Medications for the Treatment of Parkinson’s Disease: The Old, The New and The Future

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Objectives:

- Discuss current pharmacological therapies for the management of Parkinson’s Disease
- Discuss new FDA approved Parkinson’s Disease medication options
- Discuss future direction in PD medication development
Etiology, pathophysiology and disease progression
Parkinson’s Disease (PD) is the second most common neurodegenerative disease after Alzheimer's Disease and affects over 10 million people worldwide.

Mean age of onset: 60-70 y.o. Prevalence increases with age, with men being affected 1.5-2 times more often than women.

Evidence currently suggests that the development of PD results from a series of interactions between both environmental and genetic factors.

- Purely environmental PD is rare – would expect to see more prevalence of “PD clusters”
- Purely genetic PD is rare – PD associated “risk genes” increase risk by <50% and even the most common PD gene mutation (LRRK2) only causes PD in 30-40% of carriers
- ? Reason behind “one size fits all” medication treatment does not work for PD patient population
Neurotransmitters

- Several neurotransmitters other than dopamine are altered in PD and play a role in the development of both motor and non-motor symptoms and disease progression.

  - Norepinephrine
  - GABA
  - Glutamate
  - Acetylcholine
  - Serotonin

- Medications targeting these neurotransmitters and their receptors are used and in development for the treatment of PD.
Update on treatments for PD
Part 1: “The Old” - Current medication therapies

- Disease modifying
- Symptomatic therapy
- Treatment of motor complications/fluctuations (“on” dyskinesias and wearing off)
- Treatment of non-motor symptoms
**Disease modifying**

- **No proven disease-modifying therapies**
  - **Failed trials:** Vitamin E, Vitamin D, CoQ10, creatine, riluzole, pioglitazone, glutathione, pramipexole, inosine, isradipine

- **Currently under investigation**
  - Targeting LRRK2, glucocerebrosidase, alpha-synuclein
Symptomatic therapy (motor symptoms)

- Levodopa
- Dopamine agonists
- MAO-B inhibitors
- Amantadine
- Anticholinergics
Levodopa formulations

1. Sinemet immediate release and sustained release (generic carbidopa/levodopa)

2. Stalevo (carbidopa/levodopa/entacapone)

3. Rytary (extended release formulation of carbidopa/levodopa)

4. Duopa (enteral suspension of carbidopa/levodopa)
Dopamine agonists

1. Ropinerole – potent and selective D2-type receptor agonist. Orally administered. IR and ER tablets.

2. Pramipexole – stimulates D2-like receptors with the highest affinity for D3 receptors. Orally administered. IR and ER tablets.

3. Rotigotine – transdermal patch formulation

4. Apomorphine – subcutaneous injection ("rescue medication")
Dopamine Agonists

**Are DA neuroprotective? – No**
- Studies on ropinirole and pramipexole – did not slow disease progression

**Do DA reduce long term motor complications? – No**
- Similar long-term outcomes (including motor complications) regardless of initial treatment with DA or LD
- Motor complications are most closely related to disease duration and medication dose, NOT the timing of when LD is initiated
- Patients who started LD later developed motor complications sooner after starting it
- Brain 2014: 137; 2625-2631

**Are DA safer than LD? – No**
- Side effects are not to be minimized – Orthostasis, Psychosis, Hypersomnia/Sleep attacks, pedal edema and impulse control disorders (ICDs)
- Over 15% of patients treated with DA found to have ICDs
- ICDs were related to DA dose and treatment duration
- Arch Neurol. 2010 May; 67(5): 589-95
MAO-B inhibitors

- Selegiline, Rasagiline (FDA indicated for monotherapy)
- Safinamide (FDA approved in 2017 for adjunct therapy) – more selective than selegiline or rasagiline for MAO-B vs MAO-A inhibition (1,000x higher in humans vs 127x for selegiline and 103x for rasagiline)
- MOA – helps block break down of dopamine in the brain, making more dopamine available for the receptors
- Modest effect in improving Parkinson’s symptoms
- Side effects – dizziness, headache, confusion, nausea, insomnia, dyskinesias, orthostatic hypotension and headaches
- Caution when using other anti-depressant medications
Anticholinergics

