New Pharmacologic Tools for Symptomatic Management of Parkinson’s Disease Since 2018

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University of Montana
Meet The Speaker

Dr. Marvanova serves as Professor and Dean of the Skaggs School of Pharmacy at the University of Montana. She is a Board Certified Psychiatric Pharmacist and Geriatric Pharmacist and Fellow of the American Society of Consultant Pharmacists. She has completed M.S. (Pharm), Pharm.D. and Ph.D. (Pathological Neurobiochemistry) degrees from the Charles University (Czech Republic) as well as a Ph.D. (Neuropharmacology) from the University of Eastern Finland. She also completed a medical research fellowship in neuropharmacology at Vanderbilt University School of Medicine and a Parkinson’s disease traineeship at Northwestern University. Her clinical expertise is neuropsychiatry and geriatrics and she has practiced in a variety of inpatient and outpatient settings. She is member of the editorial board for Continuum: Life-long Learning in Neurology (American Academy of Neurology) and also serves as a clinical pharmacy specialist consultant in neurology and psychiatry for Lexicomp, Wolters Kluwer.
Disclosure

Dr. Marvanova has no relevant financial relationships with ineligible companies to disclose.

Dr. Marvanova will discuss off-label use of amantadine extended-release.
Learning Objectives

At the end of the presentation, participants will be able to:

1. Compare and contrast pharmacology, clinical indications and place in therapy between newly approved medications since 2018 with other medications from the same class or with different formulations of the same active pharmacologic agent

2. List new agents in the pipeline (phase 3 studies) for symptomatic management of Parkinson’s disease

3. Given a patient case or scenario, select the most appropriate medication for symptomatic management of Parkinson’s disease
Parkinson’s Disease (PD)

- Chronic, progressive neurodegenerative disease
- Motor (parkinsonian) and non-motor symptoms
- No cure and no effective neuroprotective/disease modifying therapy
- Symptomatic therapy:
  1) **Motor symptoms and fluctuations:**
     - Dopaminergic therapies
     - Anticholinergic therapies
     - Miscellaneous
  2) **Non-motor symptoms:**
     - Treatment of specific symptom/complaint

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**CARDINAL MOTOR SYMPTOM**

- **T:** TREMOR (resting tremor)
- **R:** RIGIDITY
- **A:** AKINESIA/BRADYKINESIA
- **P:** POSTURAL INSTABILITY

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# U.S. Available Antiparkinson Therapy

## Dopaminergic

<table>
<thead>
<tr>
<th>Description</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine Precursor</td>
<td>Carbidopa/levodopa immediate-release (IR) (Sinemet™, Parcopa™, Dhivy™)</td>
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<tr>
<td></td>
<td>Carbidopa/levodopa extended-release (ER) (Sinemet CR™, Rytary™)</td>
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<td></td>
<td>Carbidopa/levodopa intestinal gel (Duopa™)</td>
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<tr>
<td></td>
<td>Levodopa powder for oral inhalation (Inbrija™)</td>
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<tr>
<td>Dopamine Agonists</td>
<td>Ropinirole IR (Requip™); pramipexole IR (Mirapex™); rotigotine (Neupro™)</td>
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<tr>
<td></td>
<td>Ropinirole ER (Requip ER™); pramipexole ER (Mirapex ER™)</td>
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<tr>
<td></td>
<td>Apomorphine (Apokyn™; Kynmobi™)</td>
</tr>
<tr>
<td>MAO-B Inhibitors</td>
<td>Rasagiline (Azilect™); selegiline (Eldepryl™; Zelapar™); safinamide (Xadago™)</td>
</tr>
<tr>
<td>COMT Inhibitors</td>
<td>Entacapone (ComTan™); tolcapone (Tasmar™); opicapone (Ongentys™)</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Amantadine IR (Symmetrel™)</td>
</tr>
<tr>
<td></td>
<td>Amantadine ER (Osmolex™; Gocovri™)</td>
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</tbody>
</table>

COMT= catechol-O-methyltransferase; MAO-B=monoamine oxidase-B

**Newly approved medication from 2018**

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U.S. Available Antiparkinson Therapy

