Pharmacological treatment of Parkinson's disease

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PD PROGRESSION

DISABILITY

- 4-6 yrs

PRECLINICAL

PRODROMAL

SIGNS AND SYMPTOMS

unilateral
dementia
psychosis
instability & falls
motor complications & dyskinesias
bilateral

- 4-6 yrs

t
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/safinamide
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

### Prevention of clinical progression

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Highest level of recommendation</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 relevancy 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 ≠ no efficacy, but no data limits knowledge

Duration of commercialization produces safety data

Is there a pharmacological class effect? Are dopamine agonist 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>
<th>Highest level of recommendation</th>
</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

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of patients in final follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L-dopa arm (n = 42)</td>
</tr>
<tr>
<td>Age (mean y)</td>
<td>57</td>
</tr>
<tr>
<td>Duration of disease (mean mo)</td>
<td>19</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr (mean stage)</td>
<td>1.6</td>
</tr>
<tr>
<td>NWUD (mean score)</td>
<td>45.8</td>
</tr>
<tr>
<td>Webster (mean score)</td>
<td>8.9</td>
</tr>
</tbody>
</table>

✓ 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 SD/CR
3. Start on levodopa + entacapone
4. Start on dopamine agonist
5. Start on MAO-B: rasagiline/selegiline/safinamide
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

<table>
<thead>
<tr>
<th>Antiparkinsonian treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breakfast</strong></td>
</tr>
<tr>
<td>08:00</td>
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<tr>
<td>Sinemet 25/100</td>
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<tr>
<td>Ropinirole 2 mg</td>
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</tbody>
</table>
To better characterise motor fluctuations and the cause of falls …

Motor fluctuation patient diaries

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<table>
<thead>
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<tbody>
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<td>hora</td>
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<td>23:30-24:00</td>
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</table>

00:00 – 08:00

Coloque, por favor, uma marca (✓) para indicar o seu estado predominante durante a última metade da noite.

08:00 – 16:00

Coloque, por favor, uma marca (✓) para indicar o seu estado predominante durante a última metade da manhã.

16:00 – 24:00

Coloque, por favor, uma marca (✓) para indicar o seu estado predominante durante a última metade da tarde.
Video
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></th>
<th>Breakfast (08:00)</th>
<th>Lunch (12:00)</th>
<th>Mid-afternoon (16:00)</th>
<th>Dinner (20:00)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinemet 25/100</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Ropinirole 2 mg</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</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/opicapone)
6. Switch to Stalevo
7. Add MAO-B inhibitor: rasagiline or selegiline or safinamide
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, Rasagiline, Entacapone, Tolcapone</td>
</tr>
<tr>
<td>EFNS</td>
<td>Entacapone, MAO-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, MAO-I</td>
</tr>
</tbody>
</table>
Entacapone for motor LD-induced motor complications

**COCHRANE SYSTEMATIC REVIEW**

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 2004

<table>
<thead>
<tr>
<th>Study</th>
<th>COMT I N</th>
<th>Placebo N</th>
<th>Mean (SD)</th>
<th>Weight (%)</th>
<th>Weighted Mean Difference (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Entacapone</td>
<td>73</td>
<td>40</td>
<td>1.10 (2.40)</td>
<td>7.0</td>
<td>0.50 [-0.43, 1.43]</td>
</tr>
<tr>
<td>PSG SEESAW 1997</td>
<td>102</td>
<td>102</td>
<td>0.80 (2.80)</td>
<td>13.0</td>
<td>0.70 [0.02, 1.38]</td>
</tr>
<tr>
<td>Poeue CELEMON 2002</td>
<td>129</td>
<td>74</td>
<td>1.60 (2.50)</td>
<td>7.6</td>
<td>0.70 [-0.19, 1.59]</td>
</tr>
<tr>
<td>Rinne NOMEOMT 1998</td>
<td>85</td>
<td>5</td>
<td>1.30 (2.28)</td>
<td>1.4</td>
<td>1.20 [-0.87, 3.27]</td>
</tr>
</tbody>
</table>