- Benztropine (Cogentin)
- Trihexyphenadyl (Artane)

- Can be beneficial for tremor predominant symptoms
- MOA – Unclear but proposed mechanism is that blocking striatal acetylcholine helps to correct the imbalance of dopamine and cholinergic pathways
- Not commonly used due to side effects
  - Blurred vision, dry mouth, constipation, urinary retention, confusion, hallucinations, dementia
Adjunct medications
Treatment of motor complications: “on” dyskinesias

- Review dosing regimen with patient to ensure not over-using dopaminergic medications (dopamine dysregulation syndrome)
- Decrease/stop adjunct medications/polypharmacy
- Use smaller, more frequent LD doses
- Anti-dyskinetic medications
  - Amantadine IR (SE of hallucinations, constipation, orthostasis, falls, nausea)
  - Amantadine ER (Osmolex ER – Combination ER/IR tablets with once daily – morning dosing – not FDA indicated for dyskinesias)
  - Gocovri (ER amantadine capsules with once daily – bedtime dosing due to median Tmax at 12 hours)
Treatment strategies: non-motor symptoms

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
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<tbody>
<tr>
<td>Pimavanserin (Nuplazid)</td>
<td>for PD psychosis (<strong>other antipsychotics are used off label)</strong></td>
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<tr>
<td>Antidepressants</td>
<td>(SSRIs most commonly used)</td>
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<td>Droxidopa (Northera)</td>
<td>for short term treatment of symptomatic orthostatic hypotension (also use midodrine and fludrocortisone)</td>
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<tr>
<td>Botulinum toxins</td>
<td>for sialorrhea</td>
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<tr>
<td>Modafinil</td>
<td>for fatigue (rarely used)</td>
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<tr>
<td>Stool softeners, miralax, hydration and exercise</td>
<td>for constipation</td>
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Update on treatments for PD
Part 2: “The New” medication therapies

- Modification of delivery method of “old drugs”
- “More selective” medications
- New classes of medications
Opicapone

- COMT inhibitor
- FDA approved in US April 2020
- Indicated for use as an adjunct treatment to carbidopa/levodopa in patients with PD experiencing “off” episodes
- Once daily formulation - Dissociates slowly from COMT, resulting in a duration of action longer than 24 hours despite its short blood plasma half life
- Greater degree of COMT inhibition than entacapone but no clear evidence that it offers clinical advantages due to this over entacapone
Levodopa inhalation powder

- Inhaled form of levodopa
- FDA approved in US in 2018 for prn use due to off periods - “rescue medication” (up to 5 times per day)
- Onset of action typically within 10 minutes and lasts 60 minutes postdose
- Side effects – cough (15%), URI (6%), nausea (5%)
- Not recommended in patients with asthma, COPD or chronic lung disease
SPAN-PD trial (randomized, double blind, placebo controlled 12 week trial) – UPDRS Part III motor score change over time post-dose (Drug n=114, placebo n=112)
Istradefylline

- Adenosine A2A receptor antagonist
- FDA indicated in US 2019 as adjunct treatment to c/l in PD patients having off episodes
- Orally administered, once daily

In PD, A2A receptor stimulation of the indirect pathway by adenosine, coupled with the dysfunction of dopamine D2 receptors due to the loss of dopamine, may lead to abnormality in signals for motor control (loss of coordination of A2 and D2 receptor function)

Istradefylline reduces overactivation of indirect pathway
Randomized, double blind, placebo controlled 12 week studies of 20 mg (study 3 n=115, study 4 n=120) and 40 mg (study 3 n=124, study 4 n=123) vs placebo (study 3 n=118, study 4 n=123) as adjunct treatment for PD patients with daily off time.
Sublingual apomorphine

