

# UNDERSTANDING MEDICATION THERAPY TREATMENT OPTIONS FOR PARKINSON'S DISEASE

A presentation for HealthTrust Members  
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# SPEAKER DISCLOSURES

- The presenter has no real or perceived conflicts of interest related to this presentation.
- Note: This program may contain the mention of suppliers, brands, products, services or drugs presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular supplier, brand, product, service or drug.

# LEARNING OBJECTIVES FOR PHARMACISTS

- Recall the pathophysiology of Parkinson's disease (PD) and determine how medications improve motor and non-motor symptoms based on their mechanism of action
- Describe pharmacologic characteristics of various medications used in the treatment of Parkinson's disease
- Select an appropriate agent based on current best practices for a specific patient to treat symptoms associated with Parkinson's disease

# LEARNING OBJECTIVES FOR PHARMACY TECHNICIANS

- Describe the mechanism of action of the drugs used to treat Parkinson's disease
- Discuss the side effects of the drugs used to treat Parkinson's disease

# AN ESSAY ON THE SHAKING PALSY - JAMES PARKINSON, 1817



- *“The disease... is of a nature highly afflictive... the unhappy sufferer has considered it as an evil, from the domination of which he has no prospect of escape...”*
- *“Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.”*

#### Sources:

- Parkinson J. An Essay on the Shaking Palsy. *J Neuropsychiatry Clin Neurosci*. 2002;14(2):223-236.
- Image from: [https://commons.wikimedia.org/wiki/File:Sir\\_William\\_Richard\\_Gowers\\_Parkinson\\_Disease\\_sketch\\_1886.jpg](https://commons.wikimedia.org/wiki/File:Sir_William_Richard_Gowers_Parkinson_Disease_sketch_1886.jpg)

# EPIDEMIOLOGY OF PD

## Prevalence

By 2020, estimated nearly one million people will be living with PD in the U.S.

- By 2030, predicted to rise to 1.2 million

## Incidence

Every year, approximately 60,000 Americans are diagnosed with PD

## Estimated U.S. Healthcare Costs

Nearly \$52 billion per year in direct and indirect costs

- Average cost of medications - \$2,500 per year
- Cost of therapeutic surgery – up to \$100,000 per person

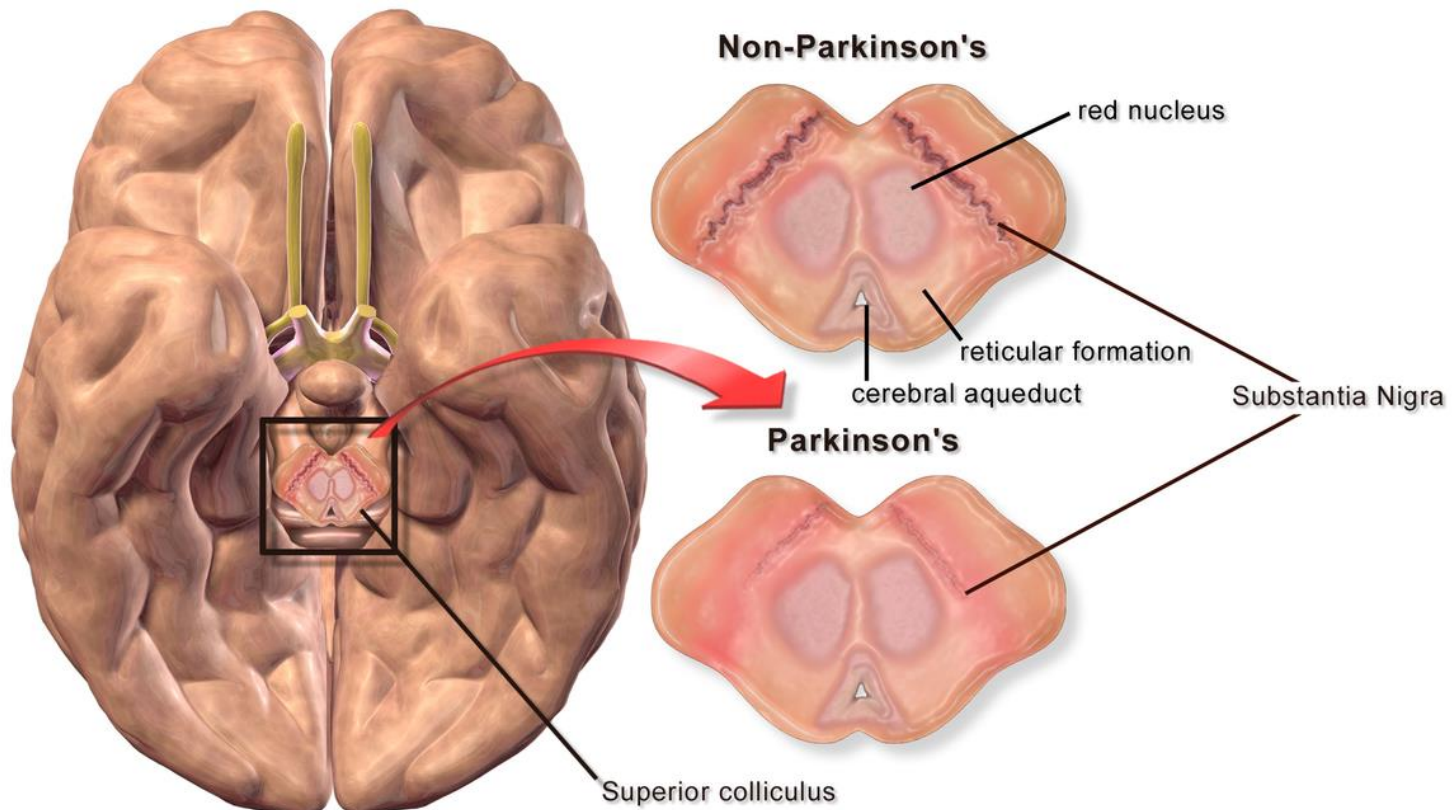
Source:

- Statistics. Parkinson's Foundation. <https://www.parkinson.org/Understanding-Parkinsons/Statistics>. Accessed 10/14/2019.

# ETIOLOGY OF PD

Modifiable Risk Factors	Non-Modifiable Risk Factors
Cigarette smoking – inversely correlated	Age
Caffeine – inversely correlated	Geographic region
Pesticide/herbicide exposure	Family history
	Sex

# PATHOLOGY OF PD



Pathological hallmark – depigmentation with dopaminergic neuronal loss in the substantia nigra

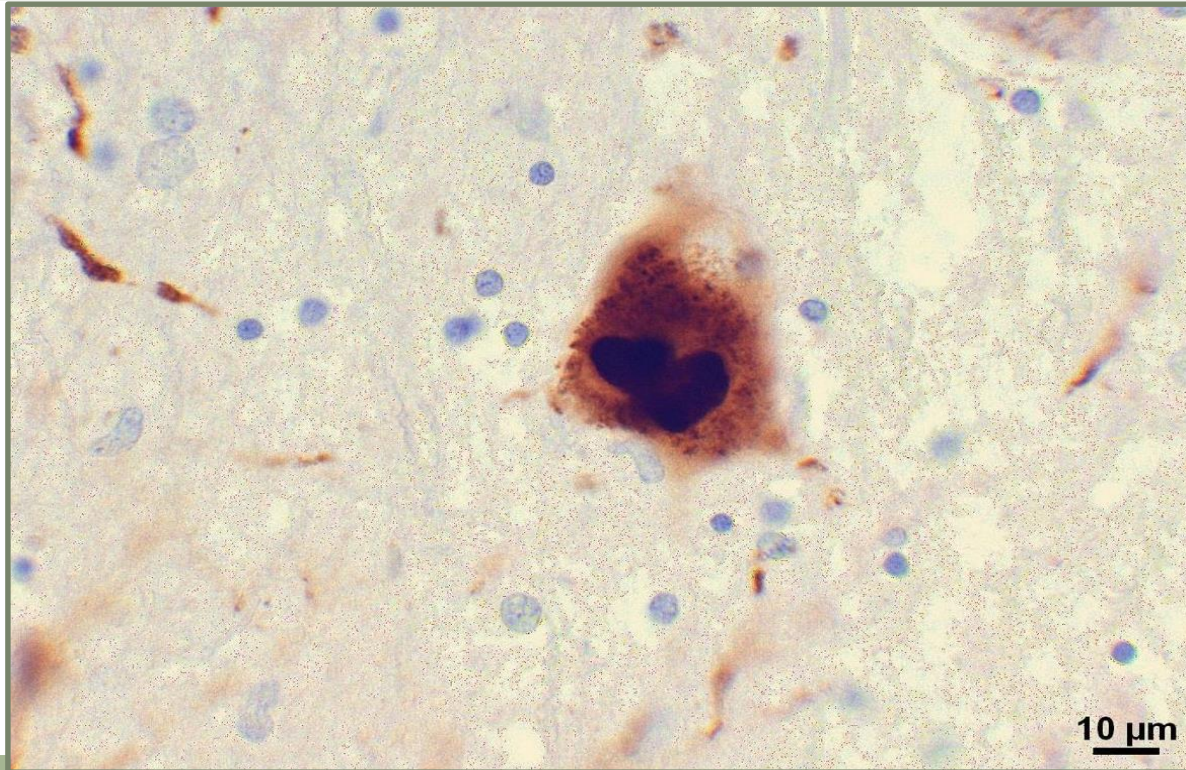
## Sources:

- Hayes MT. Parkinson's Disease and Parkinsonism. *Am J Med.* 2019;132:802-807. DOI:10.1016/j.amjmed.2019.03.001
- Image from: [https://commons.wikimedia.org/wiki/File:Blausen\\_0704\\_ParkinsonsDisease.png](https://commons.wikimedia.org/wiki/File:Blausen_0704_ParkinsonsDisease.png)



# PATHOLOGY OF PD

Lewy bodies\* noted in affected areas of neuronal loss



\*Lewy body: an immunoreactive, abnormal cytoplasmic deposit of the protein  $\alpha$ -synuclein within neuronal cell bodies

## Sources:

- Antonina K, Torsney KM, Kuan W. *Parkinson's Disease: Pathogenesis and Clinical Aspects. Chapter 1 Parkinson's Disease: Etiology, Neuropathology, and Pathogenesis*. Brisbane, QLD 4122, Australia: Codon Publication; 2018.
- Hayes MT. Parkinson's Disease and Parkinsonism. *Am J Med*. 2019;132:802-807. DOI:10.1016/j.amjmed.2019.03.001
- Image from: [https://commons.wikimedia.org/wiki/File:Lewy\\_bodies\\_\(alpha\\_synuclein\\_inclusions\)\\_1.jpg](https://commons.wikimedia.org/wiki/File:Lewy_bodies_(alpha_synuclein_inclusions)_1.jpg)

# CLINICAL PRESENTATION OF PD

Motor  
symptoms

```
graph TD; A[Motor symptoms] --- B[Tremor]; A --- C[Bradykinesia]; A --- D[Postural instability]; A --- E[Rigidity]
```

Tremor

Bradykinesia

Postural  
instability

Rigidity

# CLINICAL PRESENTATION OF PD

Non-motor  
symptoms

```
graph TD; A[Non-motor symptoms] --- B[Anosmia]; A --- C[Cognitive decline]; A --- D[Mood changes]; A --- E[Dysautonomia]; A --- F[Sleep disturbances];
```