**Dopaminergic**
- Dopamine Precursor
- Dopamine Agonists
- MAO-B Inhibitors
- COMT Inhibitors
- Amantadine

**Anticholinergic (oral therapies)**
- Muscarinic Antagonists
  - Benztropine (Cogentin™)
  - Trihexyphenidyl (Artane™)

COMT = catechol-O-methyltransferase; MAO-B = monoamine oxidase-B

Newly approved medication from 2018

U.S. Available Antiparkinson Therapy

**Dopaminergic**
- Dopamine Precursor
- Dopamine Agonists
- MAO-B Inhibitors
- COMT Inhibitors
- Amantadine

**Anticholinergic**
- Muscarinic Antagonists

**Miscellaneous**
- Adenosine Antagonists
  - Istradefylline (Nourianz™)
  - NMDA Antagonists
  - amantadine IR (Symmetrel™)
  - amantadine ER (Osmolex™, Gocovri™)

COMT= catechol-O-methyltransferase; MAO-B=monoamine oxidase-B; NMDA=N-methyl-D-aspartate

Newly approved medication from 2018

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Important Points About the New Approved Medications Between 2018-Present?

• **Place in Therapy:** 5 are an adjunctive treatments to CD/LD with or without other dopaminergic therapies (advanced PD) and 1 is new fractional tablet of CD/LD for maintenance therapy (early and advanced PD)
  - A. Maintenance adjunct therapies = lengthen the effect of CD/LD dose
  - B. Maintenance monotherapy/main therapy = more individualized dosing
  - C. Rescue, intermittent therapies = as needed to cover “off” period

• **Type of Therapy:** Symptomatic addressing motor symptoms/complications

• **Pharmacologic Effect:** Restoration of dopaminergic tone in the striatum

• **Impact on PD:** only dopamine-dependent motor features
  - o Management of motor fluctuations (“off” periods or dyskinesia) and reducing “off” time
  - o Improvement of function and quality of life

CD/LD= carbidopa/levodopa
2018 Approvals (N=2)

- Adjunctive therapy to manage dyskinesia
- Rescue therapy for “off” periods
Amantadine in PD

• Primarily used as an antidyskinetic agent

• **Mechanisms of action:**
  1. Noncompetitive NMDA glutamate receptor antagonism: aids with dyskinesia
  2. Direct/indirect effect on dopaminergic system: aids with motor symptoms
  3. Mild anticholinergic effect: PD benefit?

• Special dosing consideration: renal adjustment (dosing and/or frequency) needed as 85% of the administered dose is excreted unchanged in urine

• Adverse effects (AEs): dopaminergic (including psychosis) and mild anticholinergic AEs but also leg swelling, dizziness, livedo reticularis

• Available as immediate-release under brand name Symmetrel™ (tablet, capsule) and two extended-release formulations (tablet, capsule)

Amantadine Extended-Release Formulations

2018
Extended-Release Tablets (Osmolex ER™)  
- Once daily administration (morning)
- Tablet
- Cannot be crushed (swallowed whole)
- Dose: 129-322 mg/daily
- Adjustments in moderate-severe renal impairments
- CI: ESRD (CrCl< 15 mL/min)
- Treatment of PD and drug-induced EPS

2017
Extended-Release Capsules (Gocovri™)  
- Once daily administration (bedtime)
- Capsule
- Can be opened/sprinkled on applesauce
- Dose: 137-274 mg/daily
- Adjustments in moderate-severe renal impairments
- CI: ESRD (CrCl< 15 mL/min)
- Treatment of dyskinesia and “off” periods

PD Rescue Therapy Introduction

• Non-dependent on duodenal absorption
• Fast onset of action in 10-15 min
• Maximum 5 times/day; the dose needs to be separated by ≥ 2 hours
• Intermittent use for “off” periods
  o Unpredictable “off periods”
  o Morning akinesia
  o Delayed-onset
  o Dose failures

https://neuroderm.com/resources-2/

SL= sublingual
Levodopa Inhalation Powder (Inbrija™)

- On-demand rescue medication for “off” periods
- ONLY administered to patients who are treated with CD/LD
- Onset in 10 minutes lasting up to 60 minutes
- Intermittent treatment: up to 5 times/day
- AEs: cough, upper respiratory tract infection, nausea, and discolored sputum
- Not recommended in patients with asthma/COPD/other chronic lung disease due to bronchospasm risk

Inhalation Levodopa Administration

• Breath-actuated inhaler (Acura System with dry powder)
• One dose is 84 mg LD = 2 separate inhalations of 42 mg capsule of LD
• No pre-loading: Capsule needs to be loaded right before administration
• Need for dexterity or caregiver support
Self-Assessment Question #1

Which of the following is TRUE about inhalation levodopa?

