PARKINSON'S DISEASE

SPOTLIGHT ON DYSKINESIA AND OFF: FEELING GOOD EVERY DAY

WEDNESDAY, JANUARY 29, 2020

AMERICAN PARKINSON DISEASE ASSOCIATION
Strength in optimism. Hope in progress.

Support for this program provided by: ADAMAS

1

WELCOME AND INTRODUCTIONS

Cathi A. Thomas, RN, MS, CNRN
Assistant Clinical Professor of Neurology
Program Director, Parkinson's Disease and Movement Disorders Center
Boston University Medical Campus (BUMC)
Coordinator, American Parkinson Disease Association
Information & Referral Center at BUMC

AMERICAN PARKINSON DISEASE ASSOCIATION
Strength in optimism. Hope in progress.

Support for this program provided by: ADAMAS

2

PRESENTATION

Rebecca Gilbert, MD, PhD
Vice President, Chief Scientific Officer
American Parkinson Disease Association

apda AMERICAN PARKINSON DISEASE ASSOCIATION
Strength in optimism. Hope in progress.

Support for this program provided by: ADAMAS™

3

FINANCIAL DISCLOSURES

Salary & Grant Support: APDA and NYULMC

Honoraria: none

Speaker's Bureau: none

Equity & Consulting Agreements: none

4

OUTLINE

A. Levodopa treatment

B. What are **motor fluctuations**?

C. What are **levodopa-induced dyskinesias**?

D. Current and future **solutions**

5

WHAT IS PARKINSON'S DISEASE?

Dopamine is a brain chemical that is needed for normal movement

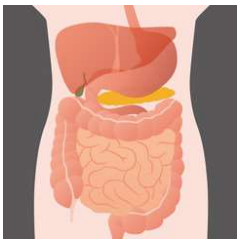
Substantia nigra is the part of the brain that produces dopamine

Slow degeneration of nerve cells in the substantia nigra and other brain areas results in **PARKINSON'S DISEASE**

6

LEVODOPA

Carbidopa/ Levodopa is ingested by **mouth**



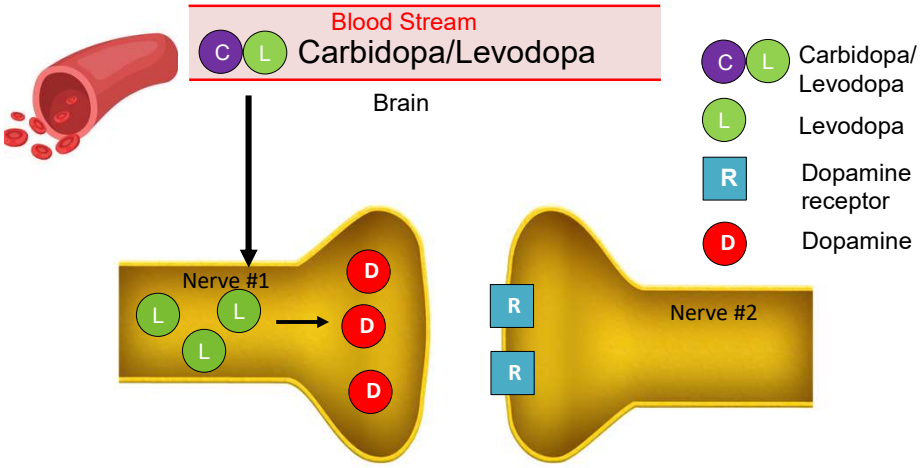
is absorbed in the **small intestine**

enters the **blood stream**

and crosses the blood brain barrier into the **brain**

7

LEVODOPA IS CONVERTED TO DOPAMINE IN THE BRAIN



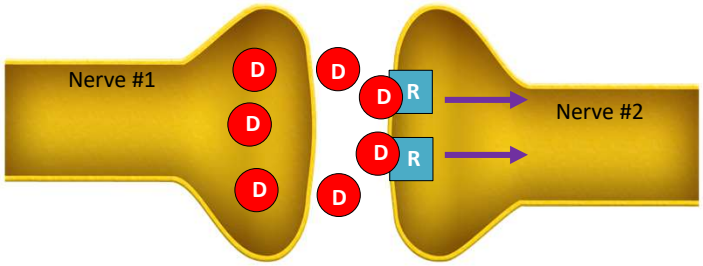
8

LEVODOPA IS CONVERTED TO DOPAMINE IN THE BRAIN

Dopamine enters the space between the neurons, binds with the dopamine receptor and allows for communication between neurons