Anosmia

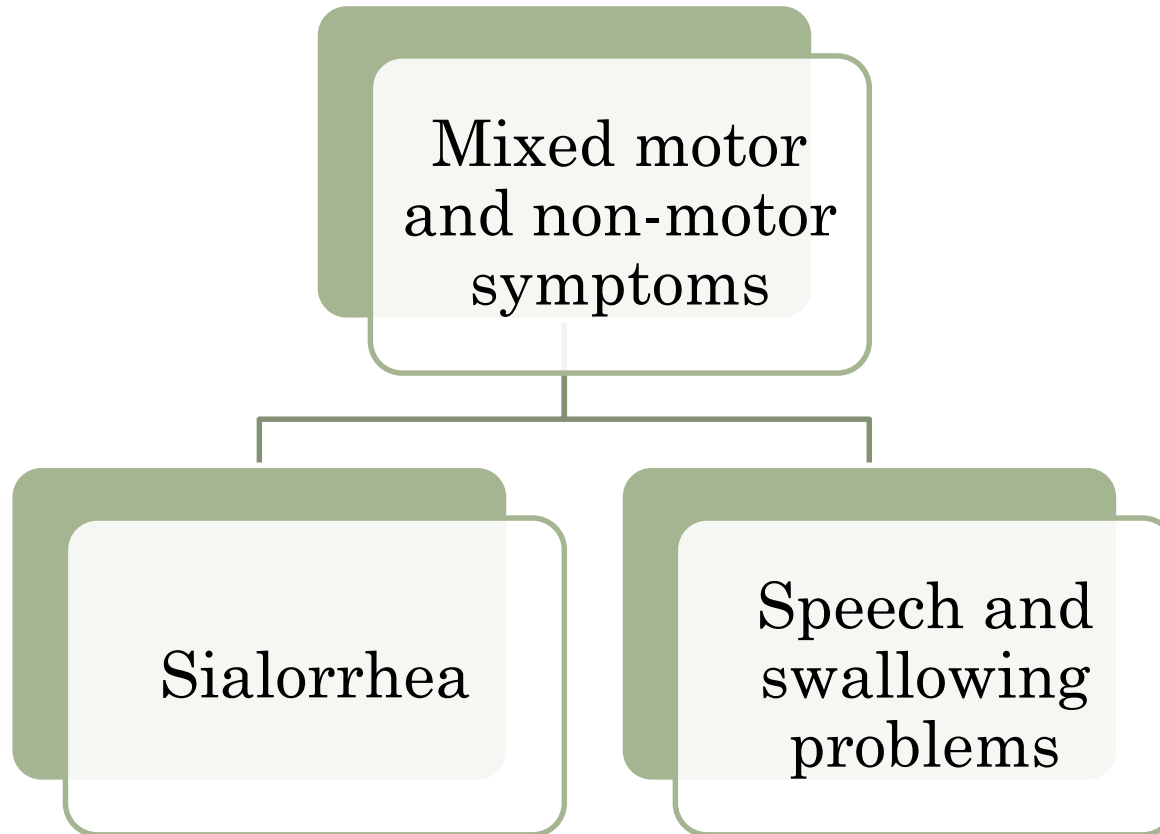
Cognitive  
decline

Mood changes

Dysautonomia

Sleep  
disturbances

# CLINICAL PRESENTATION OF PD



# DIAGNOSIS OF PD

## Movement Disorder Society (MDS) Diagnostic Criteria for PD

- Parkinsonism:
  - Bradykinesia PLUS
  - Tremor or rigidity
- Parkinsonism is an ESSENTIAL criteria required for diagnosis
- Examination of all cardinal manifestations should be carried out using MDS-Unified Parkinson Disease Rating Scale

### Sources:

- Antonina K et al. *Parkinson's Disease: Etiology, Neuropathology, and Pathogenesis*. 2018.
- Chou KL. Diagnosis and differential diagnosis of Parkinson disease. 2019.
- How a Diagnosis is made. Parkinson's Foundation.
- International Parkinson and Movement Disorder Society. MDS-UPDRS: The MDS-sponsored Revision of the Unified Parkinson's Disease Rating Scale. 2008. [https://www.movementdisorders.org/MDS-Files1/PDFs/Rating-Scales/MDS-UPDRS\\_English\\_FINAL\\_Updated\\_August2019.pdf](https://www.movementdisorders.org/MDS-Files1/PDFs/Rating-Scales/MDS-UPDRS_English_FINAL_Updated_August2019.pdf). Accessed 10/5/2019.

# DIAGNOSIS OF PD

## Movement Disorder Society Unified Parkinson Disease Rating Scale (MDS-UPDRS)

### Part I:

- Non-motor experiences of daily living

### Part II:

- Motor experiences of daily living

### Part III:

- Motor examination

### Part IV:

- Motor complications

#### Sources:

- Chou KL. Diagnosis and differential diagnosis of Parkinson disease. Hurtig HI and Eichler AF, ed. UpToDate. Waltham, MA: UpToDate Inc. [https://www.uptodate.com/contents/diagnosis-and-differential-diagnosis-of-parkinson-disease?search=diagnosis%20of%20parkinsons&source=search\\_result&selectedTitle=1~150&usage\\_type=default&display\\_rank=1](https://www.uptodate.com/contents/diagnosis-and-differential-diagnosis-of-parkinson-disease?search=diagnosis%20of%20parkinsons&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1). Updated August 5, 2019. Accessed October 3, 2019.
- International Parkinson and Movement Disorder Society. MDS-UPDRS: The MDS-sponsored Revision of the Unified Parkinson's Disease Rating Scale. 2008. [https://www.movementdisorders.org/MDS-Files1/PDFs/Rating-Scales/MDS-UPDRS\\_English\\_FINAL\\_Updated\\_August2019.pdf](https://www.movementdisorders.org/MDS-Files1/PDFs/Rating-Scales/MDS-UPDRS_English_FINAL_Updated_August2019.pdf). Accessed 10/5/2019.

# DIAGNOSIS OF PD



## Supportive Criteria

- Clear and dramatic response to dopaminergic therapy
- Presence of levodopa-induced dyskinesia
- Resting tremor of a limb
- Presence of either olfactory loss or cardiac sympathetic denervation on  $^{131}\text{I}/^{123}\text{I}$ -metaiodobenzylguanidine (mIBG) scintigraphy

## Absolute Exclusion Criteria and Red Flags

- Examples include:
  - Drug-induced parkinsonism
  - Absence of observable response to high-dose levodopa



# DIAGNOSIS OF PD

## Movement Disorder Society (MDS) Diagnostic Criteria for PD

- Diagnosis of clinically established PD requires:
  - 1. Absence of absolute exclusion criteria
  - 2. At least two supportive criteria, and
  - 3. No red flags
- Diagnosis of clinically probable PD requires:
  - 1. Absence of absolute exclusion criteria
  - 2. Presence of red flags counterbalanced by supportive criteria



# CLINICAL PRESENTATION OF PD

Motor  
symptoms

```
graph TD; A[Motor symptoms] --- B[Tremor]; A --- C[Bradykinesia]; A --- D[Postural instability]; A --- E[Rigidity]
```

Tremor

Bradykinesia

Postural  
instability

Rigidity

## QUESTION 1:

- What is the most common medication used for the treatment of motor symptoms in PD?

# CORRECT RESPONSE

- carbidopa/levodopa

# MEDICATIONS FOR MOTOR SYMPTOMS

Carbidopa/  
Levodopa

Dopamine  
Agonists

Monoamine  
Oxidase Type B  
(MAO-B)  
Inhibitors

Catechol-O-Methyl  
Transferase  
(COMT) Inhibitors

Amantadine

Anticholinergic  
Drugs

# MEDICATIONS FOR MOTOR SYMPTOMS

Carbidopa/  
Levodopa

Dopamine  
agonists

MAO-B  
Inhibitors

COMT  
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Amantadine

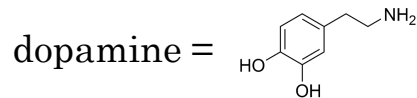
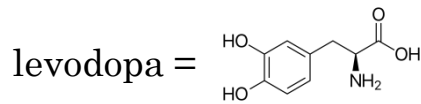
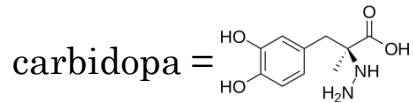
Anticholinergic  
Drugs

# CARBIDOPA/LEVODOPA

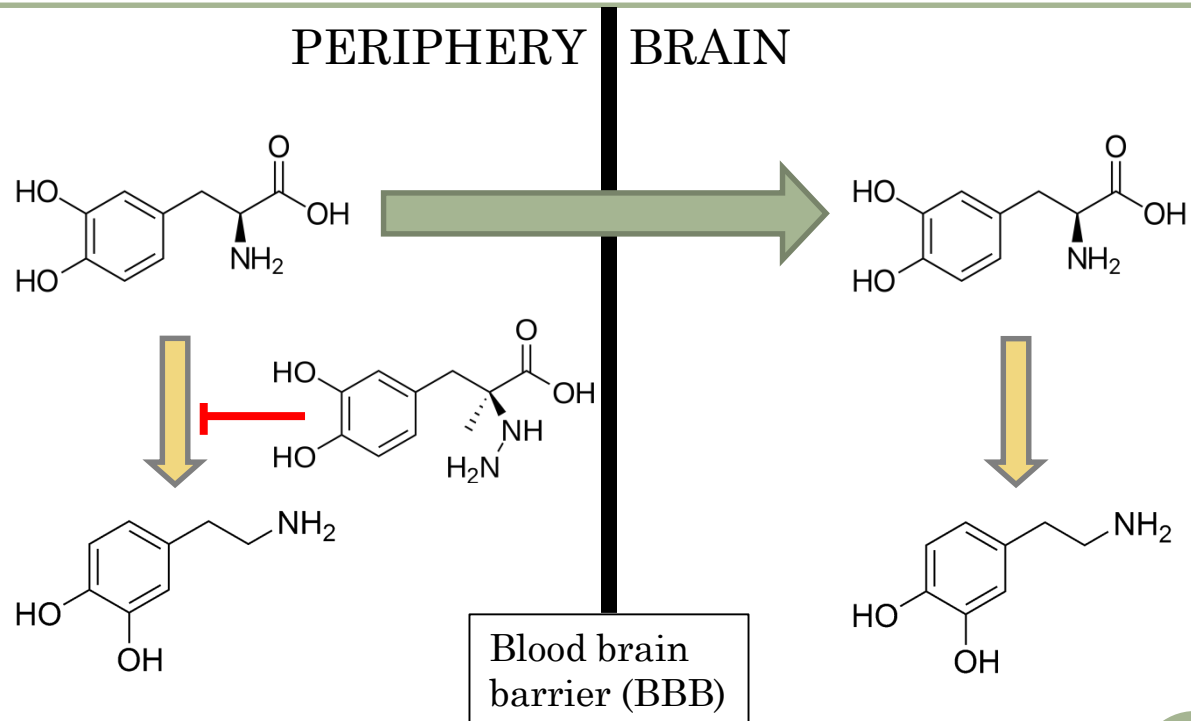
## Mechanism of Action

- Levodopa converts to dopamine in brain
- Carbidopa inhibits **peripheral** plasma conversion of levodopa to dopamine

