CARBIDOPA/ LEVODOPA

June 2024

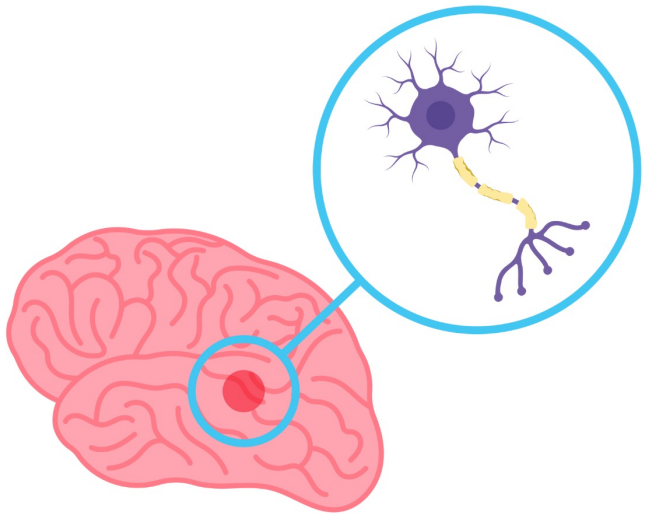
LEVEL SET: PARKINSON'S[1]

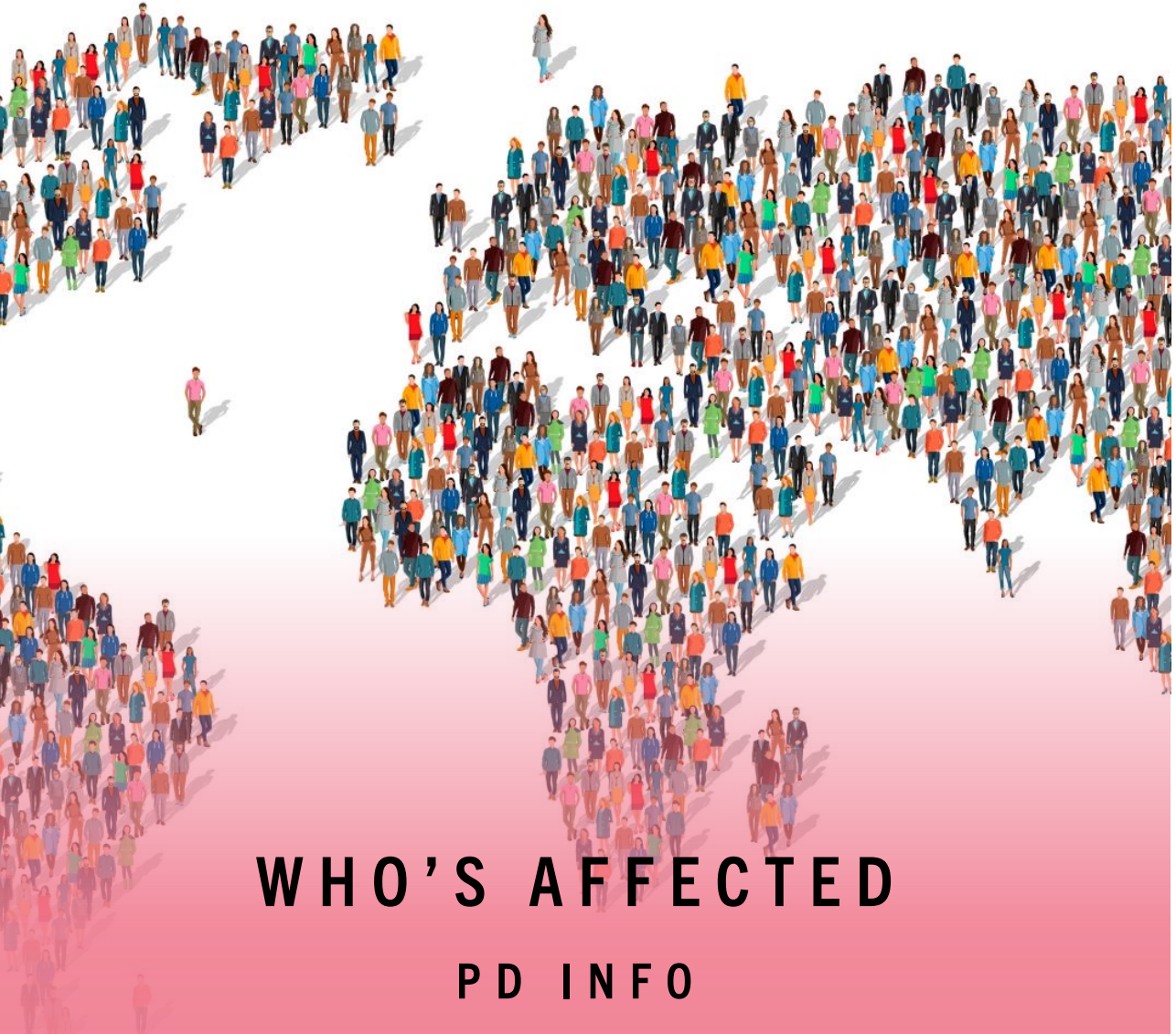
- Neurological disease
- Affects over 8.5 million people
- Current treatment options:
  - Dopamine agonists (Levodopa/carbidopa)
  - Surgical brain stimulation
- Unmet needs:
  - Symptom management – no cure
  - Preventive action

PARKINSON'S DISEASE

PD INFO[17]

- Primary parkinsonians
  - Parkinson’s disease
  - Parkinson’s plus syndromes
- Neurodegenerative
- Dopamine deficiency
  - Advanced symptoms typically occur after 10 years





WHO'S AFFECTED

PD INFO

PD is common[1]

- 100-200 people out of 100,000
- 15 new cases out of 100,000 people every year
  - Onset of PD usually occurs at 65-70 years of age
  - Onset before age of 40 seen in less than 5% of cases

CAUSE AND RISK FACTORS - PD INFO

- Root cause of Parkinson's is a lack of dopamine generating brain cells[7]

- Risk factors[1]
  - Age
  - Gender
  - Genetics

DISEASE PRESENTATION[6] - PD INFO

- Cardinal signs
  - Tremors
  - Stiffness
  - Postural instability
  - Slow movement

MORE SYMPTOMS OF PARKINSON'S[7]