R Dopamine receptor

D Dopamine

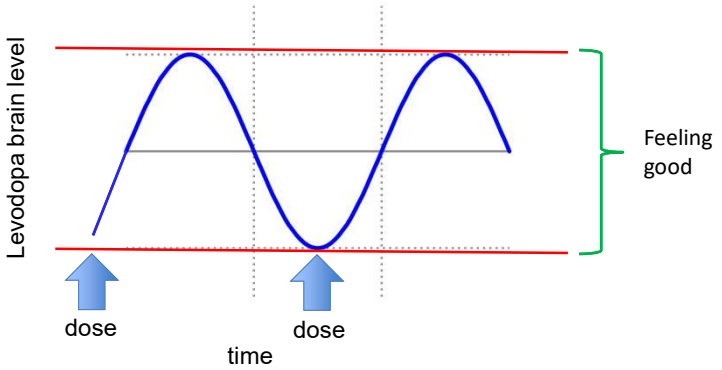


9

MOTOR FLUCTUATIONS IN PARKINSON'S DISEASE

With each Levodopa dose, the levels of Levodopa in the brain rise and then fall.

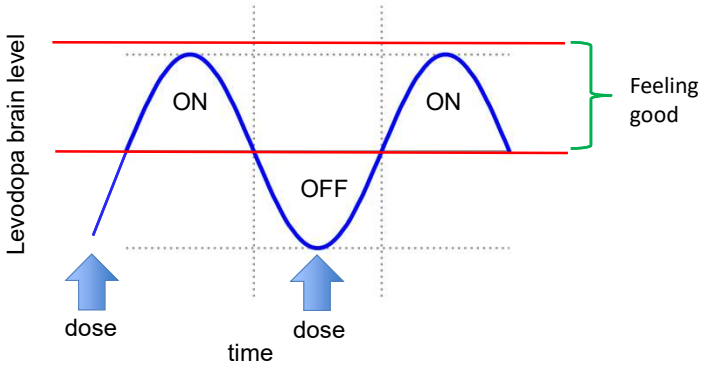
Early on, these changes don't matter.



10

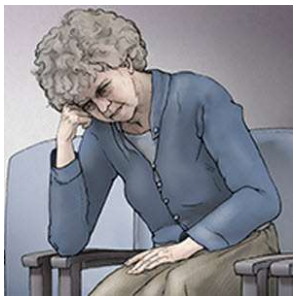
MOTOR FLUCTUATIONS IN PARKINSON'S DISEASE

As the disease progresses, there is a narrower range of levodopa brain levels that leads to a good clinical response.



11

OFF TIME



Motor symptoms

- Slowness
- Stiffness
- Difficulty walking
- Tremor

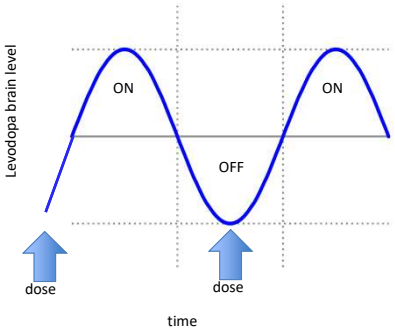
Non-motor symptoms

- Anxiety
- Depression
- Pain

12

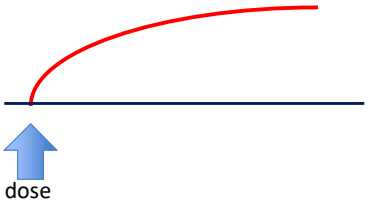
MANAGING OFF TIME

WITHOUT managing OFF time

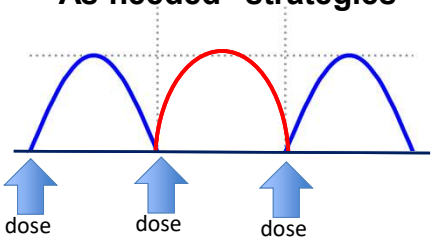


WITH managing OFF time

More continuous drug delivery



"As needed" strategies

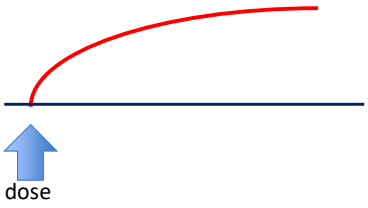


13

MANAGING OFF TIME

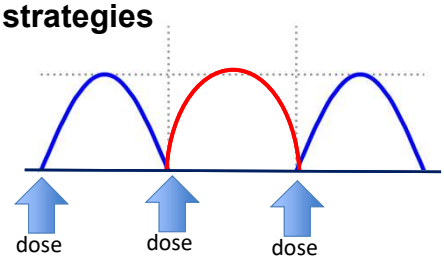
More continuous drug delivery

- Use a longer acting levodopa formulation
- Add another medication with a different mechanism of action to lengthen the effect of a dose
- Deep brain stimulation



