Medical management of advanced PD

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What is advanced PD?

- Levodopa is the most effective symptomatic treatment for PD
- All PD patients eventually require levodopa.
- Chronic levodopa treatment -> motor complications
  - ELLDOPA: 9 months on levodopa 200 mg tid: 16% developed dyskinesia and 20% had motor fluctuations
  - Higher risk with younger age at onset and high dose of levodopa
- Motor complications (MF and/or LID) = advanced PD

Olanow et al., 2001; Agid et al., 2002; Miyasaki et al., 2002; Rascol et al., 2002; Korczyn et al., 2002
OFF
Why does it happen?

• Motor effects of levodopa
  – Presynaptic mechanisms (synthesis and storage of dopamine in remaining nigral neurons)
  – Postsynaptic mechanisms (activation of postsynaptic dopamine receptors on striatal neurons)

Fabbrini et al., 1988
L Dopa central pharmacodynamic

Early PD  Late PD

Mouradian et al., 1988
Change in therapeutic window with PD progression

Years from symptom onset

0 5 10 15

ON

OFF

DYSKINESIA

THERAPEUTIC WINDOW

BRADYKINESIA
Early Parkinson’s disease

Dyskinesia Threshold

“on”

“off”

Levodopa

2 4 6 hours

Striatal Dopamine Level (Hypothetical)
Moderate Parkinson’s disease

Striatal Dopamine Level (Hypothetical)

Dyskinesia Threshold

Levodopa 2 4 6 hours

“on”

“off”
Late Parkinson’s disease

Dyskinesia Threshold

“on”

off”

Striatal Dopamine Level (Hypothetical)

Levodopa 2 4 6 hours

2 4 6 hours

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ON w LID
How can we manage it?

- Medical management.
- Deep Brain Stimulation
- Infusion therapies.
How can we manage it?

• Medical management.
• Deep Brain Stimulation
• Infusion therapies.
Medical management

• MF
  – Manipulate C/L
  – Dopamine agonists
  – MAO-I
  – COMT-I

• LID
  – Fractionating
  – Amantadine
  – Namenda? Clozapine? Levetiracetam?
Manipulate C/L

- Dropped dose or delayed latency: Take far form high protein meals (1 hour b/a)
- Unpredictable effects of dose: Switch CR to IR
- Delayed latency: Dissolvable C/L (Madopar, parcopa) or diluting IR in ascorbic acid drink

Nutt JG et al., 1984; Leenders et al., 1986; Stocchi et al., 1996; Stocchi et al., 2008
COMT-I

- Entacapone, Tolcapone
- Addition to C/L
- Increases ON time by 1.3 to 1.8 hours/day and increases UPDRS.
- Increases risk of LID if used in early PD

Rinne et al., 1998; The Parkinson Study Group 1997; Deane et al., 2004, Stocchi et al., 2010
• Rasagiline
• PRESTO
  – n= 472, RCT, add on Rasagiline 0.5 mg vs 1 mg vs placebo, f/u 26 weeks.
  – Decreased OFF time by 1.85h (1mg), 1.41h (0.5mg) and 0.91h (P)
• LARGO
  – n= 687, RCT, add on Rasagiline 1 mg (R) vs Entacapone (E) vs placebo (P), 18 weeks f/u.
  – Decreased OFF time by 1.2h with R or E, 0.4 h with P
  – Increased ON w/o troublesome LID: 0.85h with R or E, 0.03 with P
MAOB-I

• Selegiline
  – Usually in early PD as dopamin paring
  – Showed to decreased OFF time when added to C/L

• Selegiline ODT
  – Bypasses first-pass hepatic metabolism
  – Add on to C/L decreases OFF time by 1.6 hours v/s placebo

Golbe et al., 1988.
Dopamine agonists

- Pergolide, cabergoline: valvular fibrotic disease/pulmonary fibrosis.
- Pramipexole, ropinirole, rotigotine.
- Added to C/L, decrease OFF time by 1.1 to 1.5 hours/day
- More so with ER tablets and patch
- Useful for nighttime symptoms
- Can decrease LID indirectly by decreasing C/L dose by up to 30%
- SE: EDS, ICD, leg edema, cognitive impairment, hallucinations

Olanow et al., 1994; Lieberman et al., 1998; Pinter et al., 1999; Clarke et al., 2001
Apomorphine