### Key:



dopa decarboxylase = 



### Sources:

- Carbidopa and levodopa. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Barbeau A, Mars H, Botez MI, and Joubert M. Levodopa combined with peripheral decarboxylase inhibition in Parkinson's disease. *Can Med Assoc J.* 1972;106(11):1169-74.
- Images from: <https://en.wikipedia.org/wiki/Carbidopa#/media/File:Carbidopa.svg>, [https://en.wikipedia.org/wiki/L-DOPA#/media/File:3,4-Dihydroxy-L-phenylalanin\\_\(Levodopa\).svg](https://en.wikipedia.org/wiki/L-DOPA#/media/File:3,4-Dihydroxy-L-phenylalanin_(Levodopa).svg), and [https://commons.wikimedia.org/wiki/File:Dopamine\\_chemical\\_structure.png](https://commons.wikimedia.org/wiki/File:Dopamine_chemical_structure.png)

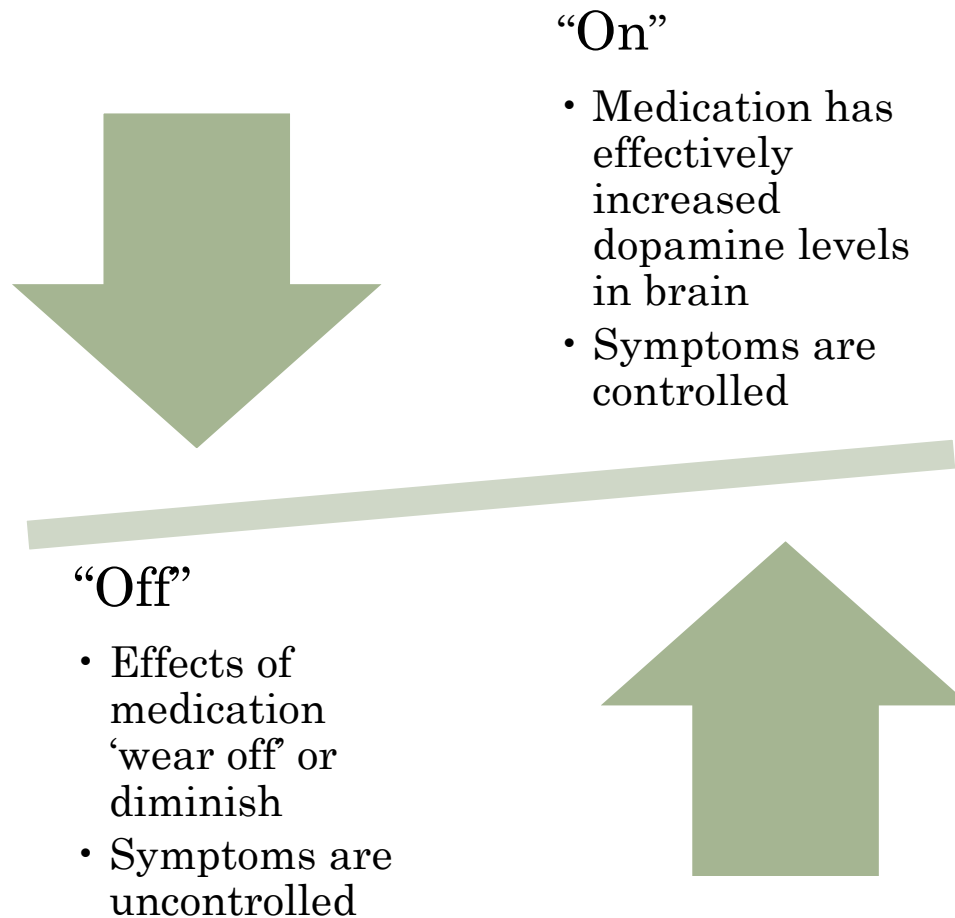
# SUMMARY OF CARBIDOPA/LEVODOPA

Formulation	Dosages in milligrams	Typical total daily dose	Usage
Carbidopa/levodopa immediate-release tablet (Sinemet®)	10/100, 25/100, 25/250	150 to 1000 mg of levodopa	Monotherapy or combination therapy for motor symptoms
Carbidopa/levodopa orally disintegrating tablet (Parcopa®)	10/100, 25/100, 25/250	150 to 1000 mg of levodopa	Same as above, plus benefit in swallowing impairment
Carbidopa/levodopa extended-release tablet (Sinemet® CR)	25/100, 50/200	150 to 1000 mg of levodopa	Monotherapy or combination therapy for motor symptoms
Carbidopa/levodopa/entacapone tablet (Stalevo®)	12.5/50/200, 18.75/75/200, 25/100/200, 31.25/125/200, 37.5/150/200, 50/200/200	150 to 1000 mg of levodopa	Same as above, plus benefit of entacapone to improve on/off fluctuations and dyskinesias
Carbidopa/levodopa extended-release capsule (Rytary®)	23.75/95, 36.25/145, 48.75/195, 61.25/245	855 to 2340 mg of levodopa	Monotherapy or combination therapy for motor symptoms
Carbidopa/levodopa enteral suspension (Duopa™)	4.63/20 per mL	Up to 2000 mg of levodopa	Advanced PD for patients who have difficulty managing on/off fluctuations and dyskinesias

Sources:

- Carbidopa and levodopa. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Houghton D, Hurtig H, and Metz S. Parkinson's Disease Medications. 2017. <https://www.parkinson.org/sites/default/files/attachments/Medications.pdf>. Accessed October 4, 2019.

# “ON/OFF” PHENOMENON WITH CARBIDOPA/LEVODOPA



\*Note: phenomenon typically seen after one to five years of levodopa use and as disease progresses

Source:

- Houghton D, Hurtig H, and Metz S. Parkinson’s Disease Medications. 2017. <https://www.parkinson.org/sites/default/files/attachments/Medications.pdf>. Accessed October 4, 2019.



# PHARMACOKINETIC CONSIDERATIONS OF CARBIDOPA/LEVODOPA

Formulation	Time to peak	Half-life	Typical dosing schedule
Carbidopa/levodopa immediate-release tablet (Sinemet®)	0.5 hours	1.5 hours	3 to 4 times daily
Carbidopa/levodopa orally disintegrating tablet (Parcopa®)	0.5 hours	1.5 hours	3 to 4 times daily
Carbidopa/levodopa extended-release tablet (Sinemet® CR)	2 hours	1.5 hours (may be prolonged due to continuous absorption)	2 times daily
Carbidopa/levodopa/entacapone tablet (Stalevo®)	0.5 hours	1.7 hours	2 to 4 times daily
Carbidopa/levodopa extended-release capsule (Rytary®)	1 to 2 hours	4 to 5 hours	3 to 5 times daily
Carbidopa/levodopa enteral suspension (Duopa™)	2.5 hours	1.5 hours	Continuous infusion over 16 hours

## Sources:

- Carbidopa and levodopa. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Houghton D, Hurtig H, and Metz S. Parkinson's Disease Medications. 2017. <https://www.parkinson.org/sites/default/files/attachments/Medications.pdf>. Accessed October 4, 2019.

# ADVERSE EFFECTS OF CARBIDOPA/LEVODOPA

Adverse Effect	Reported Frequency
Nausea	3 to 20%
Vomiting	2 to 5%
Anorexia	1%
Dizziness	2 to 19%
Orthostatic hypotension	1 to 5%
Confusion	2 to 8%
Dyskinesias	2 to 17%

## Sources:

- Carbidopa and levodopa. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Houghton D, Hurtig H, and Metz S. Parkinson's Disease Medications. 2017. <https://www.parkinson.org/sites/default/files/attachments/Medications.pdf>. Accessed October 4, 2019.

# DYSKINESIAS WITH CARBIDOPA/LEVODOPA

Dyskinesias: involuntary, erratic, writhing movements

- Typically not seen until 3 to 5 years after starting levodopa
- Higher doses of levodopa necessary for symptom control as disease progresses
- Difficult in later stages of disease to have smooth “on” phases
- Occurs when the levodopa dose required to produce an “on” phase is too high



# MEDICATIONS FOR MOTOR SYMPTOMS

Carbidopa/  
Levodopa

Dopamine  
agonists

MAO-B  
Inhibitors

COMT  
Inhibitors

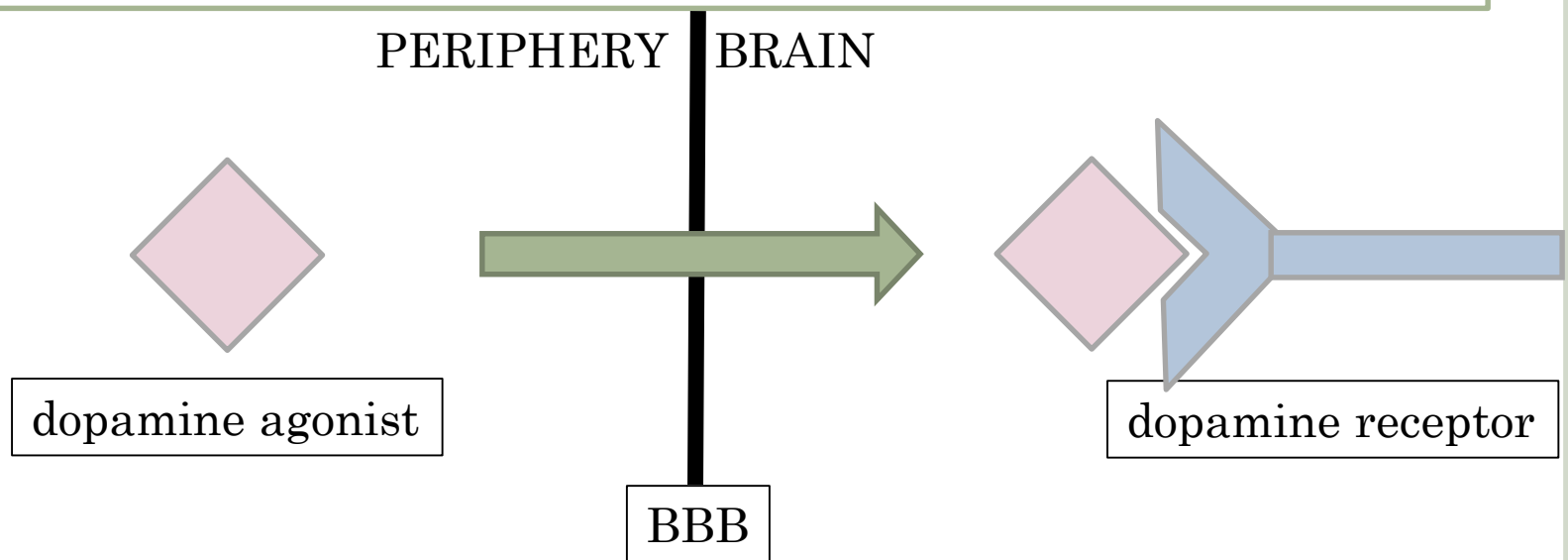
Amantadine

Anticholinergic  
Drugs

# DOPAMINE AGONISTS

## Mechanism of Action

- Directly bind to dopamine receptors in the brain



### Sources:

- Ropinirole. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Houghton D, Hurtig H, and Metz S. Parkinson's Disease Medications. 2017. <https://www.parkinson.org/sites/default/files/attachments/Medications.pdf>. Accessed October 4, 2019.