A. It is used as a maintenance therapy in advanced Parkinson disease
B. It can be used up to 5 times daily
C. It cannot be combined with other carbidopa/levodopa formulations
D. It is a maintenance therapy designed for patients with dysphagia
Self-Assessment Question #1

Which of the following is TRUE about inhalation levodopa?

A. It is used as a maintenance therapy in advanced Parkinson’s disease
B. **It can be used up to 5 times daily**
C. It cannot be combined with other carbidopa/levodopa formulations
D. It is a maintenance therapy designed for patients with dysphagia
2019 Approvals (N=1)

• Adjunctive therapy to manage “off” periods
Istradefylline (Nourianz™) and Adenosine Receptors

• Novel mechanism of action: Selective adenosine A2A receptor antagonist
• Oral formulation (tablets)
• Adjunctive to carbidopa/levodopa for management “off” episodes
  o Increased “on time” and decreased “off time” by about 60 minutes

Adenosine A2A Receptor Antagonists in PD

DOPAMINERGIC DEFICIT

Adenosine A$_{2A}$ receptors OVERACTIVATION

OVERACTIVATION of striatopallidal output

SUPPRESSION of the thalamocortical activation

ISTRADEFYLLINE

DOPAMINERGIC DEFICIT

Adenosine A$_{2A}$ receptors blockade

REDUCTION of the overactive striatopallidal output

INDUCTION of the thalamocortical activation

Istradeffylline (Nourianz™)

• Initial daily dose 20 mg (max 40 mg/day)
• Primarily metabolized via CYP1A1 and CYP3A4

• Special dosing considerations:
  - Patient smoking ≥ 20 cigarettes/day requires 40 mg/day
  - Patients on strong CYP3A4 inhibitors: 20 mg/day
  - Patient on strong CYP3A4 inducers: avoid use

• AEs: dyskinesia, dizziness, constipation, nausea, hallucination, insomnia

• Not causing orthostatic hypotension as other dopaminergic medications
2020 Approvals (N=2)

- Adjunctive therapy to manage “off” periods
- Rescue therapy for “off” periods
COMT Inhibitors

- New addition in 2020: opicapone (Ongentys™)
- Block degradation of LD/Increased LD brain bioavailability = Only as adjunct to CD/LD therapy
- Decrease “off” time by 60 minutes

![Diagram of COMT Inhibitors]

INCREASED LEVODOPA EXPOSURE

UP TO 74%
Up to 74% increase in total levodopa exposure, which may allow more levodopa to reach the brain\textsuperscript{1,2}

Opicapone vs Entacapone

**Opicapone (Ongentys™)**
- Brand
- High COMT affinity but similar efficacy
- Long effect: once-daily dosing (50 mg capsule at bedtime)
- Unique AEs*: constipation
- Special lab monitoring: no

**Entacapone (Comtan™)**
- Generic
- Lower COMT affinity but similar efficacy
- Short effect: 200 mg needs to be given with each dose of CD/LD
  o CD/LD/entacapone (Stalevo™)
- Unique AEs*: delayed diarrhea, orange/brown urine discoloration
- Special lab monitoring: no

* Common AEs of all COMT inhibitors: dyskinesia, confusion, hallucinations, orthostasis, nausea/vomiting

# Opicapone vs Tolcapone

**Opicapone (Ongentys™)**
- Brand
- High COMT affinity but similar efficacy
- Long effect: once-daily dosing (50 mg at bedtime)
- Unique AEs*: constipation
- Special lab monitoring: no

* Common AEs of all COMT inhibitors: dyskinesia, confusion, hallucinations, orthostasis, nausea/vomiting

**Tolcapone (TasMar™)**
- Generic
- Lower COMT affinity but similar efficacy
- Shorter effect: 100-200 mg TID dosing
- Unique AEs*: delayed diarrhea, orange/brown urine discoloration
- Special lab monitoring: yes
  - LFT at baseline and follow-up in the first 6 months and patient needs to sign a consent form