PD INFO

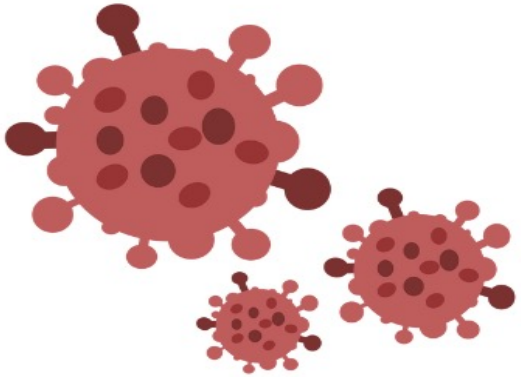
Motor symptoms

- Rigidity
- Freezing of gait
- Dyskinesias
- Masked face

Non-motor Symptoms

- Parkinson's disease psychosis (PDP)[6]
- Depression/anxiety[7]

COMPLICATIONS OF PARKINSON'S - PD OVERVIEW



Infection

Inability to swallow

Dangerous accidents

UNMET NEEDS OF PD TREATMENT

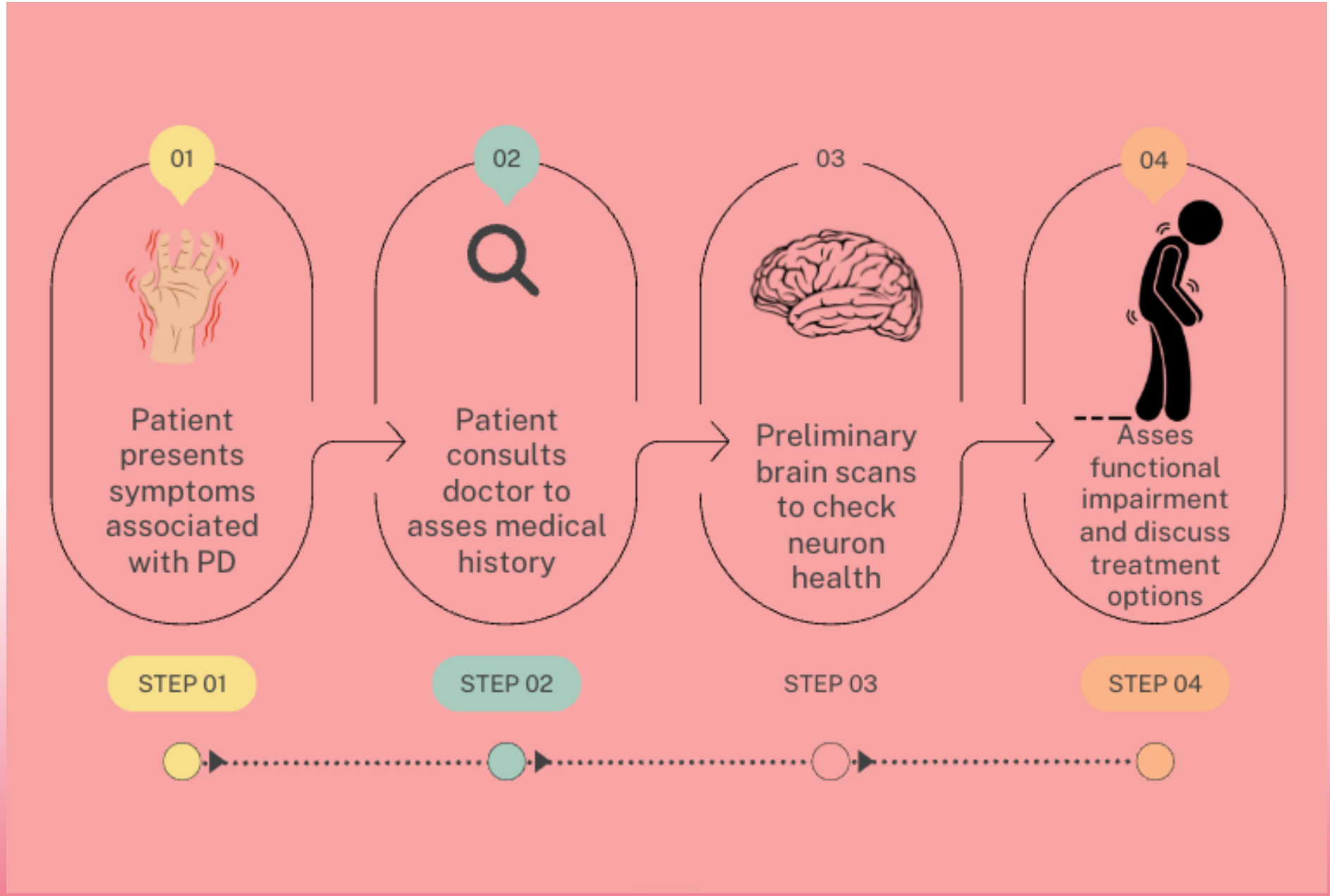
Neuroprotection/regeneration[3]

No current treatment options address the neurodegeneration of PD – just the symptoms

Low concentration of drug effectiveness[5]