# SUMMARY OF DOPAMINE AGONISTS

Formulation	Dosages in milligrams	Typical total daily dose	Usage
Ropinirole tablet (Requip®)	0.25, 0.5, 1, 2, 3, 4, 5	9 to 24 mg	Monotherapy or combination therapy for motor symptoms
Ropinirole extended-release tablet (Requip XL®)	2, 4, 6, 8, 12	8 to 24 mg	Same as above
Pramipexole tablet (Mirapex®)	0.125, 0.25, 0.5, 0.75, 1, 1.5	1.5 to 4.5 mg	Same as above
Pramipexole extended-release tablet (Mirapex ER®)	0.375, 0.75, 1.5, 2.25, 3, 3.75, 4.5	1.5 to 4.5 mg	Same as above
Rotigotine transdermal system (Neupro®)	1, 2, 3, 4, 6, 8	4 to 8 mg	Same as above plus benefit of non-oral formulation if difficulty swallowing
Apomorphine Injection (Apokyn®)	30 per 3 mL vial	2 to 6 mg	Adjunct therapy for sudden “wearing off”

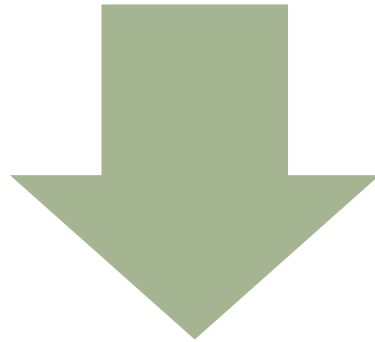
## Sources:

- Ropinirole. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Pramipexole. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Rotigotine. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Apomorphine. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Houghton D, Hurtig H, and Metz S. Parkinson's Disease Medications. 2017. <https://www.parkinson.org/sites/default/files/attachments/Medications.pdf>. Accessed October 4, 2019.

# “ON/OFF” PHENOMENON WITH CARBIDOPA/LEVODOPA

## “On”

- Medication has effectively increased dopamine levels in brain
- Symptoms are controlled



## “Off”

- Effects of medication ‘wear off’ or diminish
- Symptoms are uncontrolled



Dopamine agonists can be utilized to reduce intensity of “wearing off”

\*Note: phenomenon typically seen after one to five years of levodopa use and as disease progresses

# PHARMACOKINETIC CONSIDERATIONS OF DOPAMINE AGONISTS

Formulation	Time to peak	Half-life	Comments
Ropinirole tablet (Requip®)	1 to 2 hours	6 hours	<ul style="list-style-type: none"> <li>• Time to peak increased by 2.5 to 3 hours when taken with high-fat meal.</li> <li>• Renally eliminated, use with caution when CrCl is &lt;30 mL/min</li> </ul>
Ropinirole extended-release tablet (Requip XL®)	6 to 10 hours	6 hours	
Pramipexole tablet (Mirapex®)	2 hours	8.5 hours	<ul style="list-style-type: none"> <li>• Half-life may be up to 12 hours in elderly patients.</li> <li>• Requires renal adjustment when CrCl is ≤50 mL/min</li> </ul>
Pramipexole extended-release tablet (Mirapex ER®)	6 hours	8.5 hours	
Rotigotine transdermal system (Neupro®)	15 to 18 hours	5 to 7 hours after removal of patch	<ul style="list-style-type: none"> <li>• Has not been studied in severe hepatic impairment</li> </ul>
Apomorphine Injection (Apokyn®)	10 to 60 minutes	40 minutes	<ul style="list-style-type: none"> <li>• With renal impairment, recommended to initially use 1 mg as a test</li> </ul>

## Sources:

- Ropinirole. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Pramipexole. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Rotigotine. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Apomorphine. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
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# ADVERSE EFFECTS OF DOPAMINE AGONISTS

Adverse effect	Reported Frequency			
	Ropinirole	Pramipexole	Rotigotine	Apomorphine
Nausea	60%	11 to 28%	15 to 48%	30%
Vomiting	10 to 12%	4%	2 to 20%	30%
Anorexia	4%	4 to 5%	2 to 9%	Frequency not reported
Dizziness	6 to 40%	2 to 26%	5 to 23%	20%
Orthostatic hypotension	6 to 14%	3 to 53%	8 to 29%	20%
Confusion	5%	4 to 10%	<1%	10%
Dyskinesias	2%	17 to 47%	14 to 17%	24 to 35%
Drowsiness	≤40%	9 to 36%	5 to 32%	35%
Visual hallucinations	5%	3%	3 to 5%	10%
Peripheral edema	7%	2 to 8%	3 to 14%	10%
Compulsivity	Frequency not reported	3 to 4%	<1%	<1%
Application site reaction	n/a	n/a	21 to 46%	n/a

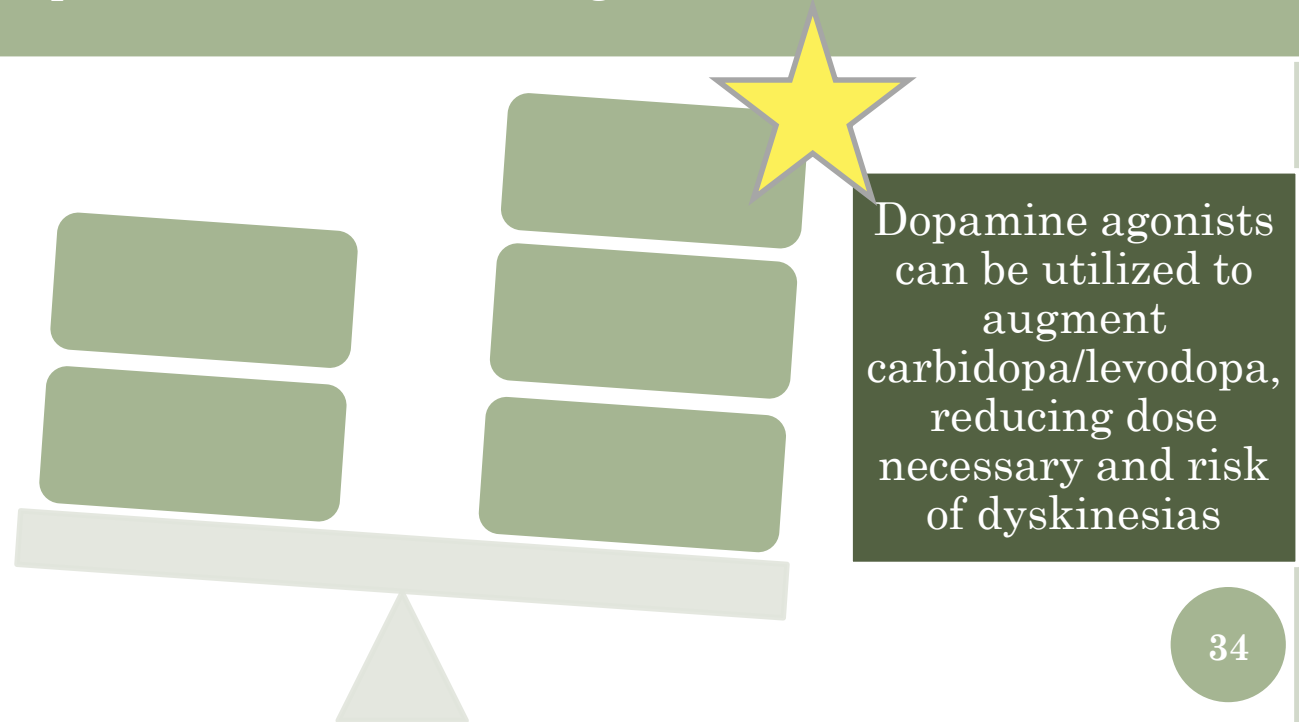
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- Pramipexole. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Rotigotine. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Apomorphine. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
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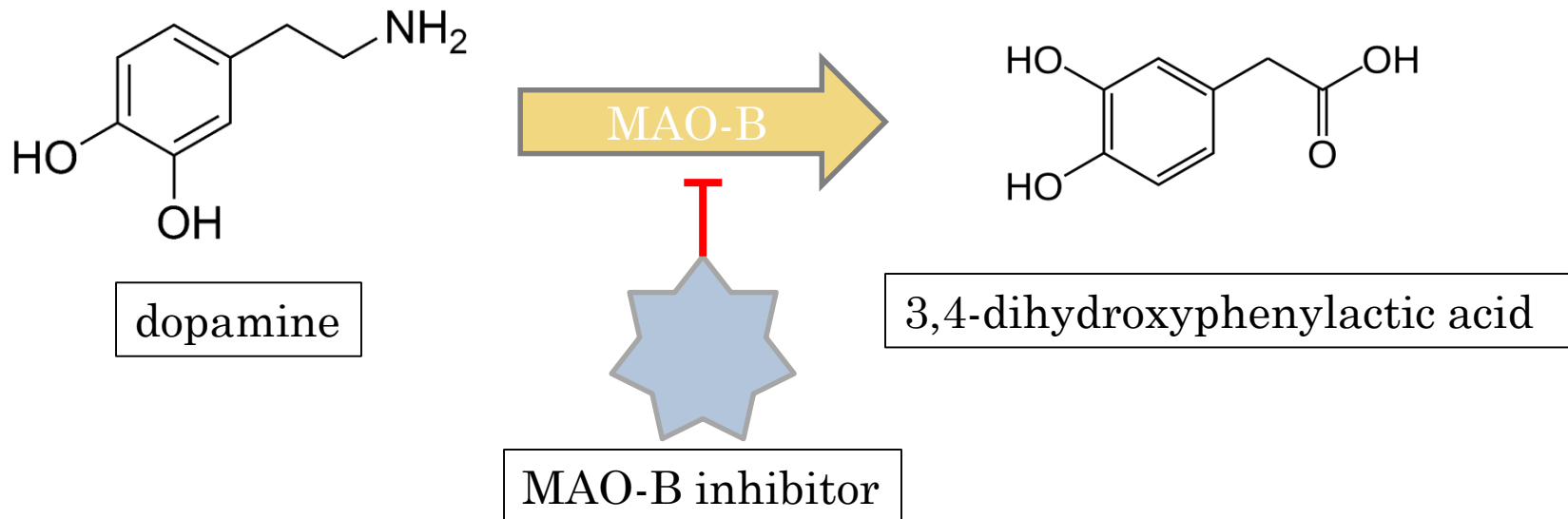
Amantadine

Anticholinergic  
Drugs

# MONOAMINE OXIDASE TYPE B (MAO-B) INHIBITORS

## Mechanism of Action

- Irreversibly inhibits MAO-B, preventing catabolism of dopamine



### Sources:

- Selegiline. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Houghton D, Hurtig H, and Metz S. Parkinson's Disease Medications. 2017. <https://www.parkinson.org/sites/default/files/attachments/Medications.pdf>. Accessed October 4, 2019.
- 3,4-Dihydroxyphenylacetic acid. U.S. National Library of Medicine National Center for Biotechnology Information. [https://pubchem.ncbi.nlm.nih.gov/compound/3\\_4-Dihydroxyphenylacetic-acid#section=GHS-Classification](https://pubchem.ncbi.nlm.nih.gov/compound/3_4-Dihydroxyphenylacetic-acid#section=GHS-Classification). Accessed October 21, 2019.
- Images from [https://commons.wikimedia.org/wiki/File:Dopamine\\_chemical\\_structure.png](https://commons.wikimedia.org/wiki/File:Dopamine_chemical_structure.png) and [https://en.wikipedia.org/wiki/3,4-Dihydroxyphenylacetic\\_acid0](https://en.wikipedia.org/wiki/3,4-Dihydroxyphenylacetic_acid0)