Apomorphine in PD

• Non-ergoline dopamine receptor agonist (D1-D5 receptors)
• Only antiparkinson medication with the same effect/potency as levodopa
• No/low oral bioavailability = only parenteral administration
• Short-acting (short half-life)
• FDA-approved formulations for intermittent “rescue” use of apomorphine
  o Onset in 15 minutes lasting up to 90 minutes
  o Administered 5 times a day
  o Each dose needs to be separated by ≥ 2 hours
• New NDA submission for new formulation of continuous subcutaneous (Sub-Q) apomorphine infusion as maintenance therapy

Apomorphine Administration Clinical Pearls

- First dose administered under medical supervision
- Need to monitor blood pressure and heart rate
- Nausea was reported with the use of apomorphine
  - Recommended to premedicate (3 days) with trimethobenzamide 300 mg three times daily. Continue with trimethobenzamide until nausea/vomiting are no longer problem (no longer < 2 months)
  - **Do NOT** administer with 5-HT3 antagonists (e.g. ondansetron): risk of severe hypotension
  - Interim *ad hoc* analysis of CTH-301 study shows 82% (145 patients) of de novo U.S. patients underwent titration without the use of an antiemetic and of these patients, 88% were successfully titrated to an effective and tolerable dose of apomorphine SL.

Apomorphine Formulations

**Apomorphine* Sublingual Film (Kynmobi™) 2020**

- Two-layer film: Apomorphine/acid neutralizer
- Starting dose: 10 mg
- Titration: 5 mg increments
- Dosing: 10-30 mg/dose
- No dose adjustment for mild-moderate renal impairment
- Avoid in CrCl<30 mL/min
- Common AEs: nausea, oropharyngeal reactions (swelling, pain), dizziness, paraesthesia, somnolence

*Educate and watch for impulse control disorder (ICD)*

**Apomorphine* Subcutaneous Injection (Apokyn™)**

- Multi-dose pen with supplied cartridges (30 mg/3mL)
- Starting dose: 0.2 ml
- Titration: 0.1 mL increments
- Dosing: 0.2-0.6 mL
- In mild-moderate renal impairment initial/testing dose: 0.1 mL
- Not studied in CrCl<30 mL/min
- Common AEs: nausea and/or vomiting, orthostasis, injection site reaction, yawning, dyskinesia, dizziness, drowsiness/somnolence, rhinorrhea


Self-Assessment Question #2

A 72-year-old male with a 6-year-old history of Parkinson’s disease is having difficulty with increasing frequency of dyskinesia and associated falls and about 30 minutes of “off” time each day. His current medications are: carbidopa/levodopa 25/100 2 tablets three times daily and pramipexole extended-release 3 mg in the evening. He is a heavy smoker (30-40 cigarettes/day). What would be the most appropriate recommendation to manage this patient?

A. Add opicapone 50 mg in the evening
B. Add amantadine extended-release tablet in the morning
C. Add sublingual apomorphine 10 mg as needed
D. Add istradefylline 40 mg once daily
Self-Assessment Question #2

A 72-year-old male with a 6-year-old history of Parkinson’s disease is having difficulty with increasing frequency of dyskinesia and associated falls and about 30 minutes of “off” time each day. His current medications are: carbidopa/levodopa 25/100 2 tablets three times daily and pramipexole extended-release 3 mg in the evening. He is a heavy smoker (30-40 cigarettes/day). What would be the most appropriate recommendation to manage this patient?

A. Add opicapone 50 mg in the evening
B. Add amantadine extended-release tablet in the morning
C. Add sublingual apomorphine 10 mg as needed
D. Add istradefylline 40 mg once daily
2022 Approvals (N=1)

- Maintenance monotherapy with individualized dosing
Carbidopa/Levodopa Immediate-Release Tablet (DHIVY™)

• Tablets: 25 mg carbidopa and 100 mg levodopa
• Unique design = Fractional tablet
  o CD/LD 6.25 mg/25 mg increments
• Accurate and reliable fractioning of tablet = Ability to better customize CD/LD therapy for personalized management based on clinical response and tolerability
  o Control of motor symptoms
  o Management of “off” episodes and dyskinesia
• Initial dose: 1 tablet TID (this provides for 75 mg of CD)
• Titration: dosage may be increased by up to one whole tablet every day or every other day
In Development/Pipeline

- Infusion device delivery system for apomorphine
- Subcutaneous infusion system of CD/LD
- Oral sustained-release formulations of CD/LD
Continuous Sub-Q Apomorphine Infusion