- SubQ only
- Very short latency and half-life
- Dropped dose, unexpected OFF
- First dose always in clinic with EKG and BP monitoring
- Individualized dose 2-5mg

Frankel et al., 1990; Hughes et al., 1993; Attanasio A, et al., 1990.
Peak dose LID vs DID
Peak dose LID

- Fractionation of C/L
  - Give smaller doses at smaller interval: try to avoid peak effect
- Decrease C/L and start/increase DA

Facca and Sanchez-Ramos, 1996; Cristina et al., 2003; Storch et al., 2005.
Amantadine

- Amantadine
  - Decreases LID scores by 45-60% w/o worsening OFF Sustained effect
  - SE: hallucination and cognitive issues

- Some concern that this effect does not last

Verhagen et al., 1998; Luginger et al., 2000.
Amantadine

- **AMANDYSK trial, 2014**
  - Multicenter RCT placebo-controlled, parallel-group, wash-out study, n=57 PD with LID, on amantadine ≥200 mg/d for ≥6 months, 3 months f/u.
  - Mean duration of therapy: 2.7 y (placebo), 4.3y (treatment), p=0.16
  - In discontinuing group:
    - LID worsened in duration and severity.
    - Drop out 2/2 LID
    - Apathy and fatigue worsened.
  - No difference in UPDRS III between the groups.

Ory-Magne et al., 2014
Antipsychotics

- Clozapine
  - Atypical antipsychotic
  - In 1 RTC, decreased LID by 1.5 hour/day
  - SE: sedation, agranulocytosis
- Other antipsychotics: not proven and likely to worsen motor symptoms of PD

Durif et al., 2004
• Zesiewicz et al., 2005
  – Open-label, n= 9 PD with LID, increased ON w/o LID from 43% to 61% of the day
  – Decreased ON with troublesome LID from 23% to 11%
  – 50% drop out (somnolence)
Leviteracetam

- **Wong et al., 2011**
  - RCT, cross over, n=16, 6 weeks x 2 + 4 week wash out. Titration of Leviteracetam 500mg weekly up to 200 mg/day.
  - Hourly videotaped dyskinesia assessments and UPDRS on 1 day at the end of each treatment period.
  - Direct observation: LID slightly less on placebo (P = .26).
  - Patient diary: LID less on placebo (P = .10).
  - Parkinsonism a little worse on levetiracetam (P = .05).
Memantine

- Wictorin and Widner, 2016
  - RCT, n=15, 3 weeks, memantine 20 mg v/s placebo
  - No change in LID ratings, but
    - 7/15 reduced LID score by 32%
    - 5/15 no change
    - 3/15 worsened by 33%
    - 35% reduction of LID in self administered diaries (25%-> 16%)
  - No side effects
DA vs MAOB-I vs COMT

• Stowe et al., 2010, Cochrane Database review.
  – Metanalysis: 44 trials, n=8436.
  – Compared to placebo, adjuvant therapy significantly
    • Reduced off-time,
    • Reduced levodopa dose
    • Improved UPDRS scores
  – However, dyskinesia and SE increased:, constipation, dizziness, dry mouth, hallucinations, hypotension, insomnia, nausea, somnolence and vomiting.
**DA vs MAOB-I vs COMT**

- **Indirect** comparisons of the three drug classes:
  - Impact on OFF time: DA: -1.54 hours/day; COMTI: -0.83 hours/day; MAOBI: -0.93 hours/day;
  - Decrease in L-dopa dose: DA: -116 mg/day; COMTI: -52 mg/day; MAOBI: -29 mg/day;
  - Change in total UPDRS scores: DA: -10.01 points; COMTI: -1.46; MAOBI: -2.20 points;
  - LID: DA: OR 2.70; COMTI: OR 2.50; than with MAOBI: OR 0.94.
  - Other side effects: DA: OR 1.52; COMTI: OR 2.0; MAOBI: OR 1.32.
Non Motor Symptoms in PD

- Depression
  - Paroxetine and venlafaxine
- Dementia
  - Donepezil and rivastigmine
- Hallucinations
  - Quetiapine, clozapine and pimavanserin
- Constipation
  - Lubiprostone and polyethylene glycol
- Urinary urgency
- Orthostatic hypotension
  - Droxidopa
- REM Sleep Behavior disorder
- EDS
- Dysphagia
  - ST
- Dysarthria
  - ST
- Falls/gait disorders
  - PT
References