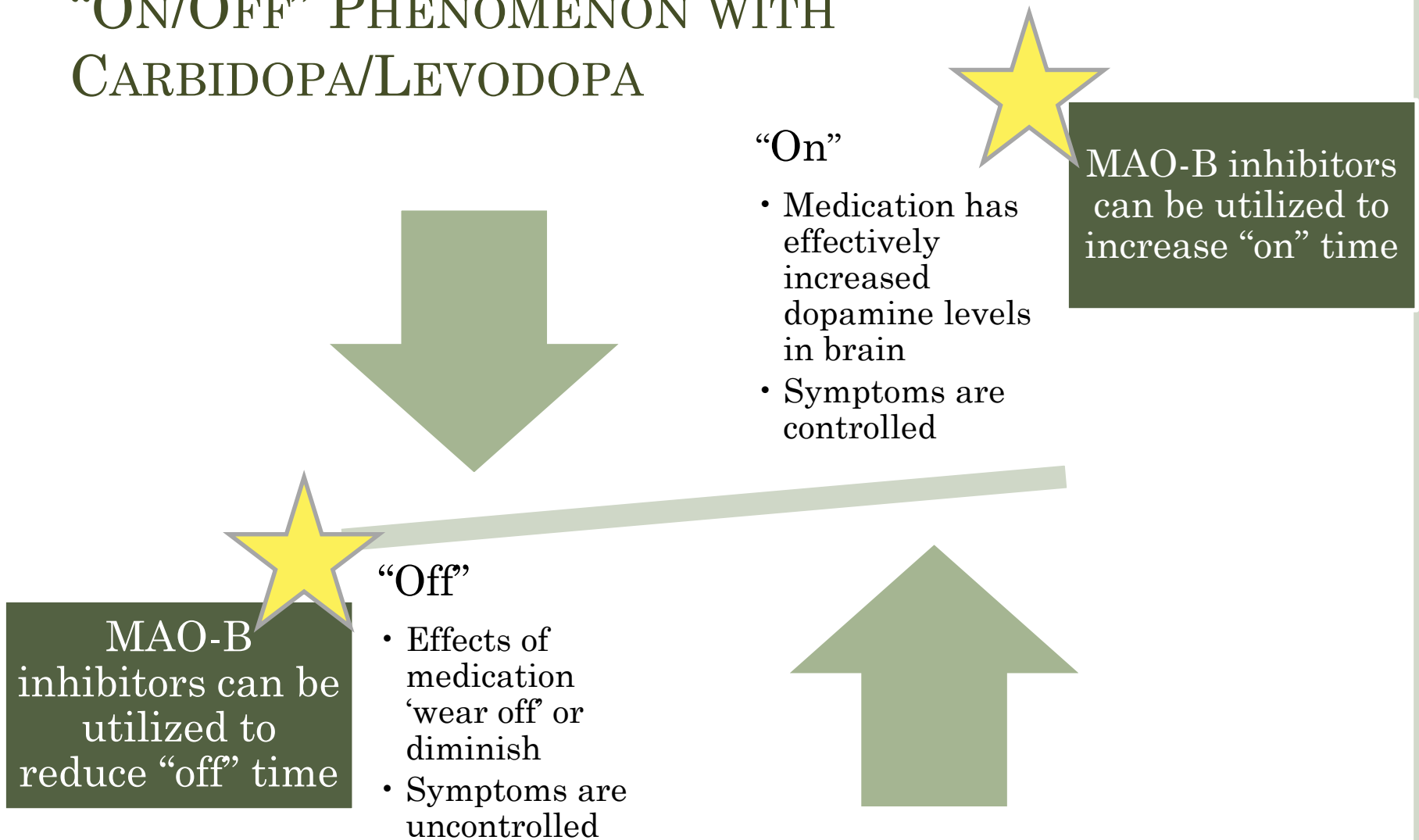
# SUMMARY OF MAO-B INHIBITORS

Formulation	Dosages in milligrams	Typical daily dose	Usage
Selegiline tablet, capsule	5	5 mg	Monotherapy for motor symptoms; adjunct therapy for motor fluctuations
Selegiline orally disintegrating tablet (Zelapar®)	1.25, 2.5	1.25 to 2.5 mg	Same as above. Formulation may be useful for patients unable to swallow tablets
Rasagiline tablet (Azilect®)	0.5, 1.0	1 mg	Monotherapy for motor symptoms; adjunct therapy for motor fluctuations
Safinamide tablet (Xadago®)	50, 100	50 to 100 mg	Same as above

## Sources:

- Selegiline. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Rasagiline. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Safinamide. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Houghton D, Hurtig H, and Metz S. Parkinson's Disease Medications. 2017. <https://www.parkinson.org/sites/default/files/attachments/Medications.pdf>. Accessed October 4, 2019.

# “ON/OFF” PHENOMENON WITH CARBIDOPA/LEVODOPA



\*Note: phenomenon typically seen after one to five years of levodopa use and as disease progresses

# PHARMACOKINETIC CONSIDERATIONS OF MAO-B INHIBITORS

Formulation	Time to peak	Half-life	Comments
Selegiline tablet, capsule	40 to 90 minutes	Single dose: 2 hours Steady state: 10 hours	<ul style="list-style-type: none"> <li>• Irreversible inhibition (duration of action longer than half-life)</li> <li>• Converts to amphetamine-like by-product in gut</li> <li>• Bioavailability increases 3 to 4 fold when taken with food</li> <li>• Has not been studied renal impairment</li> <li>• Has not been studied in hepatic impairment</li> </ul>
Selegiline orally disintegrating tablet (Zelapar®)	10 to 15 minutes	Single dose: 1.3 hours Steady state: 10 hours	<ul style="list-style-type: none"> <li>• Bioavailability increases 60% in fed state compared to fasted state</li> <li>• Not recommended if CrCl &lt;30 mL/min</li> <li>• Requires dose adjustment in mild to moderate hepatic impairment</li> <li>• Not recommended in severe hepatic impairment</li> </ul>
Rasagiline tablet (Azilect®)	1 hour	3 hours	<ul style="list-style-type: none"> <li>• Irreversible inhibition (duration of action one week)</li> <li>• Has not been studied in severe renal impairment</li> <li>• Requires dose adjustment in mild hepatic impairment</li> <li>• Not recommended in moderate to severe hepatic impairment</li> </ul>
Safinamide tablet (Xadago®)	2 to 3 hours	20 to 26 hours	<ul style="list-style-type: none"> <li>• Requires dose adjustment in moderate hepatic impairment</li> <li>• Contraindicated in severe hepatic impairment</li> </ul>

Sources:

- Selegiline. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Rasagiline. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Safinamide. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Houghton D, Hurtig H, and Metz S. Parkinson's Disease Medications. 2017. <https://www.parkinson.org/sites/default/files/attachments/Medications.pdf>. Accessed October 4, 2019.

# ADVERSE EFFECTS OF MAO-B INHIBITORS

Adverse effect	Reported Frequency		
	Selegiline	Rasagiline	Safinamide
Nausea	11 to 20%	6 to 12%	6%
Xerostomia	4 to 8%	2 to 6%	Not reported
Dizziness	11 to 14%	7%	4%
Constipation	1 to 4%	4 to 9%	Not reported

## Sources:

- Selegiline. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Rasagiline. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Safinamide. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Houghton D, Hurtig H, and Metz S. Parkinson's Disease Medications. 2017. <https://www.parkinson.org/sites/default/files/attachments/Medications.pdf>. Accessed October 4, 2019.



# MEDICATIONS FOR MOTOR SYMPTOMS

Carbidopa/  
Levodopa

Dopamine  
agonists

MAO-B  
Inhibitors

COMT  
Inhibitors

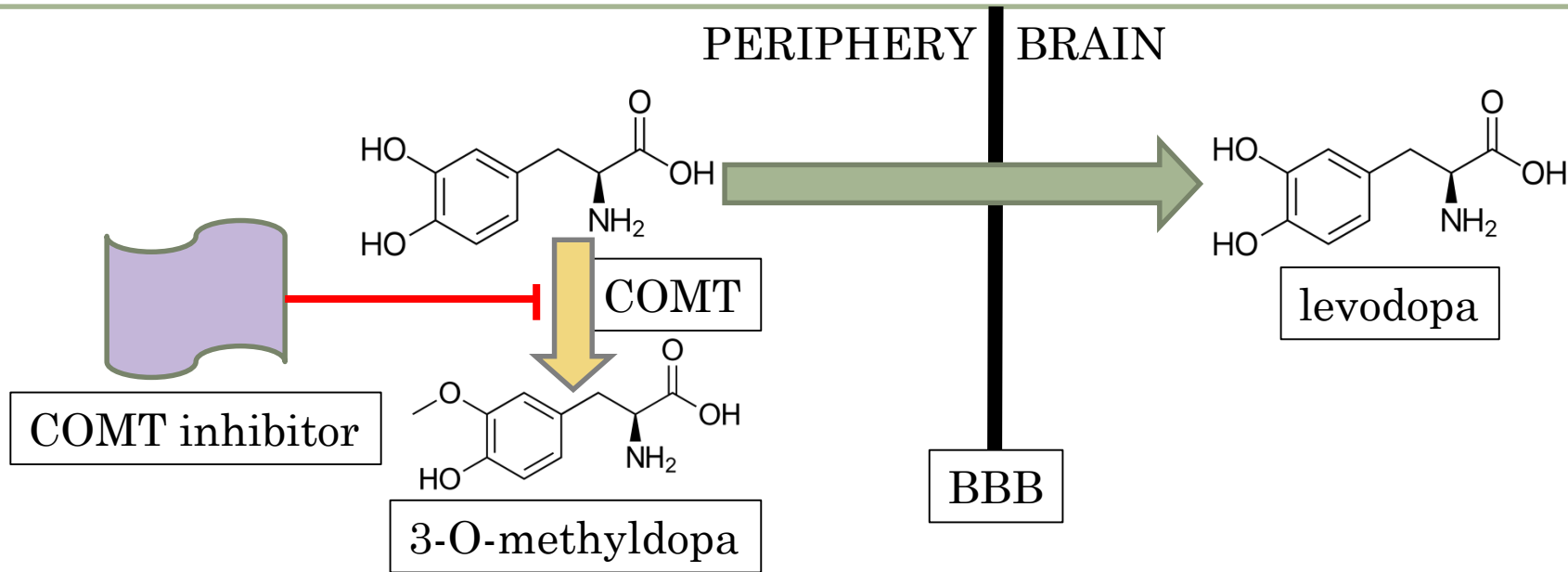
Amantadine

Anticholinergic  
Drugs

# CATECHOL-O-METHYL TRANSFERASE (COMT) INHIBITORS

## Mechanism of Action

- Block the action of COMT in the periphery, increasing levodopa in the brain



### Sources:

- Entacapone. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Houghton D, Hurtig H, and Metz S. Parkinson's Disease Medications. 2017. <https://www.parkinson.org/sites/default/files/attachments/Medications.pdf>. Accessed October 4, 2019.
- Images from [https://en.wikipedia.org/wiki/L-DOPA#/media/File:3,4-Dihydroxy-L-phenylalanin\\_\(Levodopa\).svg](https://en.wikipedia.org/wiki/L-DOPA#/media/File:3,4-Dihydroxy-L-phenylalanin_(Levodopa).svg) and <https://en.wikipedia.org/wiki/3-O-Methyldopa>