- Apomorphine infusion device (SPN-830) from Supernus Pharmaceuticals
  - Resubmission of New Drug Application (NDA) in December 2022 for the continuous treatment of motor fluctuations in PD
- Continuous delivery of apomorphine through 16-24 hours
- Target: Patients with advanced PD with motor fluctuations not optimally controlled by oral medications
- Less invasive than intrajejunal CD/LD infusion or DBS and fully reversible method of delivery of apomorphine with minimal contraindications
- NOTE: Currently, a phase 3 trial (EARLY-PUMP) is underway to determine if continuous Sub-Q apomorphine administration in earlier stages of PD

DBS=deep brain stimulation
Continuous Sub-Q Apomorphine Infusion

- 16-24 hour daytime treatment
- Total daily dose:
  - Maintenance dose with possibility of extra bolus
- Initiation through gradual titration during hospital stay or clinic visits every few days/week
- Benefits:
  - Reduction of “off” time by ~2 h and CD/LD dose
  - Improvement of nocturnal akinesia (24-hour infusion)
  - CD/LD dose reduction and dose reduction/elimination of other antiparkinson medications
  - Dyskinesia improvement
- AEs: skin nodules, nausea, somnolence, hallucinations, orthostatic hypotension, hemolytic anemia (<1%; Coombs test). Watch for development of ICD.

Very thin small needle applied under skin in abdomen, upper thigh or upper back

Continuous Sub-Q CD/LD Infusion (Phase 3)

• Provision of 16-24-hour continuous subcutaneous delivery of liquid formulation of CD/LD (1:4) via external pump

• Increased bioavailability and reduced variability of LD plasma levels = more reliable, sustained relief of motor fluctuations in PD

• Patients with advanced PD with motor fluctuations not optimally controlled by oral medications

• Less invasive, reversible and easily implemented in-office setting that intrajejunal CD/LD gel

• Several different devices/formulations:
  o Phase 3: ABBV-951 and ND0612
  o Phase 1: Infudopa SubC (NCT03419806)
Continuous Sub-Q CD/LD Infusion (Phase 3)

**ABBV-951**: AbbVie (NCT0438042)
- Foslevodopa/Foscarbidopa = soluble formulation of LD and CD phosphate prodrugs
  - Stability, solubility
- Delivered via ChronoPar ambulatory infusion pump

**ND0612**: NeuroDerm (NCT04006210)
- 2 doses in development:
  - Low-dose (ND0612L): moderate PD
  - Higher dose (ND0612H): severe PD
- Delivered via belt pump
- Delivered via patch-pump
New Oral Formulations of CD/LD (Phase 3)
Possibly slight improvement over CD/LD extended-release capsule (Rytary™)

Accordion Pill (NCT02605434)
- CD/LD (1:4) extended-release with gastro-retentive properties
- Multilayer biodegradable polymeric film enclosed in capsule that unfolds in the stomach
- Stomach retention~8 hours without meal requirements
- Improved pharmacokinetics (improved absorption, more stable LD exposure)
- Failed meet the primary end-points (Accordance Trial)

IPX203 (NCT03670953)
- CD/LD (1:4) extended-release formulation (gastro-retentive capsule)
- Special beads releasing CD/LD more continuously in a steady-state for a prolonged period of time
  - IR granules: quick rise of LD concentration,
  - ER granules: prolonged/steady LD levels
- Increased on time with non-troublesome dyskinesia
- Less frequent dosing (2-3 times daily vs 4-5 times daily with IR CD/LD)
- Amneal Pharmaceuticals plans for NDA submission in mid 2022

Concluding Remarks

• No disease modifying/neuroprotective therapy available

• Between 2018 to 2022, 6 newly-approved adjunct medications to CD/LD for management of motor symptoms/motor fluctuations in advanced PD

  **(A) Maintenance daily therapies for “off” episode or dyskinesia**
  - COMT inhibitor (oral opicapone)
  - Adenosine A2A receptor antagonist (oral istradefylline)
  - NMDA-receptor antagonist/dopamine modulator (oral amantadine extended-release)
  - Dopamine precursor (oral CD/LD immediate-release tablet with 6.25/25 mg increment scoring)

  **(B) Intermittent “rescue” therapies**
  - Dopamine precursor (inhalation levodopa)
  - Dopamine receptor agonist (sublingual apomorphine film)

• New promising formulations/delivery systems of apomorphine and CD/LD are in development
What questions do you have?

Thank you for attending!

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