"As needed" strategies

- Give Levodopa doses more frequently
- Use a quick acting medication as needed if a dose wears off



14

LEVODOPA FORMULATIONS

Drug	Formulation	Brand Name	Continuous or As Needed
Carbidopa / Levodopa	Immediate release (IR)	Sinemet®	
Carbidopa / Levodopa	Extended release (ER)	[N/A - generic only]	Continuous
Carbidopa / Levodopa	Extended release capsules (ER)	Rytary®	Continuous
Carbidopa / Levodopa	Intestinal gel	Duopa®	Continuous
Carbidopa / Levodopa	Orally disintegrating	Parcopa®	As Needed
Levodopa	Inhalation powder	Inbrija™	As Needed

15

LEVODOPA-INDUCED DYSKINESIAS

Levodopa-induced dyskinesias (LIDs) are **movements** that are:

- Involuntary
- Uncontrolled
- Purposeless

….and are a **side effect of Levodopa**

16

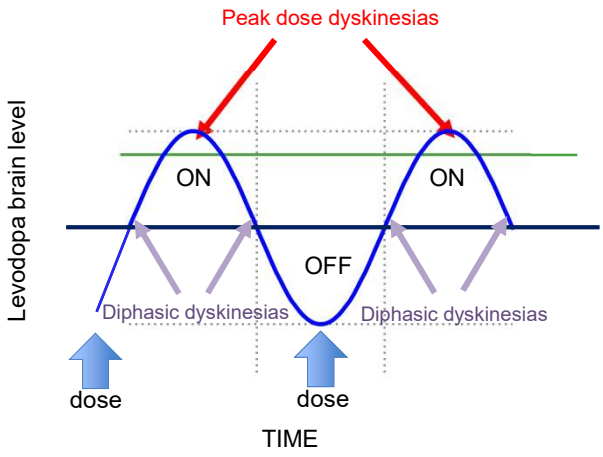
LEVODOPA-INDUCED DYSKINESIAS

In order to get LIDs, you need:

- Intermittent exposure to Levodopa
  AND
- Progressive loss of dopamine neurons

17

TYPES OF LEVODOPA-INDUCED DYSKINESIAS



18

LEVODOPA-INDUCED DYSKINESIAS

- Typically affect the more parkinsonian side first
- Affect various parts of the body including neck, face, limbs, shoulders, torso
- Typically start in mild form and become more noticeable over time
- Can interfere with walking, daily activities, and social life
- Stress and excitement can exacerbate LIDs
- Can contribute to weight loss associated with PD

19

LEVODOPA-INDUCED DYSKINESIAS

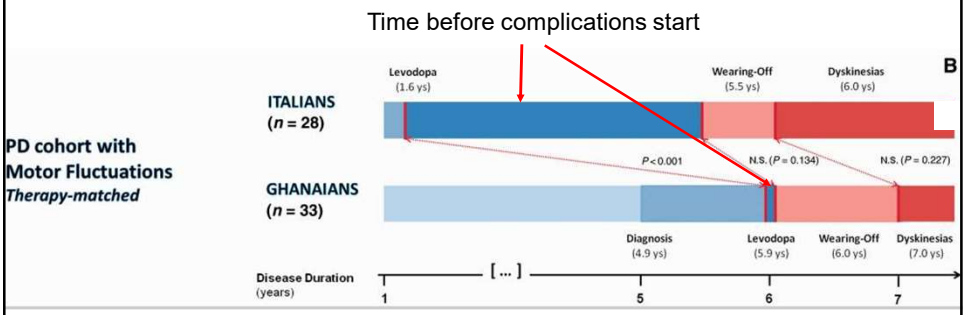
- About 50% of persons with PD develop LIDs after 5-years of Levodopa therapy
- Unlike tremor, LIDs are not regular and rhythmic. Some people may have a hard time distinguishing between tremor and dyskinesias
- If a patient mistakes LIDs for tremor, the doctor may increase Levodopa and make LIDs inadvertently worse
- Some people may not be aware that they have LIDs, whereas others may be very bothered by them
- If a person is not bothered by the LIDs, they do not need to be treated

20

CAN DYSKINESIAS BE PREVENTED?

Q: Does delaying Levodopa treatment affect LIDs?