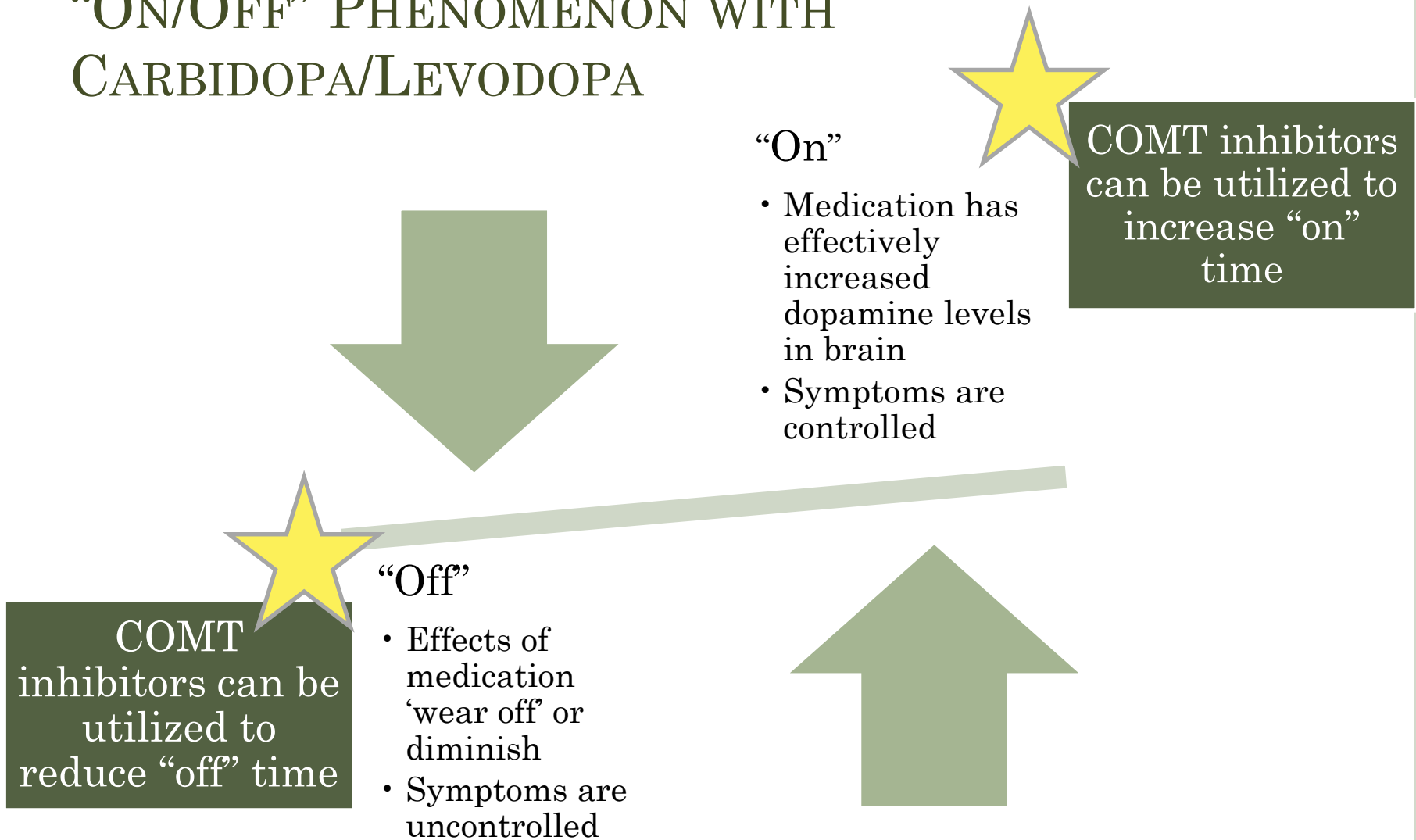
# SUMMARY OF COMT INHIBITORS

Formulation	Dosages in milligrams	Typical daily dose	Usage
Entacapone tablet (Comtan®)	200	200 mg	Combination therapy with levodopa for motor fluctuations
Tolcapone tablet (Tasmar®)	100, 200	100 mg	Same as above

## Sources:

- Entacapone. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Tolcapone. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Houghton D, Hurtig H, and Metz S. Parkinson's Disease Medications. 2017. <https://www.parkinson.org/sites/default/files/attachments/Medications.pdf>. Accessed October 4, 2019.

# “ON/OFF” PHENOMENON WITH CARBIDOPA/LEVODOPA



\*Note: phenomenon typically seen after one to five years of levodopa use and as disease progresses

# PHARMACOKINETIC CONSIDERATIONS OF COMT INHIBITORS

Formulation	Time to peak	Half-life	Comments
Entacapone tablet (Comtan®)	1 hour	Beta phase 0.4 to 0.7 hours Gamma phase 2.4 hours	<ul style="list-style-type: none"> <li>• Use with caution in hepatic impairment</li> <li>• Administer in association with levodopa</li> </ul>
Tolcapone tablet (Tasmar®)	2 hours	2 to 3 hours	<ul style="list-style-type: none"> <li>• Use with caution in CrCl &lt;25 mL/min</li> <li>• Administer in association with levodopa</li> <li>• Contraindicated in liver disease (Boxed warning)</li> </ul>

## Sources:

- Entacapone. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Tolcapone. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Houghton D, Hurtig H, and Metz S. Parkinson's Disease Medications. 2017. <https://www.parkinson.org/sites/default/files/attachments/Medications.pdf>. Accessed October 4, 2019.

# ADVERSE EFFECTS OF COMT INHIBITORS

Adverse effect	Frequency	
	Entacapone	Tolcapone
Dyskinesias	25%	42 to 51%
Confusion	<1%	10 to 11%
Hallucinations	≤1%	8 to 24%
Urine discoloration	10%	2 to 3%
Diarrhea	10%	16 to 34%
Liver toxicity	Not reported	Incidence not reported

## Sources:

- Entacapone. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Tolcapone. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Houghton D, Hurtig H, and Metz S. Parkinson's Disease Medications. 2017. <https://www.parkinson.org/sites/default/files/attachments/Medications.pdf>. Accessed October 4, 2019.

# MEDICATIONS FOR MOTOR SYMPTOMS

Carbidopa/  
Levodopa

Dopamine  
agonists

MAO-B  
Inhibitors

COMT  
Inhibitors

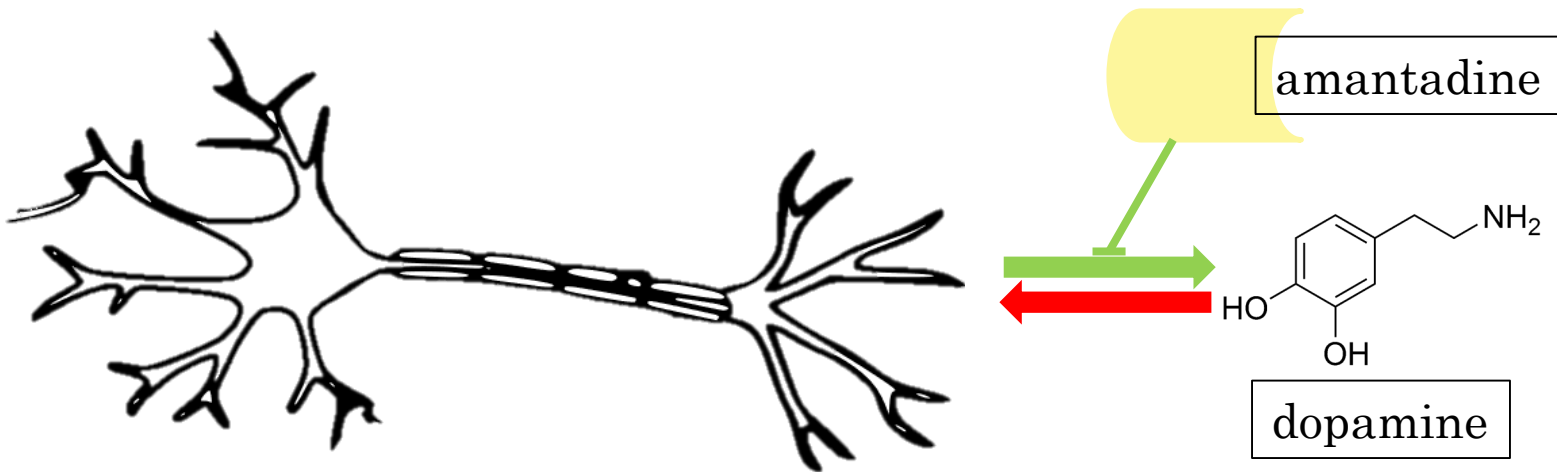
Amantadine

Anticholinergic  
Drugs

# AMANTADINE

## Mechanism of Action

- Exact mechanism unknown
- Weak, noncompetitive NMDA receptor antagonist
  - Hypothesized to **increase neuronal release** and **reduce reuptake** of dopamine
- Potentially exerts central anticholinergic effects



### Sources:

- Amantadine. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Houghton D, Hurtig H, and Metz S. Parkinson's Disease Medications. 2017. <https://www.parkinson.org/sites/default/files/attachments/Medications.pdf>. Accessed October 4, 2019.
- Image from: [https://commons.wikimedia.org/wiki/File:Dopamine\\_chemical\\_structure.png](https://commons.wikimedia.org/wiki/File:Dopamine_chemical_structure.png)



# SUMMARY OF AMANTADINE

Formulation	Dosages in milligrams	Typical daily dose	Usage
Amantadine capsule, tablet, syrup	100 (tablet, capsule) 50 per 5 mL (syrup)	100 mg	<ul style="list-style-type: none"><li>• Monotherapy for motor symptoms</li><li>• Useful adjunct for managing dyskinesias</li></ul>

Sources:

- Amantadine. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Houghton D, Hurtig H, and Metz S. Parkinson's Disease Medications. 2017. <https://www.parkinson.org/sites/default/files/attachments/Medications.pdf>. Accessed October 4, 2019.

# PHARMACOKINETIC CONSIDERATIONS OF AMANTADINE

Formulation	Time to peak	Half-life	Comments
Amantadine capsule, tablet, syrup	2 to 4 hours	9 to 31 hours	<ul style="list-style-type: none"><li>Requires renal adjustment if CrCl &lt;50 mL/min</li></ul>

## Sources:

- Amantadine. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Houghton D, Hurtig H, and Metz S. Parkinson's Disease Medications. 2017. <https://www.parkinson.org/sites/default/files/attachments/Medications.pdf>. Accessed October 4, 2019.