Subtotal (95% CI) 389 221 0.68 [0.22, 1.13] 28.9

Test for heterogeneity chi-square=0.39 df=3 p=0.9419
Test for overall effect=2.91 p=0.004

41 minutes!
95% CI: 13 min, 1 hour 8 min, P=0.004
STN DBS vs BEST MEDICAL TREATMENT

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

1. Which to add first: COMT inhibitors or MAO-B inhibitors or dopamine agonists?

Unknown “effectiveness” (therapeutic strategy)
COMT inhibitors vs MAO-B inhibitors

Rasagiline vs Entacapone vs Placebo

Rasagiline/Entacapone vs Placebo

Change from baseline (hours)

***p<0.001 vs placebo

Rascol et al, Lancet 2005

*** -48 min
Pragmatic questions

1. Which dopamine agonist?

   Unknown (no dopamine agonist has proven better)

   Recommendations based on safety
# 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>
</tbody>
</table>
| EFNS      | Predictable ON-OFF: DBS (STN); subcutaneous apomorphine (penject)  
|           | Unpredictable ON-OFF: DBS (STN) |
| AAN       | No data                         |
| NICE      | Unpredictable ON-OFF: intermittent apomorphine |

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>
<thead>
<tr>
<th>Guideline</th>
<th>Highest level of recommendation</th>
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<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

### FREQUENCY OF NEUROPSYCHIATRIC SYMPTOMS

<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>

Witjas 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
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, selegilene, 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
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
Pharmacological interventions
Positive effect on freezing

LD, entacapone, DAs improve Off-related FOGs in advanced PD (by decreasing Off time)

MAO-B inhibitors
- Rasagiline: Largo sub-study: improvement of FOG-Q (10 w)
- Selegiline: Datatop post-hoc analysis (freezing, gait)

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)
• primary outcomes were daily falls and near falls

<table>
<thead>
<tr>
<th>Table</th>
<th>Outcomes during donepezil and placebo phases*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment phase</td>
</tr>
<tr>
<td></td>
<td>Donepezil</td>
</tr>
<tr>
<td>Fall frequency (falls/day)</td>
<td>0.13 (0.13)</td>
</tr>
<tr>
<td>Near fall frequency (near falls/day)</td>
<td>2.50 (4.1)</td>
</tr>
<tr>
<td>Global impression of change</td>
<td>3.07 (0.32)</td>
</tr>
<tr>
<td>Change in ABC Scale, %</td>
<td>3.6 (0.04)</td>
</tr>
<tr>
<td>Change in Berg Balance</td>
<td>1.65 (1.37)</td>
</tr>
<tr>
<td>Change in motor UPDRS</td>
<td>1.06 (0.96)</td>
</tr>
<tr>
<td>Change in Folstein MMSE</td>
<td>0.17 (0.86)</td>
</tr>
<tr>
<td>DBS group (fall frequency) (n = 6)</td>
<td>0.10 (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; Rodriquez-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.

Evidence-Based Analysis of Physical Therapy in Parkinson’s Disease with Recommendations for Practice and Research

Samyra H.J. Keus, PT, MSc; Bastiaan R. Bloem, MD, PhD; Erik J.M. Hendriks, PT, PhD; Alexandra B. Broedsers-Cohen, and Marten Mummeke, PT, PhD, on behalf of the Practice Recommendations Development Group.
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>
<thead>
<tr>
<th>Guideline</th>
<th>Highest level of recommendation</th>
</tr>
</thead>
<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

- **Early**
  - Levodopa
  - Dopamine Agonists
  - MAO-B I
  - COMT I
  - Amantadine
- **Stable**
- **Advanced**
  - DBS
Treatment of daytime somnolence in PD (EFNS/MDS-ES 2010)

**General measures:**
- Assessment of nocturnal sleep (good practice point)
- Optimise nocturnal sleep by reducing disturbing factors, such as akinesia, tremor, urinary frequency, etc. (good practice point)
- Recommendation to stop driving (good practice point)

**Drug therapy:**
- Decrease dose or discontinue sedative drugs (good practice point)
- Decrease dose of dopaminergic drugs (mainly dopamine agonists - good practice point)
- Switch to other DA (good practice point)
- Add modafinil (level B)
- Add other wake-promoting agents like methylphenidate (good practice point)
Treatment of other sleep disorders (EFNS/MDS-ES 2010)

• Add a bed time intake of LD SR or CR (level B)

• Transdermal rotigotine, pramipexole and prolonged release ropinirole improve sleep quality in advanced PD patients with motor fluctuations (criteria for studies entry was not sleep disturbance!)

