PD and Medication: What’s New?

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Disclosers

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Parkinson Disease: Unmet Needs

➢ Off time including on demand therapies
➢ Dyskinesia
➢ Psychosis
➢ Orthostatic hypotension and other autonomic symptoms
➢ Dementia
➢ Slowing disease progression
➢ Falls
New & Future Therapies

New Treatments

➢ PD Psychosis: Pimavanserin (Nuplazid)
➢ Orthostatic Hypotension: Droxidopa (Northera)
➢ Off time:
  ➢ Carbidopa Levodopa Enteral Suspension (Duopa)
  ➢ Safinamide (Xadago)
➢ On Demand Therapies: Levodopa Inhalation (Inbrija)
➢ Dyskinesia: Amantadine ER capsules (Gocovri)
➢ Drooling: Botulinum toxin (Xeomin)

Future Treatments

➢ On Demand Therapy: Sublingual apomorphine
➢ Drooling: Botulinum toxin (Myobloc)
➢ Off time
  ➢ Adenosine A2 antagonist: Istradefylline
  ➢ Subcutaneous apomorphine infusion
  ➢ Subcutaneous carbidopa/levodopa infusion
  ➢ Carbidopa/levodopa extended release
What Is Parkinson Disease Psychosis (PDP)?

➢ Presence of at least one of the following
  ➢ Hallucination: Seeing/hearing/feeling/smelling things that are not there
  ➢ Illusions: Things that are wrongly perceived
  ➢ False sense of presence
  ➢ Delusions: False beliefs

➢ Approximately 50% of PD patients will have these symptoms sometime in the disease course

➢ Can be present
  ➢ With or without memory problems
  ➢ With or without PD medications
  ➢ With or without having insight
Why Should Parkinson’s Disease Psychosis (PDP) Be Treated?

**Patient**
- Can be disabling
- Limits treatment options for motor symptoms
- 2\textsuperscript{nd} most common reason for PD patient ER visits
- Most common reason for nursing home placement

**Caregiver**
- Relationship with patient affected
- Increased caregiver burden
- Increased physical decline
- Increased depression
Pimavanserin (Nuplazid)

- First and only approved treatment for PDP
- Unlike other anti-psychotics does not worsen Parkinson’s disease motor symptoms
- Majority of patients benefit (over 70% have some benefit)
- Acts on serotonin
- One capsule daily
- Improves hallucination, delusions, night time sleep, daytime sleepiness and reduces caregiver burden
- Common side effects: nausea, confusion, hallucination
What is Orthostatic Hypotension?

- Orthostatic hypotension is a fall in blood pressure on standing that causes
  - Common symptoms: lightheadedness, dizziness, feeling of passing out, passing out
  - Less common symptoms: weakness, legs giving away, fatigue, slowed thinking, vision problems, headache, neck pain, chest pain

- Symptoms commonly occur on standing
- Typically worse in the morning
- May be worse after meals
- Parkinson’s disease is a common cause
- Approximately 20% of PD patients have symptoms
Droxidopa (Northera)

➢ For symptoms of light headedness or feeling of passing out
➢ It is believed to increase the chemical norepinephrine
➢ Should be taken 3 times a day: 8a, 12n, 4p
➢ Starting dose 100 mg 3 times/day increased to 600 mg 3 times/day
➢ Avoid taking it within 5 hours of bedtime
➢ Common side effects: headache, dizziness, nausea, fatigue, high blood pressure on lying down
What is OFF Time?

- Levodopa is the most efficacious medication
- Converted to dopamine which is reduced with PD
- When initiated, levodopa improves symptoms throughout the day and night
- Over time patients develop OFF time
  - 40% in 5 years, 90% in 10 years
- OFF time is the time during the day when PD symptoms return or worsen
- OFF time PD symptoms may include:
  - Motor: Tremor, slowness, stiffness, balance difficulty, etc
  - Non motor: Anxiety, cloudy mind, aching, tiredness, etc
OFF Periods

➢ Early morning OFF
➢ Wearing OFF
➢ Delayed ON
➢ Dose Failure

ALL OFF PERIODS THROUGHOUT THE DAY ADD UP TO THE TOTAL DAILY OFF TIME
Carbidopa Levodopa Enteral Suspension (Duopa)

Carbidopa Levodopa Enteral suspension is infused via an intrajejunal tube in the abdomen and an external pump.

How is Duopa delivered?