# ADVERSE EFFECTS OF AMANTADINE

Adverse Effect	Frequency
Livedo reticularis	1 to 6%
Nausea	5 to 10%
Xerostomia	1 to 16%
Dizziness	≤29%
Insomnia	5 to 10%
Confusion	1 to 5%
Hallucinations	≤25%
Urinary retention	<1%

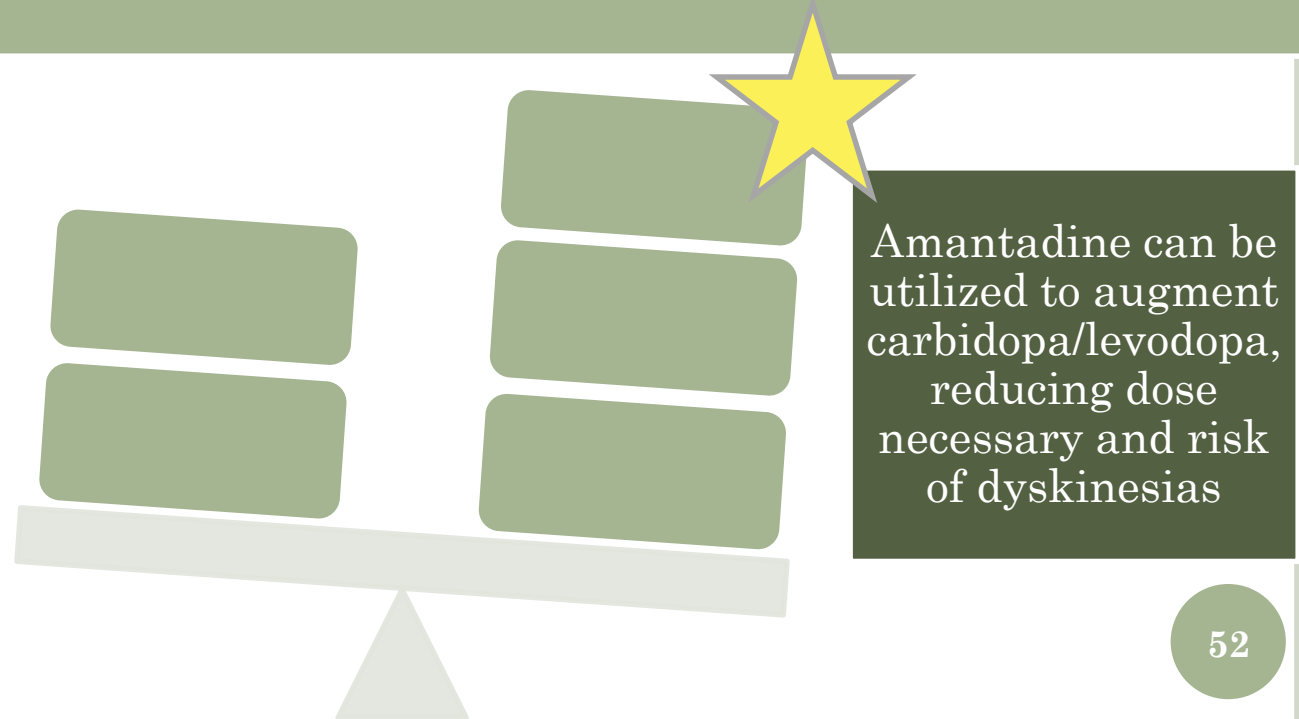
Sources:

- Amantadine. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Houghton D, Hurtig H, and Metz S. Parkinson's Disease Medications. 2017. <https://www.parkinson.org/sites/default/files/attachments/Medications.pdf>. Accessed October 4, 2019.

# DYSKINESIAS WITH CARBIDOPA/LEVODOPA

Dyskinesias: involuntary, erratic, writhing movements

- Typically not seen until 3 to 5 years after starting levodopa
- Higher doses of levodopa necessary for symptom control as disease progresses
- Difficult in later stages of disease to have smooth “on” phases
- Occur when the dose to produce an “on” is too high



# MEDICATIONS FOR MOTOR SYMPTOMS

Carbidopa/  
Levodopa

Dopamine  
agonists

MAO-B  
Inhibitors

COMT  
Inhibitors

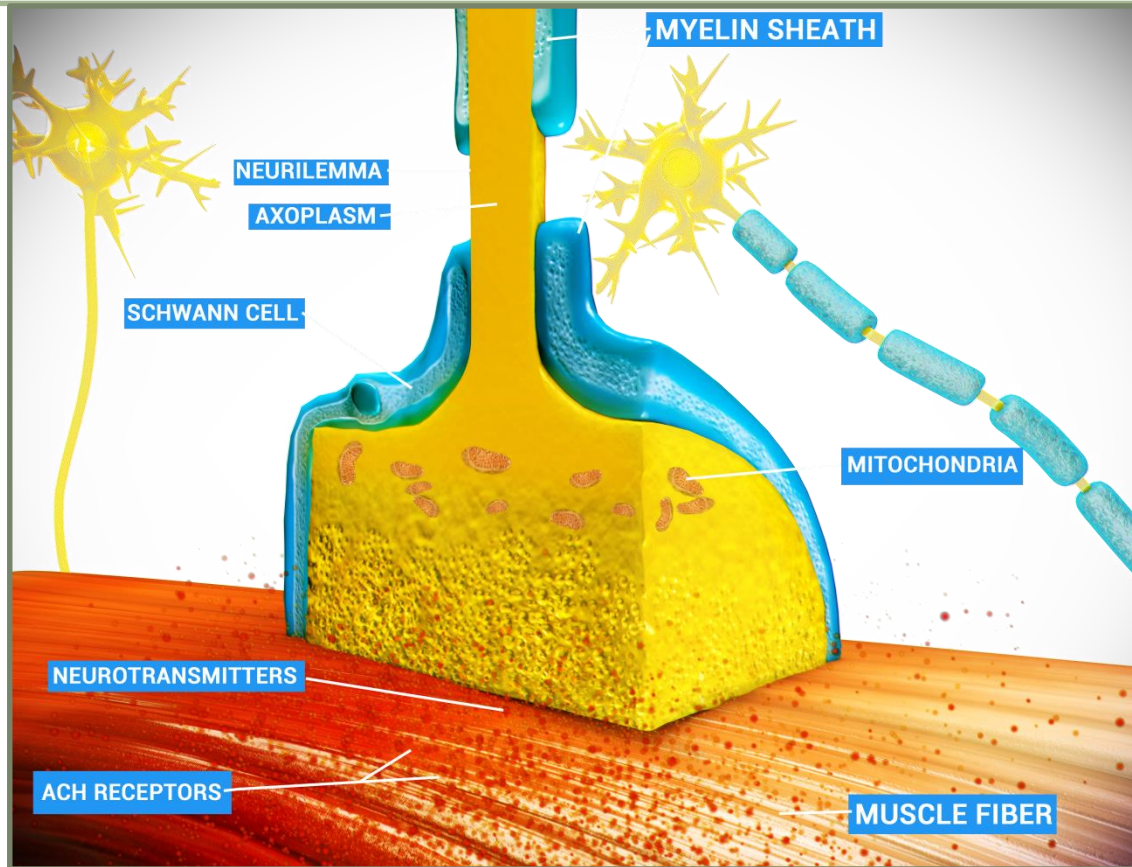
Amantadine

Anticholinergic  
Drugs

# ANTICHOLINERGIC DRUGS

## Mechanism of Action

- Directly inhibits parasympathetic nervous system
  - Leads to muscular relaxation



### Sources:

- Trihexyphenidyl. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019. Houghton D, Hurtig H, and Metz S. Parkinson's Disease Medications. 2017. <https://www.parkinson.org/sites/default/files/attachments/Medications.pdf>. Accessed October 4, 2019.
- Image from: [https://es.m.wikipedia.org/wiki/Archivo:Neuro\\_Muscular\\_Junction.png](https://es.m.wikipedia.org/wiki/Archivo:Neuro_Muscular_Junction.png)

# SUMMARY OF ANTICHOLINERGIC DRUGS

Formulation	Dosages in milligrams	Typical daily dose	Usage
Trihexyphenidyl tablet (Artane®)	2, 5	1–2 mg	Monotherapy or combination therapy, predominantly for tremor in younger people; <b>should be avoided in elderly</b>
Benztropine tablet (Cogentin®)	0.5, 1, 2	0.5–2 mg	Same as above

## Sources:

- Trihexyphenidyl. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Benztropine. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Houghton D, Hurtig H, and Metz S. Parkinson's Disease Medications. 2017. <https://www.parkinson.org/sites/default/files/attachments/Medications.pdf>. Accessed October 4, 2019.

# PHARMACOKINETIC CONSIDERATIONS OF ANTICHOLINERGIC DRUGS

Formulation	Time to peak	Half-life	Comments
Trihexyphenidyl (Artane®)	1.3 hours	33 hours	<ul style="list-style-type: none"><li>• Use with caution in renal and hepatic impairment</li></ul>
Benzotropine (Cogentin®)	7 hours (onset of action 1 hour)	Not reported	<ul style="list-style-type: none"><li>• No adjustments reported</li></ul>

## Sources:

- Trihexyphenidyl. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Benzotropine. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Houghton D, Hurtig H, and Metz S. Parkinson's Disease Medications. 2017. <https://www.parkinson.org/sites/default/files/attachments/Medications.pdf>. Accessed October 4, 2019.



# ADVERSE EFFECTS OF ANTICHOLINERGIC DRUGS

Confusion

Hallucinations

Amnesia

Xerostomia

Blurry vision

Urinary  
retention

## Sources:

- Trihexyphenidyl. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Benztropine. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
- Houghton D, Hurtig H, and Metz S. Parkinson's Disease Medications. 2017. <https://www.parkinson.org/sites/default/files/attachments/Medications.pdf>. Accessed October 4, 2019.

## QUESTION 2: PATIENT CASE

- DP is a 63 year-old male who has had Parkinson's disease for 2 years. He takes carbidopa/levodopa 25/250 mg three times daily. He takes his first dose at 7 AM. After initial motor symptom relief, he begins to experience worsening bradykinesia around 1030 AM.
- What phase of the “on/off” phenomenon is DP likely experiencing?

## RESPONSE 2:

- Off Phase

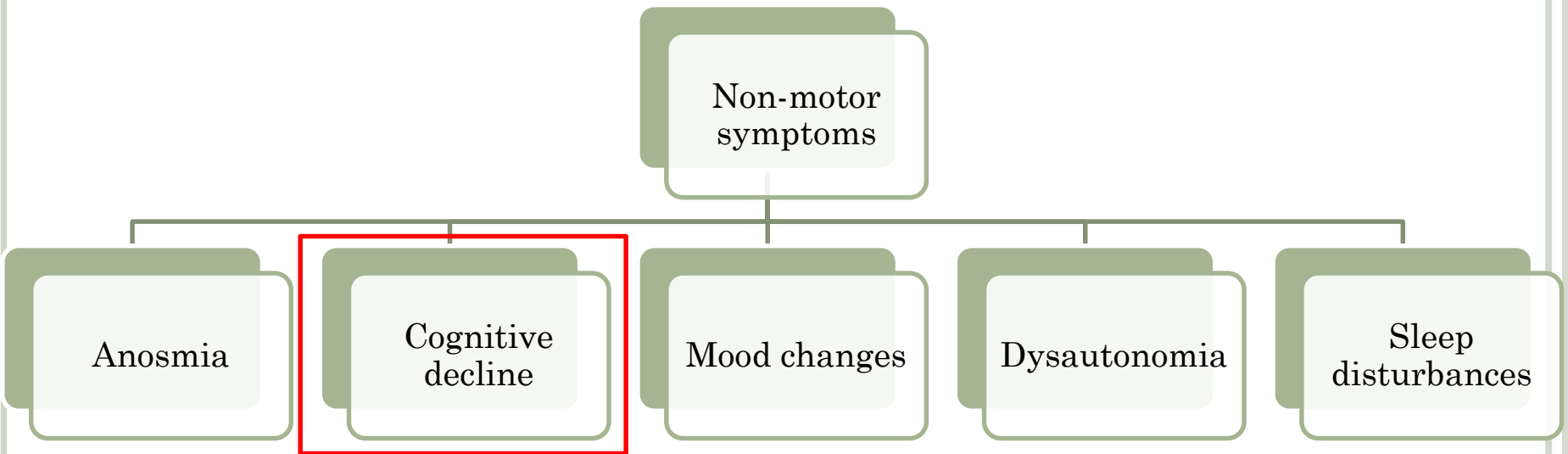
## QUESTION 3: PATIENT CASE

- DP is a 63 year-old male who has had Parkinson's disease for 2 years. He takes carbidopa/levodopa 25/250 mg three times daily. He takes his first dose at 7 AM. After initial motor symptom relief, he begins to experience worsening bradykinesia around 1030 AM.
- What medication would NOT be expected to provide relief of bradykinesia?
  - a) entacapone
  - b) selegiline
  - c) trihexyphenidyl
  - d) pramipexole