• STN DBS improves sleep quality in advanced PD (no improvement on PLM, RLS, RBD and excessive daytime sleepiness) (level B)
Treatment of RBD in PD  
(EFNS/MDS-ES 2010)

• No controlled trials in PD

• General measures:
  • Protective measures (safeguard bedroom environment) (good practice point)
  • Reduce or withdraw antidepressants, primarily SSRIs (good practice point)

• Drug therapy:
  • Add clonazepam at bedtime (0.5–2 mg) (level C)
Treatment of urinary disturbances (EFNS/MDS-ES 2010)

• General measures:
  • Exclude urinary tract infection
  • Nocturia: Reduce intake of fluid after 6 pm. Sleep with head-up tilt of bed.

• Drug therapy:
  • Use anticholinergic drugs (good practice point). Trospium chloride (10-20 mg 2-3 times per day), tolterodine (2 mg bid), oxybutynin (2.5 – 5 mg bid).
  • Risk of cognitive AE
  • Optimisation of night-time dopaminergic therapy (good practise point). Apomorphine injections can be considered if outflow obstruction is the dominating problem (good practice point).
  • Botulinum toxin type A injected in the detrusor muscle
Treatment of dysphagia

• Recommendations (good practice points):
  • Optimization of motor symptom control (LD and apomorphine)
  • Referral to speech therapist
  • Enteral feeding options (short-term nasogastric tube feeding or longer term feeding systems (percutaneous endoscopic gastrostomy))
Treatment of gastric dysfunction

- Delayed gastric emptying
- Nausea and vomiting

Recommendations:
- Domperidone (30-60 mg/daily)
- Avoid metoclopramide, cinarizine, and prochlorperazine (good practice point)
Treatment of constipation

• Most common gastrointestinal symptom in PD
• Pre-motor stages of the disease

• Recommendations:
  • Discontinue anticholinergic drugs (good practice point)
  • Increased intake of fluid and fibre (good practice point)
  • Increased physical activity (good practice point)

• Drug therapy:
  • Macrogol (polyethylene glycol solution) (Level A)
  • Fibre supplements such as psyllium (Level B) or methylcellulose and osmotic laxatives (e.g. lactulose) (good practice point)
Treatment of erectile dysfunction

• General measures:
  • Urological investigation
  • Treat co-morbidities (e.g. hypothyroidism, hyperprolactinemia, low testosterone, depression)
  • Discontinue drugs associated with erectile dysfunction (e.g. alpha-blockers) or anorgasmia (e.g. SSRIs)

• Drug therapy:
  • Sildenafil (50-100 mg) (Level B)
  • Tadalafil (10 mg, ½-12 hours before sex) or vardenafil (10 mg, 1 hour before sex) (good practice point)
  • Apomorphine injections (5-10 minutes before sex) (good practice point)
  • Intracavernous injections of papaverine or alprostadil (good practice point)
Treatment of sialorrhea

- **Drug therapy:**
  - Botulinum toxin type A and B improve drooling
  - Anticholinergics
    - Sublingual ipratropium bromide spray – neg study
Treatment of pain

• Treatments:
  • No controlled clinical trials on the treatment of pain in PD
  • Adjustment of antiparkinsonian medication and treat wearing-off phenomena
  • Treat depression

• Treat specific pain syndromes (dissociation between pain complains and analgesic prescription)

• Open label positive results with STN and GPi DBS and duloxetine
The International Parkinson and Movement Disorder Society