A: No. The clock to LIDs starts ticking when PD starts, not when Levodopa is started



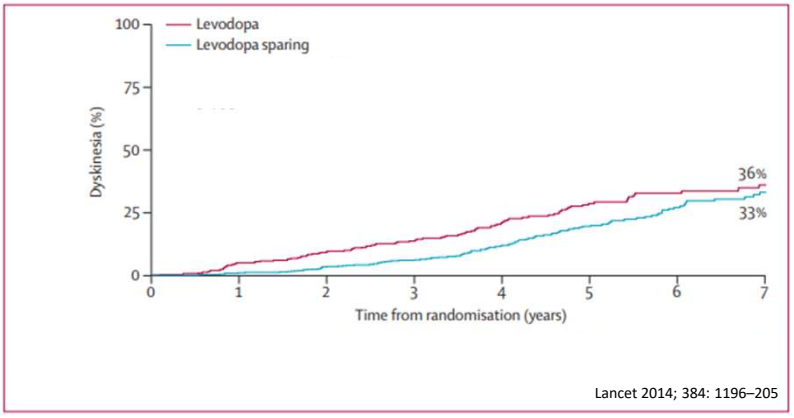
Brain. 2014 Oct; 137(10): 2731–2742.

21

CAN DYSKINESIAS BE PREVENTED?

Q: Does avoiding Levodopa when PD is first diagnosed affect subsequent emergence of LIDs?

A: No



Lancet 2014; 384: 1196–205

22

CAN DYSKINESIAS BE PREVENTED?

Q: Does introduction of Levodopa in a more continuous manner (as opposed to a pulsatile manner) affect development of LIDs?

A: Not yet known. There has been no clinical trial of LIDs in those who receive long-acting vs short-acting Levodopa **as the first treatment.**

23

TREATMENT OF LEVODOPA INDUCED DYSKINESIAS

Treatments include:

- Change levodopa dosage and/or timing
- Convert to a long-acting levodopa formulation
- Add an amantadine formulation
- Deep brain stimulation

Physicians consider multiple factors including whether the LIDs are peak dose or diphasic when deciding on treatment

24

CONVERT TO LONG-ACTING LEVODOPA?

The **"ADVANCE-PD"** clinical trial examined the effect of **extended release** capsules

Drug	Formulation	*ON Time** BASELINE	*ON Time** END OF STUDY	*ON Time** DIFFERENCE
Sinemet	Immediate release	10.1 hours	10.91 hours	+0.8 hours
Rytary 	Capsule contains Immediate Release **AND Extended Release** beads	9.96 hours	11.84 hours	**+1.88** hours

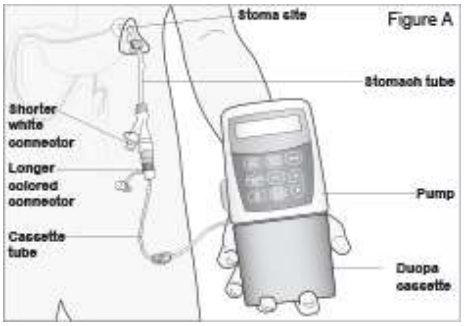
ON Time* here refers only to ON time *without* troublesome dyskinesias

Lancet 2013; 12(4): 346-356

25

CONVERT TO LONG- ACTING LEVODOPA?

Levodopa-carbidopa intestinal gel (LCIG)



https://www.pdr.net/full-prescribing-information?druglabelid=3668

26

CONVERT TO LONG-ACTING LEVODOPA?

Patients treated with Levodopa Carbidopa Intestinal gel (LCIG) had less time with troublesome dyskinesias and more ON time without troublesome dyskinesias than those treated with Carbidopa/Levodopa immediate release

Mov Disorder 2016 Apr; 31(4): 530–537.

27

AMANTADINE

Amantadine:

- has been used to treat LIDs for decades
- reduced LIDs in clinical trials
- has anti-parkinsonian effects, so can help the motor symptoms of Parkinson's disease as well