## RESPONSE 3

- What medication would NOT be expected to provide relief of bradykinesia?
  - a) entacapone
  - b) selegiline
  - c) trihexyphenidyl**
  - d) pramipexole

# CLINICAL PRESENTATION OF PARKINSON'S DISEASE



# MEDICATIONS FOR COGNITIVE DECLINE

## Acetylcholinesterase Inhibitors

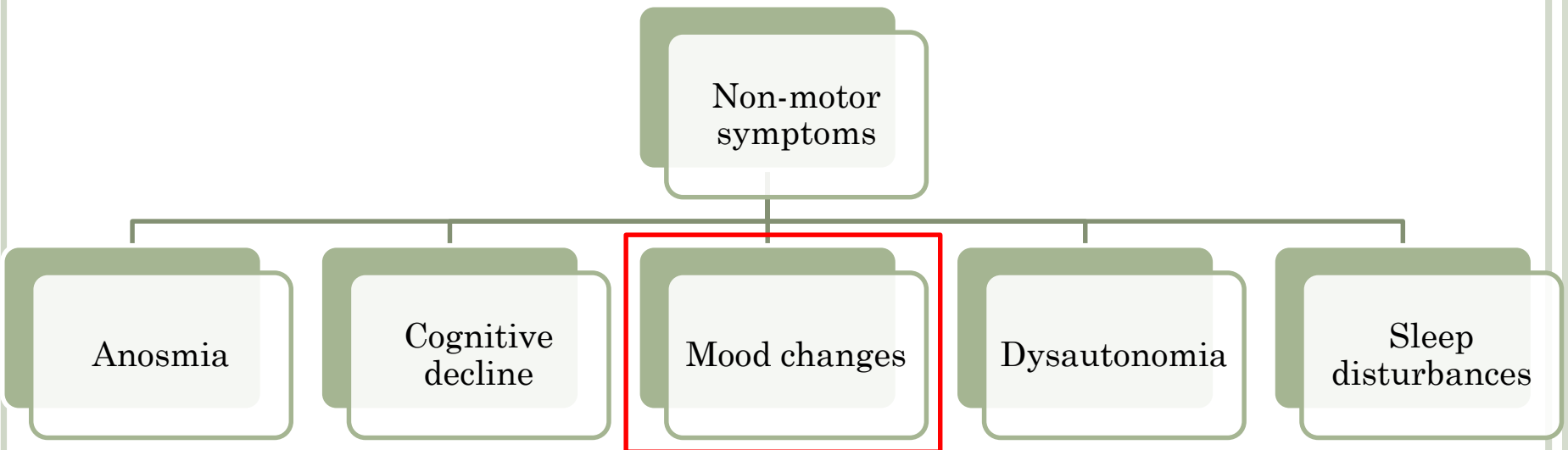
- Examples:
  - Donepezil
  - Rivastigmine

Memantine

Methylphenidate

Modafinil

# CLINICAL PRESENTATION OF PARKINSON'S DISEASE





# MEDICATIONS FOR DEPRESSION

## SSRIs

- Examples:
  - Fluoxetine
  - Sertraline

## SNRIs

- Examples:
  - Venlafaxine
  - Duloxetine

## Tricyclic Antidepressants

- Examples:
  - Amitriptyline
  - Nortriptyline

Trazodone

Bupropion

Mirtazapine

# MEDICATIONS FOR ANXIETY

## SSRIs

- Examples:
  - Fluoxetine
  - Sertraline

## SNRIs

- Examples:
  - Venlafaxine
  - Duloxetine

## Tricyclic Antidepressants

- Examples:
  - Amitriptyline
  - Nortriptyline

Trazodone

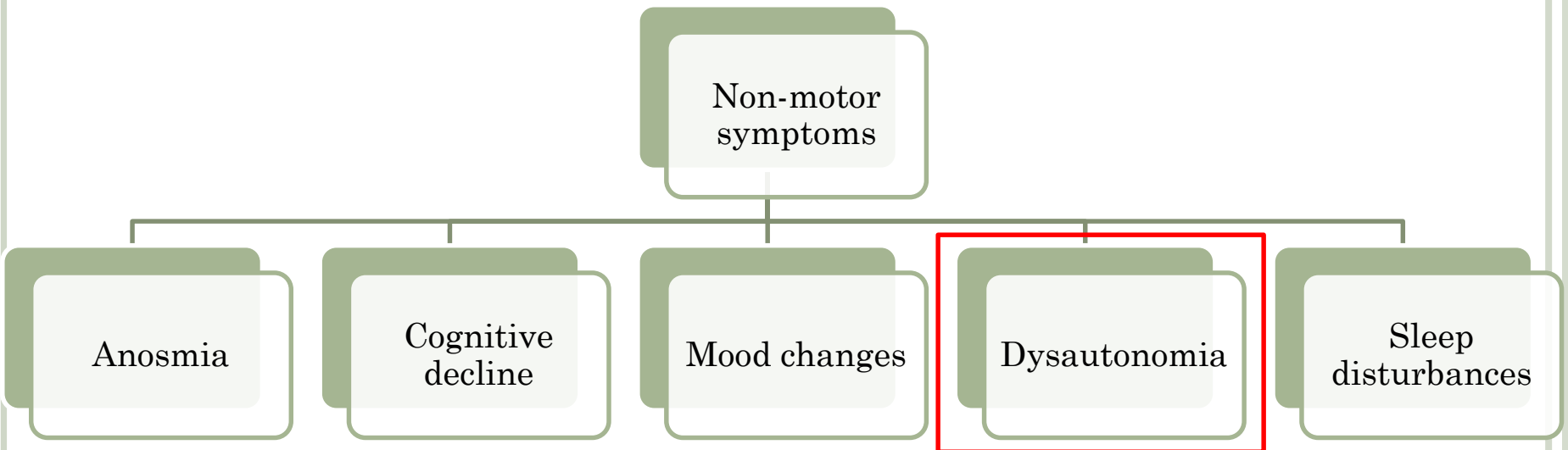
## Benzodiazepines

- Examples:
  - Alprazolam
  - Lorazepam

Buspirone

Propranolol

# CLINICAL PRESENTATION OF PARKINSON'S DISEASE



# MEDICATIONS FOR NAUSEA AND VOMITING

Carbidopa

Ondansetron

Trimethobenzamide

Metoclopramide

Prochlorperazine

Promethazine

# MEDICATIONS FOR CONSTIPATION

Lubiprostone

Polyethylene  
glycol 3350

# MEDICATIONS FOR EXCESSIVE DROOLING

Atropine  
drops

Glycopyrrolate

Scopolamine  
patch

Botulinum  
toxin A

# MEDICATIONS FOR ORTHOSTASIS

Fludrocortisone

Midodrine

Pyridostigmine

Droxidopa

# MEDICATIONS FOR URINARY SYMPTOMS

## Anticholinergics

- Examples:
  - Oxybutynin
  - Tolterodine
  - Solifenacin

## Alpha-adrenergic receptor blockers

### Examples:

- Tamsulosin
- Alfuzosin

## Tricyclic antidepressants

- Examples:
  - Amitriptyline
  - Nortriptyline

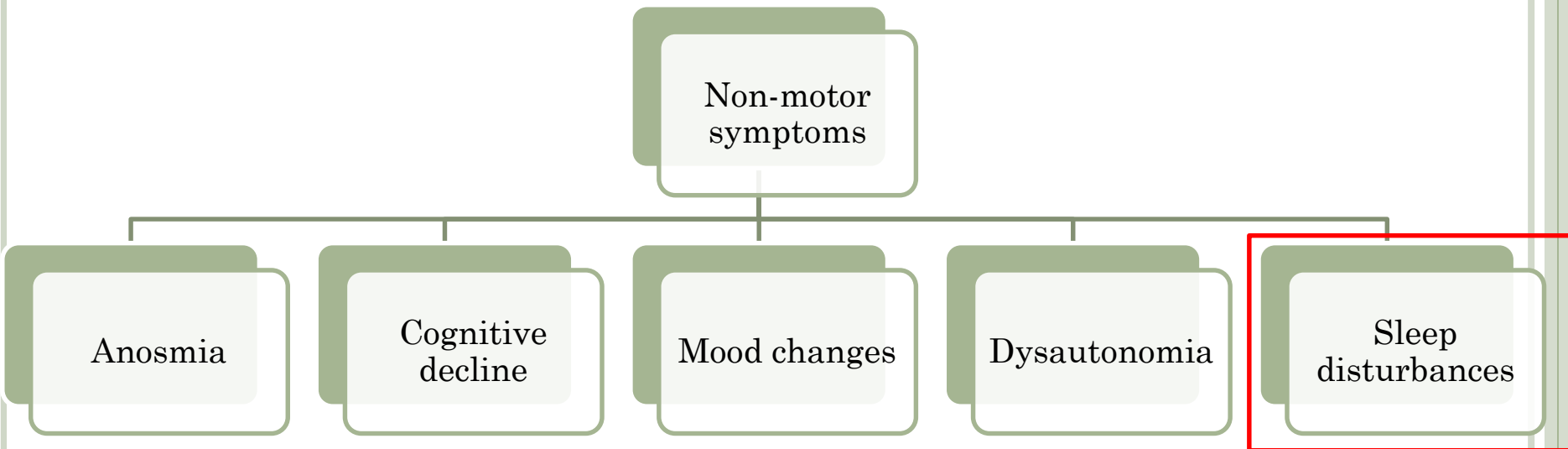


# MEDICATIONS FOR ERECTILE DYSFUNCTION

## Phosphodiesterase-5 Inhibitors

- Examples:
  - Sildenafil
  - Tadalafil
  - Vardenafil

# CLINICAL PRESENTATION OF PARKINSON'S DISEASE



# MEDICATIONS FOR INSOMNIA

Trazodone

Mirtazapine

Anticholinergics:

- Example:
  - Diphenhydramine

## QUESTION 4: PATIENT CASE

- LR is a 70 year-old female who has had Parkinson's disease for 8 years. She takes carbidopa/levodopa CR 50/200 mg three times daily. She often has involuntary writhing movements in the afternoon.
- What may LR be experiencing?

(Free Response)

## RESPONSE 4

- Answer: dyskinesias

## QUESTION 5: PATIENT CASE

- LR is a 70 year-old female who has had Parkinson's disease for 8 years. She takes carbidopa/levodopa CR 50/200 mg three times daily. She often has involuntary writhing movements in the afternoon.
- What medication could be considered to augment carbidopa/levodopa to reduce her dyskinesias?
  - a) ropinirole
  - b) modafinil,
  - c) trazodone,
  - d) metoclopramide

## RESPONSE 5

- What medication could be considered to augment carbidopa/levodopa to reduce her dyskinesias?
  - a) **ropinirole**
  - b) modafinil
  - c) trazodone
  - d) metoclopramide

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- International Parkinson and Movement Disorder Society. MDS-UPDRS: The MDS-sponsored Revision of the Unified Parkinson's Disease Rating Scale. 2008. [https://www.movementdisorders.org/MDS-Files1/PDFs/Rating-Scales/MDS-UPDRS\\_English\\_FINAL\\_Updated\\_August2019.pdf](https://www.movementdisorders.org/MDS-Files1/PDFs/Rating-Scales/MDS-UPDRS_English_FINAL_Updated_August2019.pdf). Accessed 10/5/2019.
- Carbidopa and levodopa. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
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- Apomorphine. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>. Accessed October 19, 2019.
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# THANK YOU!

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