Blood-brain barrier

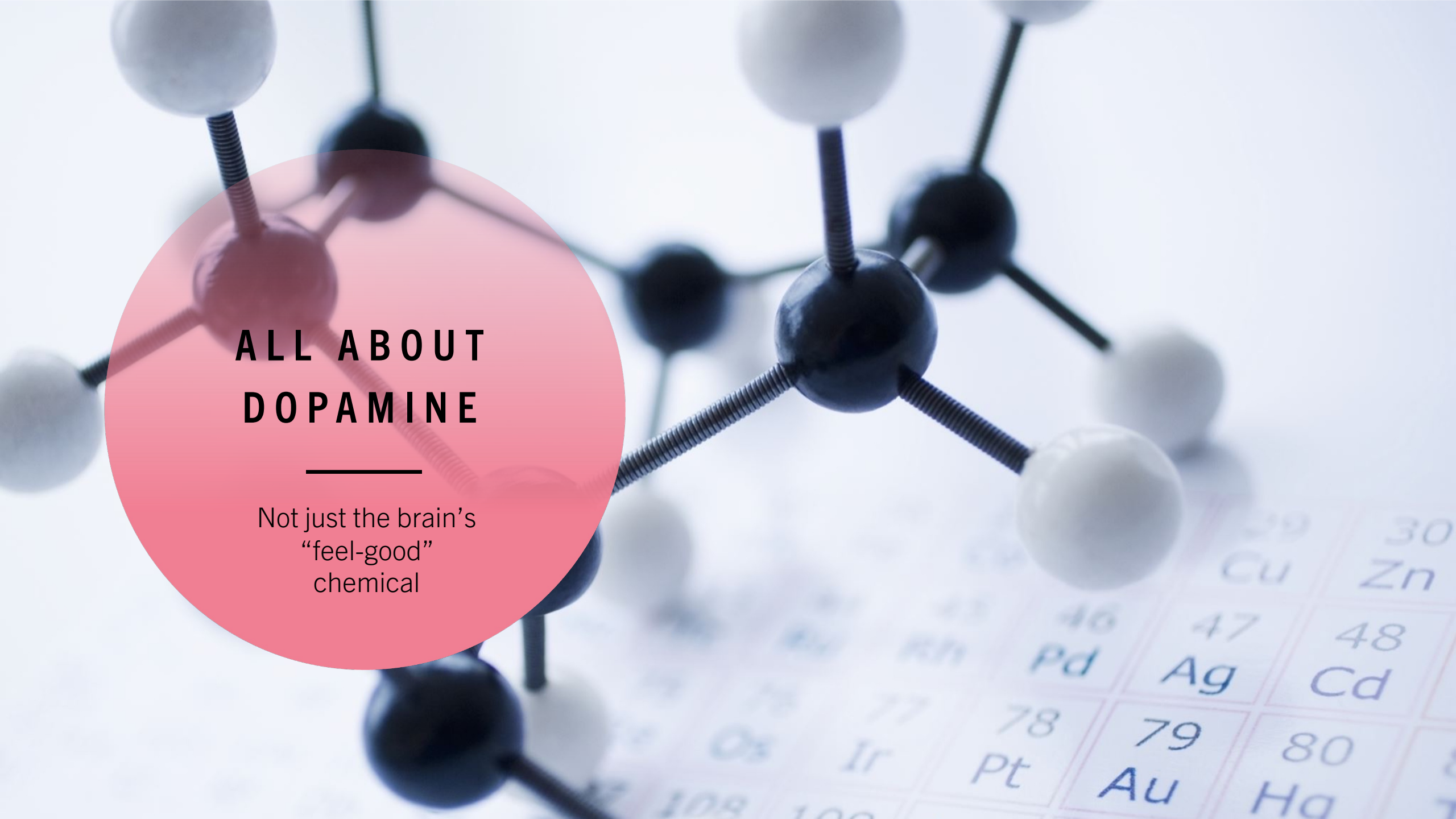
DIAGNOSIS OF PD[9]



PD PATHOLOGY – WHAT'S HAPPENING IN YOUR BRAIN

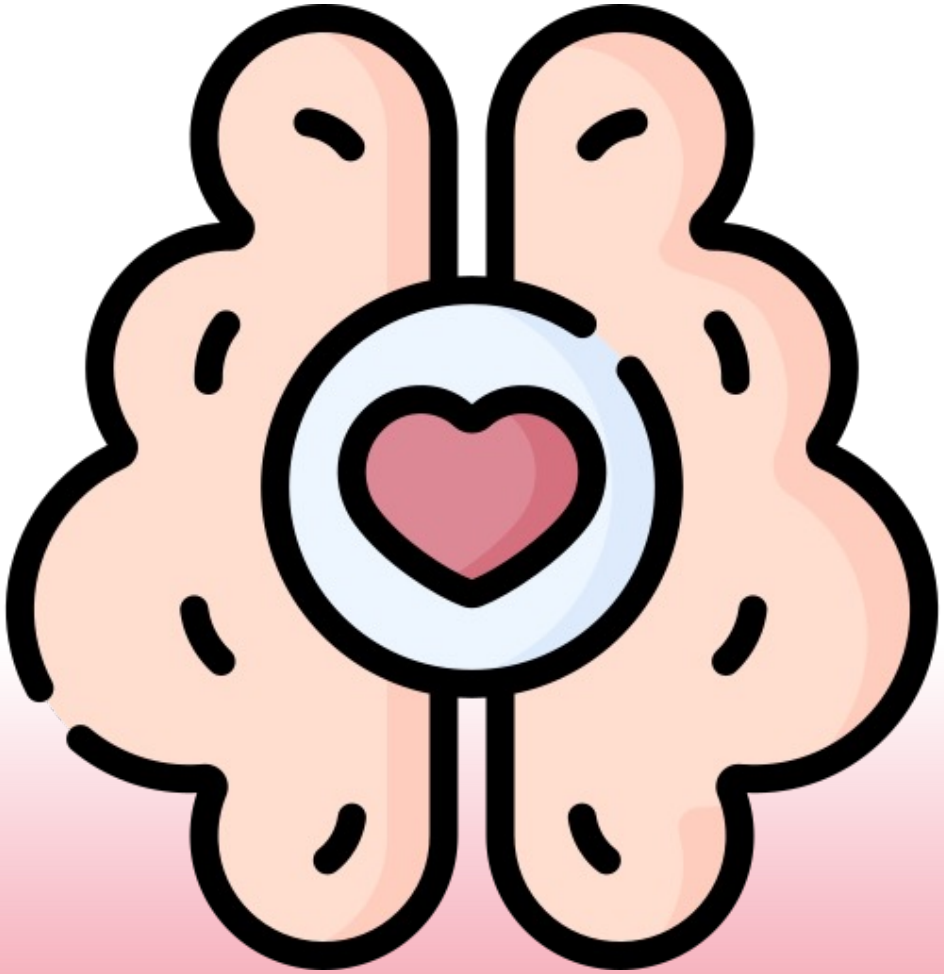
- Gradual loss of dopamine-generating cells in the brain in a region called the **substantia nigra**[1]

- Misshapen proteins called **lewy bodies** interfere with the **substantia nigra**[10]


ALL ABOUT
DOPAMINE
Not just the brain's
"feel-good"
chemical
Cu
Zn
Pd
Ag
Cd
Pt
Au
Hg

ALL ABOUT DOPAMINE[11]

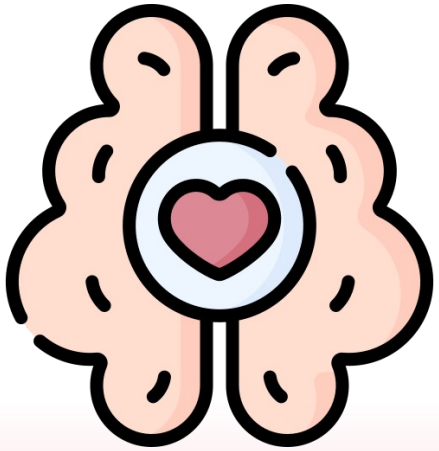
- Produced in our brains
- Commonly thought of as the ”feel-good” chemical. But that’s an oversimplification.