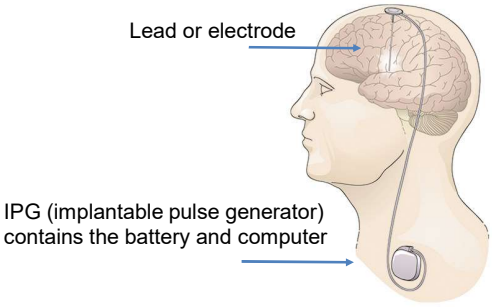
28

AMANTADINE EXTENDED RELEASE CAPSULES

- Amantadine extended release capsules (Gocovri®) is approved by the FDA for treatment of LIDs
- In clinical trials, it improved dyskinesias and reduced OFF time (*Mov Disorder* 2015; 30: 788-795; *Mov Disorder* 2017; 32: 1701-1709; *JAMA Neurol* 2017; 74: 941-949)
- The formulation provides an initial lag in amantadine concentration, then a slow rise during the night, and a high concentration in the morning and through the waking day
- Additional clinical studies are necessary to directly compare efficacy of extended release amantadine to immediate release amantadine for control of LIDs

29

DEEP BRAIN STIMULATION (DBS)



https://www.ninds.nih.gov/About-NINDS/Impact/NINDS-Contributions-Approved-Therapies/DBS

DBS can reduce dyskinesias by
- allowing for reduction of levodopa dosage
- directly affecting electrical activity in the brain

30

TREATMENT OF DYSKINESIAS IN THE RESEARCH PIPELINE

- Buspirone – 5HT1A serotonin receptor agonist
  - Phase 3 trial completed. No published results yet
- IRL790 – dopamine D3 receptor agonist
  - Phase 1b trial published – showed good safety and tolerability
  - Phase 2 trial completed. No published results yet
- Eltoprazine - 5HT1A/B serotonin receptor agonist
  - Phase 1/2a trial published - showed benefit
- Foliglurax – modulator of MGluR4 glutamate receptors
  - Phase 2 trial underway in Europe
- NLX-112, befiradol, F13640 - 5HT1A serotonin receptor agonist
  - Preclinical studies in rodents show benefit
- Focused ultrasound – procedure to help control dyskinesias
  - Phase 3 clinical trial underway

31

FOCUSED ULTRASOUND

- Focused beams of ultrasound energy converge within the brain tissue to form a small lesion
- Interferes with the electrical activity of the brain
- Being studied for people with dyskinesias

https://www.insightec.com/

32

SUMMARY

- Levodopa-induced dyskinesias and OFF time can adversely affect quality of life in patients with Parkinson's disease
- LIDs may be treated by alteration in Levodopa dose, timing or formulation
- Amantadine (now also available in extended release) can be used to treat LIDs
- Deep brain stimulation may reduce LIDs
- Other medications and procedures for treatment of LIDs are being researched

33

QUESTION & ANSWER

Rebecca Gilbert, MD, PhD
Vice President, Chief Scientific Officer
American Parkinson Disease Association

AMERICAN PARKINSON DISEASE ASSOCIATION
Strength in optimism. Hope in progress.

Support for this program provided by:
ADAMAS™

34

CLOSING REMARKS

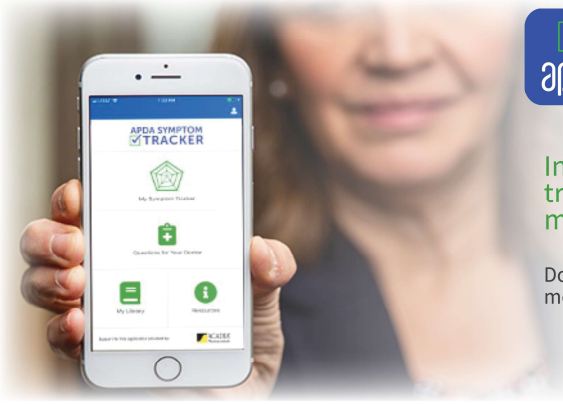
Cathi A. Thomas, RN, MS, CNRN
Assistant Clinical Professor of Neurology
Program Director, Parkinson's Disease and Movement Disorders Center
Boston University Medical Campus (BUMC)
Coordinator, American Parkinson Disease Association
Information & Referral Center at BUMC

apda AMERICAN PARKINSON DISEASE ASSOCIATION
Strength in optimism. Hope in progress.

Support for this program provided by: ADAMAS™

35

APDA SYMPTOM TRACKER APP



apda APDA SYMPTOM TRACKER

Introducing an easier way to track your symptoms and manage your care.

Download the free APDA Symptom Tracker mobile app today.

GET IT ON Google Play

Download on the App Store

36

FOR ADDITIONAL INFORMATION, ANSWERS TO YOUR QUESTIONS, OR FOR ADDITIONAL RESOURCES

Please visit our website
apdaparkinson.org

Or call us
1-800-223-2732

AMERICAN PARKINSON DISEASE ASSOCIATION
Strength in optimism. Hope in progress.

Support for this program provided by:

ADAMAS™

37