- Sublingual, avoids first pass metabolism when absorbed through the oral mucosa

- FDA approved in US 2020 for prn use up to 5 times daily for off episodes (rescue medication)

- Do not use with 5HT3 antagonists (including antiemetics) as can cause profound hypotension and LOC – based on SC apomorphine data

- Antiemetic – (trimethobenzamide 300 mg tid) is recommended beginning 3 days prior to initial dose due to risk of nausea and vomiting with apomorphine. Antiemetic discontinued when not needed and generally discontinued within 2 months.
Drug (n=54) vs placebo (n=55) – 12 week Phase 3, Randomized, double blind, placebo controlled trial for intermittent off periods in PD.
Update on treatments for PD
Part 2: “The Future”
medication therapies

- Modification of delivery method of “old drugs”
Carbidopa/levodopa novel formulations

- Subcutaneously administered c/l
  - ND 0612 and ABBV951

- Accordion pill

- Intranasal c/l
Subcutaneous C/L

- ND0612
  - An investigational drug-device combination designed to continuously deliver liquid levodopa/carbidopa (60/7.5 mg/mL) by sc infusion.

- 2 pharmacokinetic studies in PD patients with motor fluctuations have shown that ND0612 maintains steady, therapeutic LD plasma concentrations.

- 1 phase II efficacy study (n=38) showed that a 24h infusion of ND0612 statistically significantly reduced daily OFF time and morning akinesia while increasing ‘good ON’ time compared to baseline.

- Currently 1 phase 3 III RCT efficacy and safety study comparing ND0612 to IR c/l patients with motor fluctuations is ongoing (BouNDless trial)
ABBV951

- 24 hour continuous infusion
- Currently enrolling in Phase 3 trial (randomized, double blind, placebo controlled study)
Oral C/L delivery

- DopaFuse: consists of an oral retainer and a single-use, prefilled, disposable drug container that continuously releases a novel LD/CD oral paste in the back of the mouth.

- The drug is a reformulation of LD/CD into a highly concentrated, stable, oral paste.

- A propellant (the same as is used in metered dose inhalers) exerts a constant pressure on the flexible diaphragm, which in turn exerts a constant pressure on the drug paste. The drug paste is forced out of the drug chamber through two flow-controlling nozzles and into the delivery tube. The delivery tube wraps around the rearmost tooth and delivers the paste near the back of the tongue. The tasteless LD/CD oral paste disperses in saliva and is swallowed, then absorbed in the gastrointestinal tract.

- Designed to deliver drug in a continuous, linear fashion within ±20% of the nominal delivery rate for 4 hours. The container is held in place by an oral retainer. The retainer is custom-made for each patient using standard, commercially-available, thermoform retainer materials and molding processes used in dental labs.

- Upon delivery, the prodrug is rapidly converted into levodopa, providing stable plasma concentrations.

- Currently in phase 2 study
The Accordion Pill drug delivery system uses biodegradable polymeric films loaded with drugs and active ingredients, folds them into an undulated shape and then places them inside a capsule.

The Accordion Pill’s drug release mechanism is independent of its gastric retention mechanism and the Accordion Pill can combine immediate and controlled-release profiles, thus allowing considerable flexibility in developing and/or optimizing a variety of therapies.

AP-CD/LD includes both immediate and controlled-release modes, enabling a portion of its active ingredients to be released immediately after reaching the stomach, and another portion over a period of eight to 12 hours.
ACCORDANCE trial:

Phase 3 trial of 320 people with advanced PD randomly assigned to either AP-CD/LD or Sinemet for 13 weeks. Prior to randomization, all went through two six-week periods to stabilize and optimize them on Sinemet and then on AP-CD/LD.

Results showed that AP-CD/LD could treat motor symptoms but failed to provide greater reductions in daily off periods compared to Sinemet. It also did not extend on time without dyskinesia or improve patients’ motor scores.