IN THE BRAIN
ALL ABOUT DOPAMINE[11]

- Motivation
- Mood regulation
- Cognitive function
- Movement

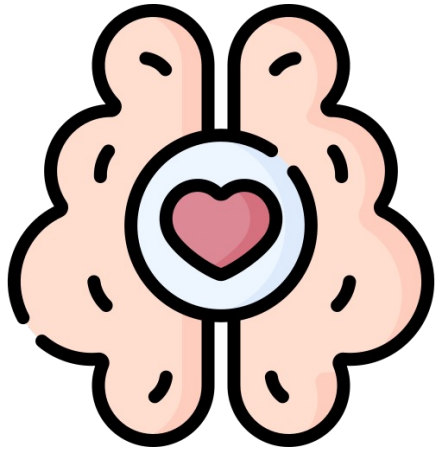
DOPAMINE IMBALANCES[11]



In the brain

In the body

IN THE BRAIN[11]



Too much

- Impulsive behavior
- Mania
- Aggression
- Paranoia/anxiety

Too little

- Motor impairment
- Bradykinesias
- Loss of concentration/motivation
- Depression/anxiety

IN THE BODY[11]

Too much

- Nausea/vomiting
- GI issues
- Elevated heart rate

Too little

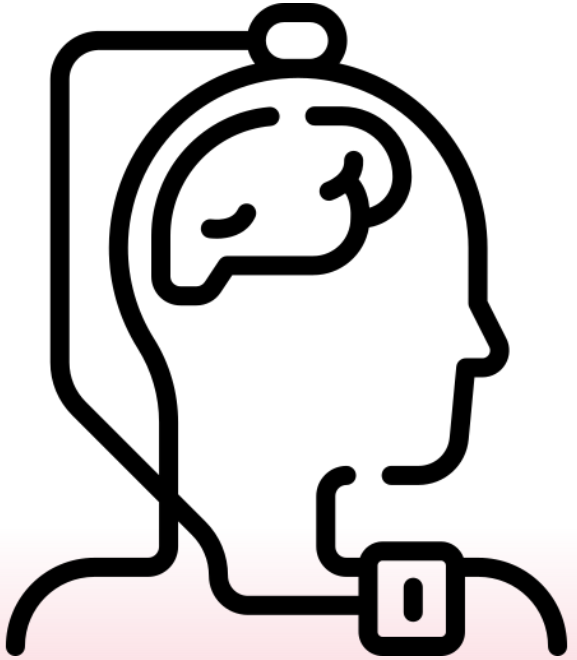
- Constipation
- Impaired kidney function
- Hypotension

TREATING PARKINSON'S

STANDARDS OF CARE FOR PD[2]

Dopamine agonists* (orally administered)

- Carbidopa/Levodopa



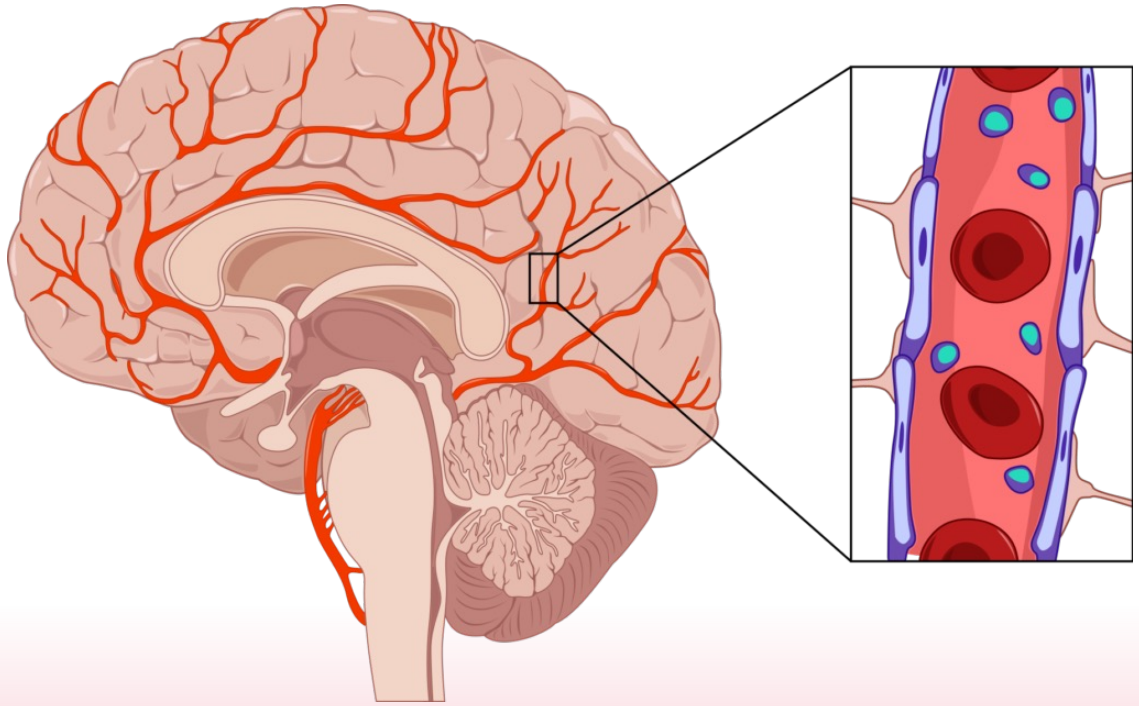
Deep brain stimulation (surgical)

*A dopamine agonist mimics the effects of dopamine on the brain

BLOOD-BRAIN BARRIER[15]