- Duopa cassette
- CADD-Legacy® 1400 pump
- Cassette tube
- Stoma
- PEG tube
- J tube
Indications for Duopa

- Diagnosis is Parkinson’s disease
- Symptoms improve with levodopa
- Other oral therapies have been used with levodopa
- Continue to have at least 3 hours of OFF daily
- Can manage pump or have support to manage it
- No contraindications to abdominal surgery

Duopa improves OFF time and Dyskinesia
Safinamide (Xadago)

- Monoamine oxidase B (MAO-B) inhibitor
- Used in addition to levodopa to treat OFF time
- Available in 2 doses: 50mg and 100mg
- Certain medications like opioid drugs (e.g. tramadol, meperidine), cyclobenzaprine, amphetamine, St John’s wort, dextromethorphan, certain antidepressants, etc. are contraindicated
- Improves ON time by approximately 55 minutes/day
Orally Inhaled Levodopa (Inbrija)

- For intermittent treatment of OFF periods in patients on carbidopa/levodopa
- Pulmonary delivery of levodopa
- Can be used up to 5 times/day
- Used with special inhaler, one capsule at a time (total 2 cap/dose)
- OFF symptoms improve as soon as 10 minutes and last for up to 60 minutes
- Main side effect: Cough
Levodopa Induced Dyskinesia

- Involuntary dance like movements that occur in patients on levodopa
- Need to differentiate with tremor
- Resolve when levodopa is reduced or discontinued
- Often lead to under treatment
- Often bother caregiver more than patient
- BUT can be very disabling and CAN limit activities of daily living, cause pain and embarrassment, falls
Amantadine ER Capsules (Gocovri)

- Used for patients with dyskinesia
- Also reduces OFF time
- ONLY PD medication that reduces dyskinesia and OFF time
- Acts on multiple chemicals especially glutamate
- Taken before bedtime
- Provides control of dyskinesia upon awakening and throughout the day
- Main side effects: Hallucination and lightheadedness
- Need to differentiate with
  - Immediate release amantadine given 2-3 times during day
  - Amantadine ER tablets (Osmolex) given in the morning, not approved for dyskinesia or OFF time
Incobotulinumtoxin A (Xeomin)

- Over 50% of PD patients can have excessive drooling
- Drooling can cause:
  - Wetness
  - Skin breakdown around mouth
  - Foul odor
  - Embarrassment
  - Choking
- Xeomin requires 2 injections on face
- Injections are required every 3-4 months
FUTURE THERAPIES
Sublingual Apomorphine: OFF Episodes

- Apomorphine is a medication that cannot be given in a form that requires swallowing
- Currently injections are available that are given by the patient under the skin
- Sublingual apomorphine strip is placed under the tongue
- Used for OFF periods
- Symptoms improve in 15 min and last for 90 min
- Main adverse effects: nausea, sleepiness, dizziness
Rimabotulinumtoxin B (Myobloc)

- Currently available for dystonia
- Used OFF-label for drooling
- Undergoing trials for drooling
- May have more flexible dosing
- Common adverse effects:
  - Dry mouth
  - Mild swallowing difficulty
  - Mild weakness in chewing
  - Change in saliva thickness
Istradefylline

- Blocks adenosine A2A receptors in the brain
- Caffeine also blocks the adenosine A2A receptor
- Istradefylline regulates the release of dopamine in the brain
- Approved in Japan
- Reduces OFF time
- Might possibly reduce dyskinesia
Subcutaneous Apomorphine Pump

- Widely available in Europe
- Provides apomorphine under the skin with a pump
- Reduces OFF time during the day
- Might reduce dyskinesia by reducing the dose of levodopa
- Patients with hallucination and dementia might not be candidates for the therapy
Subcutaneous Carbidopa/Levodopa Pump

- 2 companies working on providing carbidopa/levodopa continuously under the skin via a pump
- In patients with OFF time
- Does not require surgery
- Uses the most effective medication
- Can be used 24 hours
Extended-Release Carbidopa/Levodopa

➢ 2 companies

➢ Accordian Pill carbidopa/levodopa (AP-CD/LD)
  ➢ Just completed enrollment Phase III study

➢ IPX203
  ➢ Increases ON time
  ➢ Phase III studies started enrolling
Opicapone

- COMT Inhibitor
- Available in Europe
- In PD patients on levodopa having OFF time
- Once a day
- Reduces OFF time
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