Later analysis suggested that the doses given in the study were not sufficient to achieve optimal efficacy — 50 mg of carbidopa, with 400 or 500 mg of levodopa, two or three times daily — and that patients who had not maxed out their dose during the optimization period did have a meaningful reduction in off periods.

Findings also showed that AP-CD/LD provided less variability in blood levels of levodopa, and that AP-CD/LD patients tolerated higher levodopa daily doses than those taking Sinemet.
INP 107

- Impel NeuroPharma is currently developing INP107 - a non-invasive, self- or caregiver-administered upper nasal formulation of carbidopa/levodopa, with the goal of providing rapid delivery of drug for the treatment of morning OFF episodes.

- Precision Olfactory Delivery (POD®) system is able to deliver a range of therapeutic molecules and formulations into the vascular rich upper nasal space. By delivering predictable doses of drug directly to the upper nasal space, it may enable increased and consistent absorption of drug.

- Phase 1 trial completed. Currently planning to initiate INP107 PK study for dose selection.
Novel formulation of Apomorphine for subcutaneous infusion (Patch-pump)

- Less acidic, more concentrated formulation that what is currently available
- Allows for a smaller volume to be administered by subcutaneous continuous infusion with a patch-pump vs a traditional syringe pump

Phase I safety, tolerability, PK and bioavailability study vs commercial apomorphine formulation (Apo-go) in mini pigs

- Local skin reactions (infusion site nodules) less severe for ND0701 vs Apo-go
- Both formulations were reported to be safe and well treated with no serious treatment related adverse effects
- Comparable bioavailability between the two formulations
Initiation of therapy in PD

**Movement disorder specialists will base initial therapy/medication choice on individual patient – symptom severity, age and comorbidities.**
Proposed algorithm for initial PD treatment – PADREC Centers 2019

1. Patient newly diagnosed with Parkinson's Disease
   - Provide group support, exercise, and nutrition counseling

2. Functional disability?
   - YES
     - Degree of disability
       - Albumin
       - Physiologic age ≧ 65 yrs and/or cognitive decline
       - Levodopa/carbidopa

3. Tremor predominate symptoms?
   - YES
     - Consider anticholinergics or amantadine
     - Relief of disabling symptoms?
       - NO
         - Levodopa/carbidopa
         - Continue current therapy
       - YES
         - Consider dopamine agonist or levodopa/carbidopa
         - Relief of disabling symptoms?
           - NO
             - Consider dopamine agonist or levodopa/carbidopa
             - Continue current therapy
           - YES
             - Titrated dopamine agonist or switch to levodopa/carbidopa
             - Relief of disabling symptoms?
               - NO
                 - Consider dopamine agonist or levodopa/carbidopa
                 - Continue current therapy
               - YES
                 - Continue current therapy

4. NO
   - Consider no therapy, MAO-B inhibitors, levodopa/carbidopa, dopamine agonist
   - Functional disability?
     - YES
     - Degree of disability
       - Moderate/severe
       - Physiologic age ≧ 65 yrs and/or cognitive decline
       - Levodopa/carbidopa

5. Relief of disabling symptoms?
   - NO
     - Reconsider diagnosis
   - YES
     - Continue current therapy

6. Reconsider diagnosis
    - Continue current therapy
    - Reconsider diagnosis
    - Continue current therapy
Adjunct Therapy

- Allied health therapies and exercise have been proven effective for improvement of both motor and non-motor symptoms in patients and improving QOL.

  - Physical therapy
  - Occupational therapy
  - Speech therapy
  - Cognitive therapy
  - Yoga, Tai Chi
  - Cycling
  - Boxing
  - Swimming and aquatherapy
  - BIG and LOUD program
Summary and recommendations

- PD is a complex progressive neurodegenerative disease with both environmental and genetic factors playing a role.
- PD medication therapy continues to develop but current therapies are for symptomatic benefit.
- PD medication therapy must be individualized to the patient and is not “set it and forget it”.
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- Efficacy | KYNMOBI™ (apomorphine HCl) sublingual film (kynmobihcp.com)
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