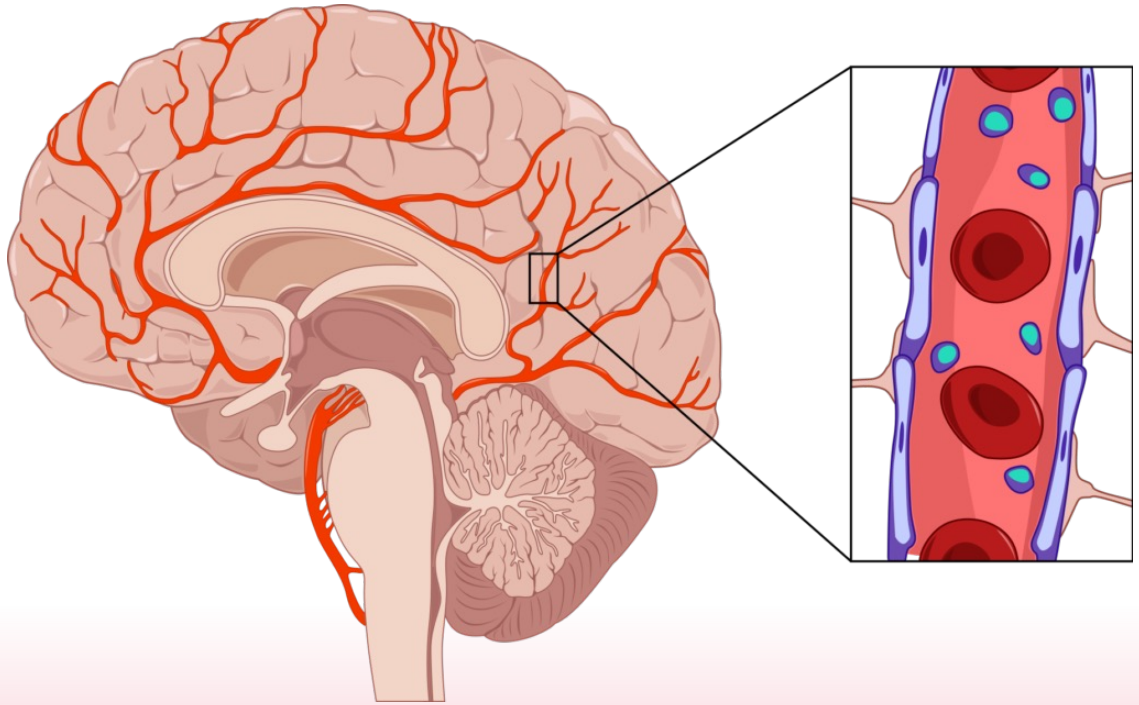
- Physical barrier

- Regulates what can enter brain from blood stream



TREATING PARKINSON'S-DOPAMINE

- Dopamine cannot cross the blood-brain barrier
- Levodopa can cross the blood-brain barrier[4]
  - Turned into dopamine by the body



TREATMENT OPTION: CARBIDOPA/LEVODOPA

TREATMENT OPTION: CARBIDOPA/LEVODOPA[3]

- Levodopa
  - Dopamine agonist
  - Pre-cursor of dopamine
  - Symptom mitigation
    - Levodopa does not slow the progression of PD
    - As PD progresses, patients will require higher doses of levodopa
- Carbidopa
  - Boosts efficiency of levodopa dosage
    - Not perfect!

TREATMENT OPTION: LEVODOPA/CARBIDOPA[3]

- Pros:
  - Alleviates disability and discomfort
  - Cost effective
  - Standard of PD therapeutics
- Cons
  - Only addresses symptoms
  - Requires gradual increase in dosage
  - Side effects occur

ADVERSE EFFECTS OF LEVODOPA/CARBIDOPA[18]

The “on/off effect”

Nausea/vomiting

Elevated heart rate
(Tachyarrhythmias)

Anxiety, hallucinations, agitation

TREATMENT OPTION: CARBIDOPA/LEVODOPA[3]

MECHANISM OF ACTION

Levodopa

1. Levodopa converted to dopamine
2. Replacement of dopamine
3. Stimulation of dopamine receptors
4. Dopamine metabolism inhibition[4,8]

