr>
<tr>
<td>NICE</td>
<td>Clozapine, but required monitoring registration</td>
</tr>
</tbody>
</table>

Likely to be ineffective or harmful
motor worsening: olanzapine (++), risperidone (+)
(cardiovascular risk in the elderly)

Treatment of psychosis

- Careful assessment and amelioration of triggering factors:
  - treat infection and metabolic disorders, rectify fluid/electrolyte balance, treat sleep disorder
- Lowering or discontinuing PD medications (e.g. anticholinergics, selegiline, amantadine, DA; stop COMT-I if recent onset)
- Discontinuing other non-essential medications (e.g. tricyclic antidepressants)

Treatment of psychosis

- Add adjunctive anti-psychotic medications
  - clozapine (6.25 – 25 mg at bedtime)
    - agranulocytosis (<0.5%) recommends weekly blood count for the first six months, followed by two weekly thereafter
  - quetiapine (12.5 – 25 mg at bedtime)
    - olanzapine and risperidone are not recommended (harmful)
- Add cholinesterase inhibitors: rivastigmine
**Recommendations for the treatment of dementia**

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Highest level of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS</td>
<td>Rivastigmine</td>
</tr>
<tr>
<td>EFNS</td>
<td>Rivastigmine, donepezol</td>
</tr>
<tr>
<td>AAN</td>
<td>Rivastigmine, donepezol</td>
</tr>
<tr>
<td>NICE</td>
<td>No drug recommended</td>
</tr>
</tbody>
</table>

**How strong is the evidence?**
Beneficial for cognition and activities of daily living

**How big is the effect?**
- Rivastigmine vs placebo
  - ADAS-Cog 2.80 [95% CI -4.26 to -1.34]
  - ADCS-ADL 2.50 [95% CI 0.43 to 4.57]

**Does the effect matter to patients?**
- Clinically meaningful improvement (moderate or marked): 5.3% more patients on rivastigmine
- Meaningful worsening: 10.1% more patients on placebo
- Clinically significant benefit in 15% of cases (responders)

**Treatment of cognitive impairment**

- Use of all antiparkinsonian drugs in demented patients may be complicated by the development of confusion and psychosis
- Several drugs, particularly anticholinergics, can impair cognitive function: considering discontinuation
- Discontinuation of unnecessary (risk/benefit balance) medications: anticholinergics, selegiline, amantadine, tricyclic antidepressants, tolterodine, oxybutynin and benzodiazepines

**Treatment of cognitive impairment / dementia**

- Add cholinesterase inhibitors:
  - Rivastigmine (highest evidence-level)
- Treat depression
- Symptomatic behavioral treatment
Treatment of falls (freezing/postural instability)

- Pharmacological interventions
- Functional neurosurgery
- Exercise/physical therapy

Recommendations for the prevention of falls

<table>
<thead>
<tr>
<th>Guideline</th>
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</tr>
</thead>
<tbody>
<tr>
<td>MDS</td>
<td>No data</td>
</tr>
<tr>
<td>EFNS</td>
<td>Physical therapy</td>
</tr>
<tr>
<td>AAN</td>
<td>No data</td>
</tr>
<tr>
<td>NICE</td>
<td>Multifactorial interventions with an exercise component (older people, non-PD)</td>
</tr>
</tbody>
</table>

Pharmacological interventions

Positive effect on freezing

- LD, entacapone, DAUs improve Off-related FOGs in advanced PD (by decreasing Off time)
- MAO-B inhibitors
  - Rasagiline
  - Selegiline
  - Large sub-study improvement of FOG-Q (10 w)
  - Clinical significance: 1.17 points FOG-Q DATATOP early stage
- Dopamine agonists
  - Ropinirole: worsening vs LD
  - Pramipexole: worsening vs LD
- Amantadine
- Methylphenidate
- Donepezil

(Giladi N, Mov Disord 2008)
Donepezil for the treatment of falls

- 23 PD patients
- randomized, placebo-controlled, crossover trial
- eligibility: falls or near falls > 2 times per week
- 6 weeks of donepezil or placebo (3-week washout)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Donepezil</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily falls</td>
<td>5.4</td>
<td>4.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Near falls</td>
<td>2.7</td>
<td>2.0</td>
<td>0.03</td>
</tr>
</tbody>
</table>

NNT = 8
8 patients needing treatment to prevent a fall

Small exploratory study!

Functional neurosurgery

- Thalamotomy and DBS - gait disorder and disequilibrium as a safety problem
  - disease progression?
  - reduction in levodopa dose?
  (Krack 2003; Rodriguez-Oroz 2005)
- Pedunculopontine nucleus DBS (unilateral/bilateral) improves falls in PD patients with gait and postural abnormalities?
  - conflicting results
  (Moro 2010; Ferraye 2010)

Exercise / physical therapy

Guidelines of The Royal Dutch Society for Physical Therapy

- Recommendations:
  - cueing strategies to improve gait
  - cognitive movement strategies to improve transfers
  - exercises to improve balance
  - training of joint mobility and muscle power to improve physical capacity.
## Recommendations for the treatment of orthostatic hypotension

<table>
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<tr>
<th>Guideline</th>
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</tr>
</thead>
<tbody>
<tr>
<td>MDS</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td>EFNS</td>
<td>Mido drine</td>
</tr>
<tr>
<td>AAN</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td>NICE</td>
<td>No data</td>
</tr>
</tbody>
</table>

## Treatment of orthostatic hypotension

**Drug therapy:**
- **Add midodrine** (selective peripheral α-adrenergic agonist) (level A) (EFNS/MDS-ES 2010)
- **Add fludrocortisone** (salt-retaining mineralocorticoid) (good practice point) (EFNS/MDS-ES 2010)
- FDA approved for OH: midodrine and L-threo-DOPS (synthetic precursor of norepinephrine)
- Unknown effectiveness: indomethacin, pyridostigmine, yohimbine, EPO or domperidone (peripheral D2 receptor antagonist)

## Treatment of orthostatic hypotension (EFNS/MDS-ES 2010)

**General measures:**
- Avoid aggravating factors (e.g. large meals, alcohol, caffeine at night, exposure to a warm environment, volume depletion and drugs)
- Increase salt intake (1g per meal)
- Head-up tilt of the bed at night (30-40°)
- Wear waist-high elastic stockings and/or abdominal binders
- Exercise as tolerated
- Introduce counter-manoeuvres to prolong the time for which the patient can be upright (leg crossing, toe raising, thigh contraction, bending at the waist)
- Highlight postprandial effects (frequent small meals may be helpful)
Recommendations for the treatment of urinary incontinence

<table>
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<tbody>
<tr>
<td>MDS</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td>EFNS</td>
<td>Recommendations based on good practice points</td>
</tr>
<tr>
<td>AAN</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td>NICE</td>
<td>No data</td>
</tr>
</tbody>
</table>

PD TREATMENT ≠ COMBINATION OF MONOTHERAPIES

International Parkinson and Movement Disorder Society