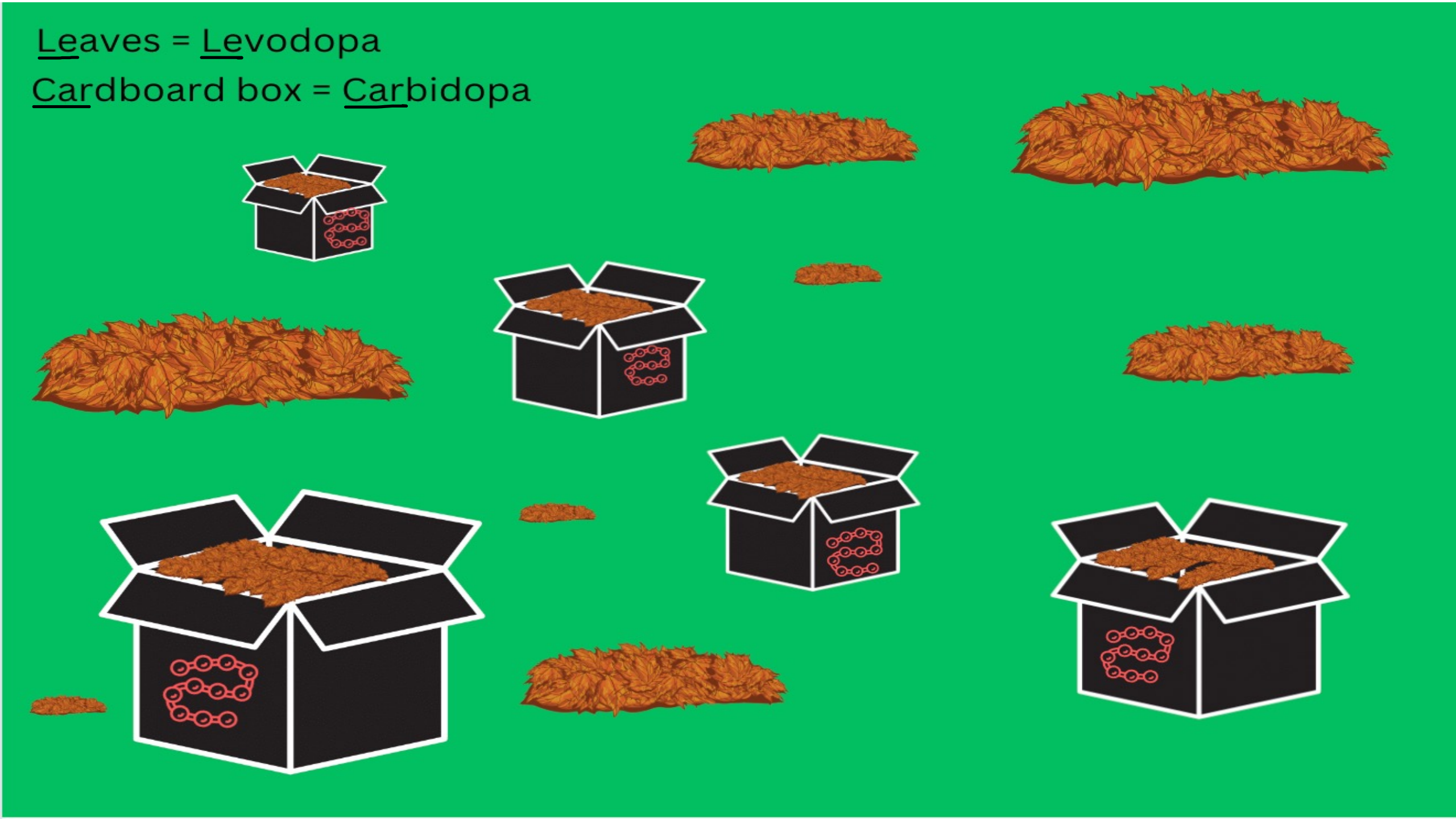
Carbidopa

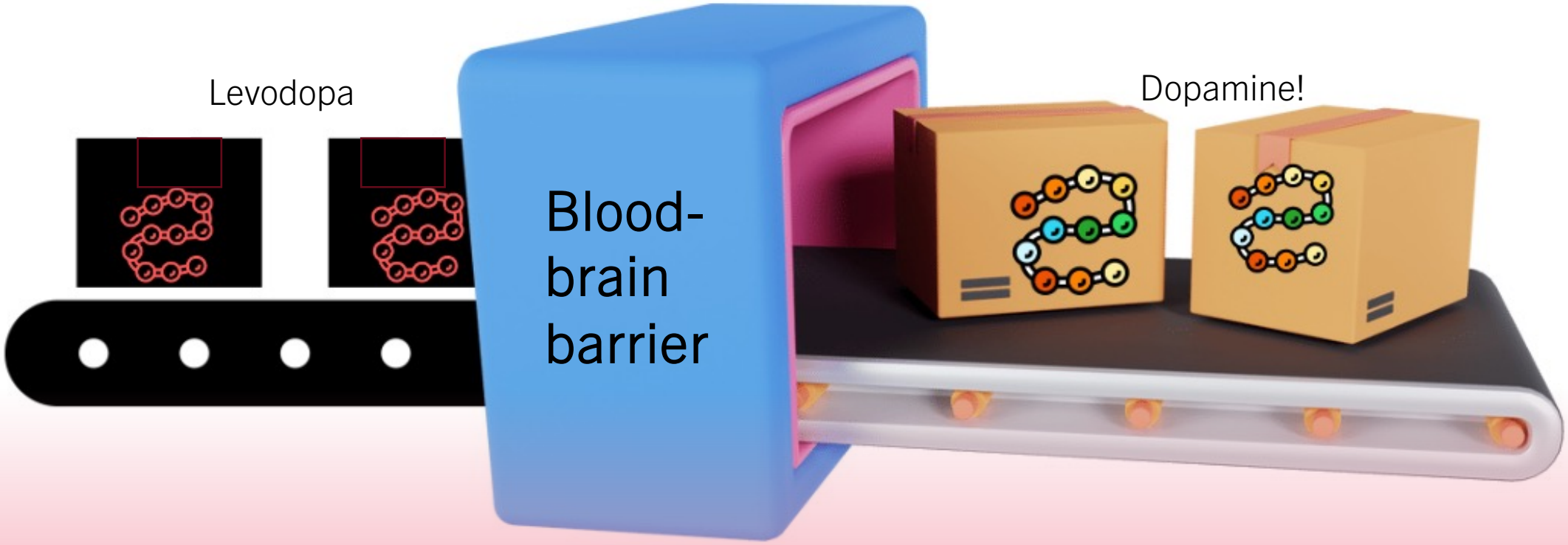
1. Blocks the conversion of levodopa into dopamine *outside the brain*
2. Increases the amount of time it takes Levodopa to decay in the body (from around 50 minutes to 1.5 hours)
3. **Only works outside the brain**

LEVODOPA/CARBIDOPA LEAF COLLECTING ANALOGY

Leaves = Levodopa

Cardboard box = Carbidopa




Levodopa
Blood-
brain
barrier
Dopamine!

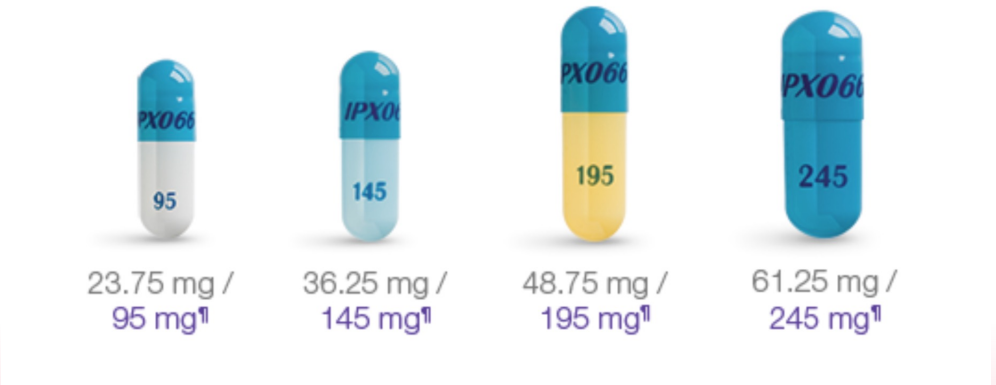
RYTARY: LEVODOPA/CARBIDOPA TREATMENT OPTION

STARTING RYTARY[14]

One of two routes:

1. Patient's who took IR CD/LD in the past
    - RYTARY dose based on old regimen
    - Dose will be different.
2. Patient's who are new to treatment
    - Prescribed standard dose of RYTARY

- Patients new to RYTARY may need to adjust dosage



2X reduction in "off" time during waking hours

Percentage of "off" time with IR CD/LD:

- Start of study:
  - 36.0% of waking hours
- End of study
  - 29.8% of waking hours

Percentage of "off" time with Rytary:

- Start of study
  - 36.9% of waking hours
- End of study
  - 23.8% of waking hour

+1.2 hours greater increase in "on" time per dose**

- 1.8 hours with RYTARY
- 0.8 hours with IR CD/LD

Better movement control§

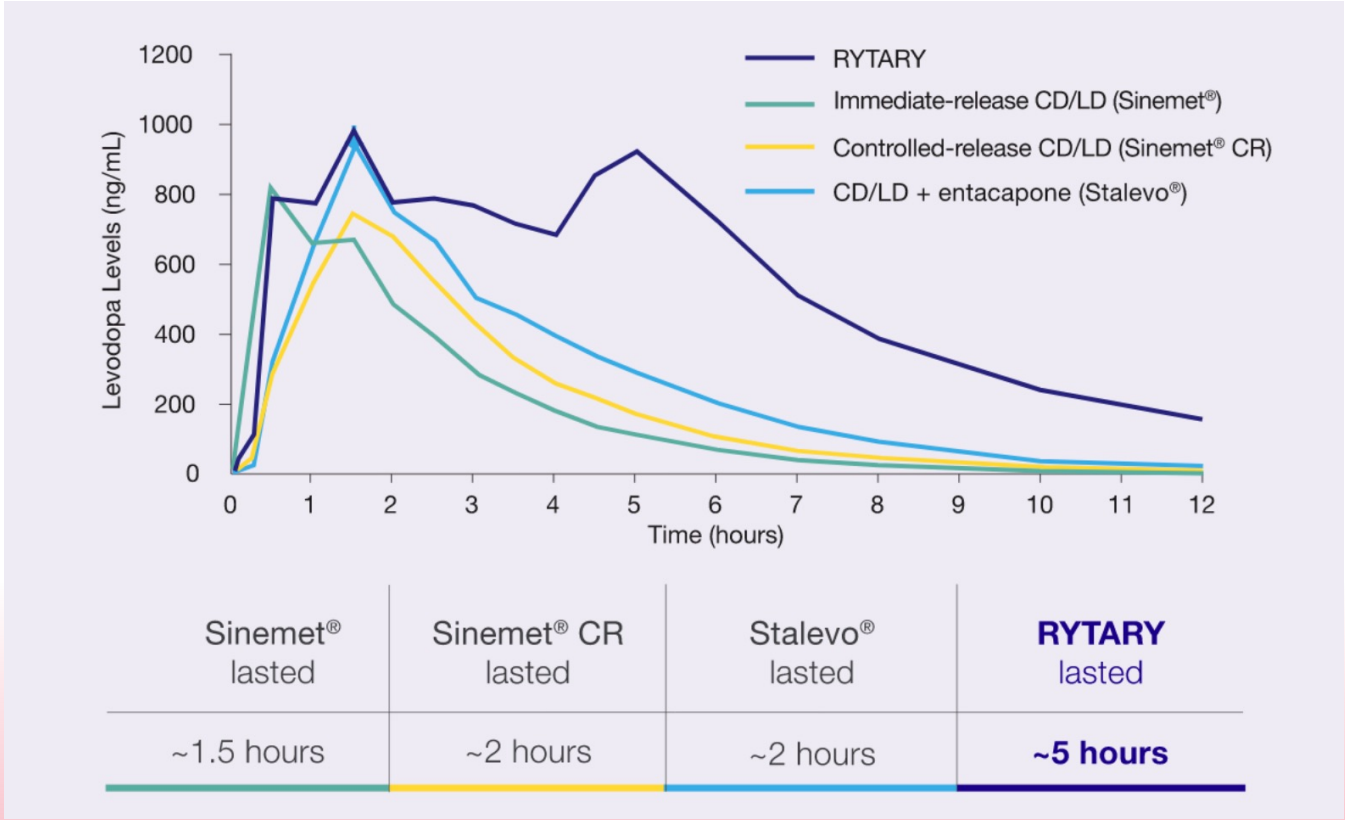
After switching to RYTARY

Source: 14

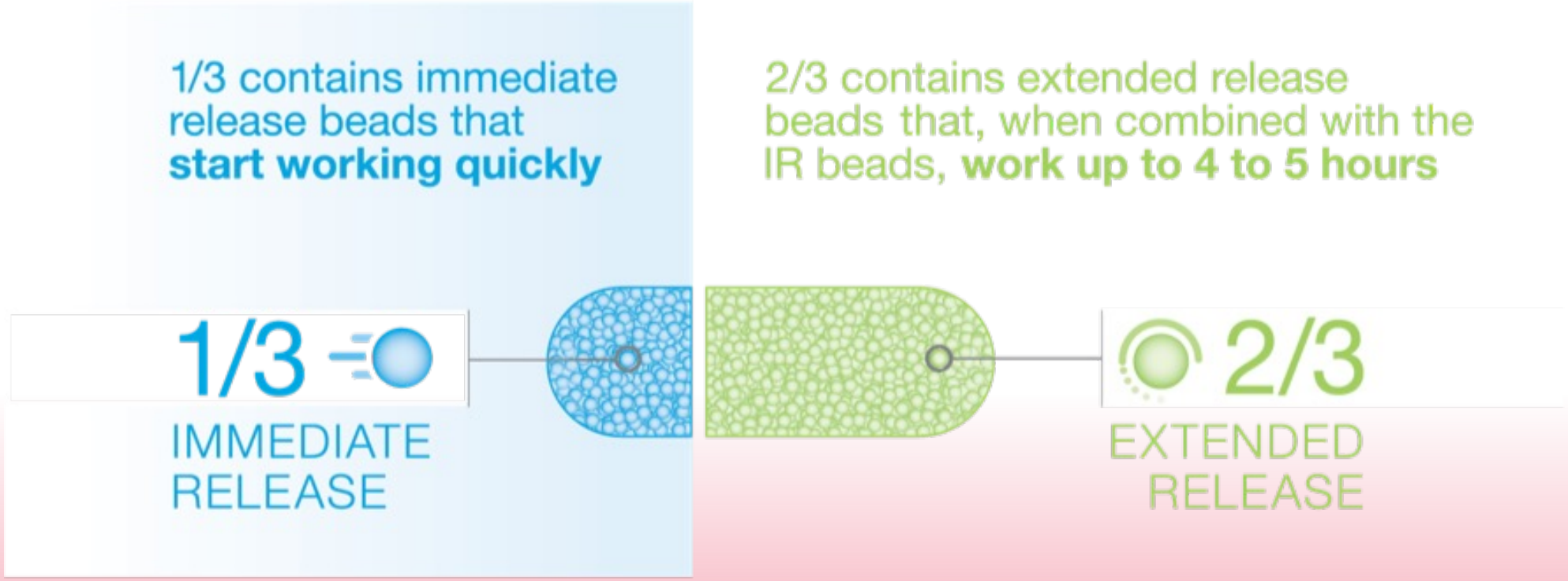
RYTARY COMPETITOR COMPARISONS[14,19]

Distinguishing Factors

- Fewer doses per day
- Less “off time”
- Less dopamine build up in the body
  - ➢ Fewer side effects



RYTARY DISTINGUISHING FACTORS[14]



*Compared to IR CD/LD.

MOST COMMON SIDE EFFECTS – RYTARY[14]

Nausea/vomiting

Headache

FUTURE DIRECTIONS

Lion’s mane mushroom

HERICIUM ERINACEUS

LION'S MANE[20]

HERICIUM ERINACEUS

LION'S MANE[20]

- Can cross blood-brain barrier
- Studies suggest:
  - Neuroprotective
  - Neuro-generative
- Preventive
  - Consistent use over time for most successful outcomes

QUESTIONS?

SOURCE BANK

1. **Tysnes, OB., Storstein, A. Epidemiology of Parkinson's disease. *J Neural Transm* 124, 901–905 (2017). https://doi.org/10.1007/s00702-017-1686-y**
2. Tintner, Ron; Jankovic, Joseph. Treatment options for Parkinson's disease. Current Opinion in Neurology 15(4):p 467-476, August 2002.
3. LeWitt, P.A. (2015), Levodopa therapy for Parkinson's disease: Pharmacokinetics and pharmacodynamics. Mov Disord., 30: 64-72. https://doi.org/10.1002/mds.26082
4. Khor SP, Hsu A. The Pharmacokinetics and Pharmacodynamics of Levodopa in the Treatment of Parkinsons Disease. *Current Clinical Pharmacology*. 2007;2(3):234-243. doi:https://doi.org/10.2174/157488407781668802
5. Tonda-Turo C, Origlia N, Mattu C, Accorroni A, Chiono V. Current Limitations in the Treatment of Parkinson's and Alzheimer's Diseases: State-of-the-Art and Future Perspective of Polymeric Carriers. *Current medicinal chemistry*. 2018;25(41):5755-5771. doi:https://doi.org/10.2174/0929867325666180221125759
6. Schneider RB, Iourinets J, Richard IH. Parkinson's disease psychosis: presentation, diagnosis and management. *Neurodegenerative Disease Management*. 2017;7(6):365-376. doi:https://doi.org/10.2217/nmt-2017-0028
7. Bloem BR, Okun MS, Klein C. Parkinson's disease. *The Lancet*. 2021;397(10291):2284-2303. doi:https://doi.org/10.1016/S0140-6736(21)00218-X
8. Gandhi KR, Saadabadi A. Levodopa (L-Dopa) [Updated 2023 Apr 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482140/
9. Rao SS, Hofmann LA, Shakil A. Parkinson's Disease: Diagnosis and Treatment. *American Family Physician*. 2006;74(12):2046-2054. https://www.aafp.org/pubs/afp/issues/2006/1215/p2046.html#diagnosis
10. Goedert, M. Alpha-synuclein and neurodegenerative diseases. Nat Rev Neurosci 2, 492–501 (2001). https://doi.org/10.1038/35081564
11. Klein, M.O., Battagello, D.S., Cardoso, A.R. et al. Dopamine: Functions, Signaling, and Association with Neurological Diseases. Cell Mol Neurobiol 39, 31–59 (2019). https://doi.org/10.1007/s10571-018-0632-3
12. Larissa Monteiro, Adelmir Souza-Machado, Silvia Valderramas, Ailton Melo, The Effect of Levodopa on Pulmonary Function in Parkinson's Disease: A Systematic Review and Meta-Analysis, Clinical Therapeutics, Volume 34, Issue 5, 2012, Pages 1049-1055, ISSN 0149-2918, https://doi.org/10.1016/j.clinthera.2012.03.001. (https://www.sciencedirect.com/science/article/pii/S0149291812001464)
13. World Health Organization
14. Rytary.com

SOURCE BANK

15. N. Joan Abbott, Adjanie A.K. Patabendige, Diana E.M. Dolman, Siti R. Yusof, David J. Begley, Structure and function of the blood–brain barrier, Neurobiology of Disease, Volume 37, Issue 1, 2010, Pages 13-25, ISSN 0969-9961, https://doi.org/10.1016/j.nbd.2009.07.030. (https://www.sciencedirect.com/science/article/pii/S0969996109002083)

16. Vala sciences

17. Types of Parkinsonisms | Parkinson's Foundation. www.parkinson.org. https://www.parkinson.org/understanding-parkinsons/what-is-parkinsons/types-parkinsonisms

18. Levodopa, Carbidopa Mnemonic for USMLE. pixorize.com. Accessed June 10, 2024. https://pixorize.com/view/6482

19. Mittur A, Gupta S, Modi NB. Pharmacokinetics of Rytary®, An Extended-Release Capsule Formulation of Carbidopa–Levodopa. *Clinical Pharmacokinetics*. 2017;56(9):999-1014. doi:https://doi.org/10.1007/s40262-017-0511-y

20. Saitsu Y, Nishide A, Kikushima K, Shimizu K, Ohnuki K. Improvement of cognitive functions by oral intake of Hericium erinaceus. Biomed Res. 2019;40(4):125-131. doi: 10.2220/biomedres.40.125. PMID: 31413233.