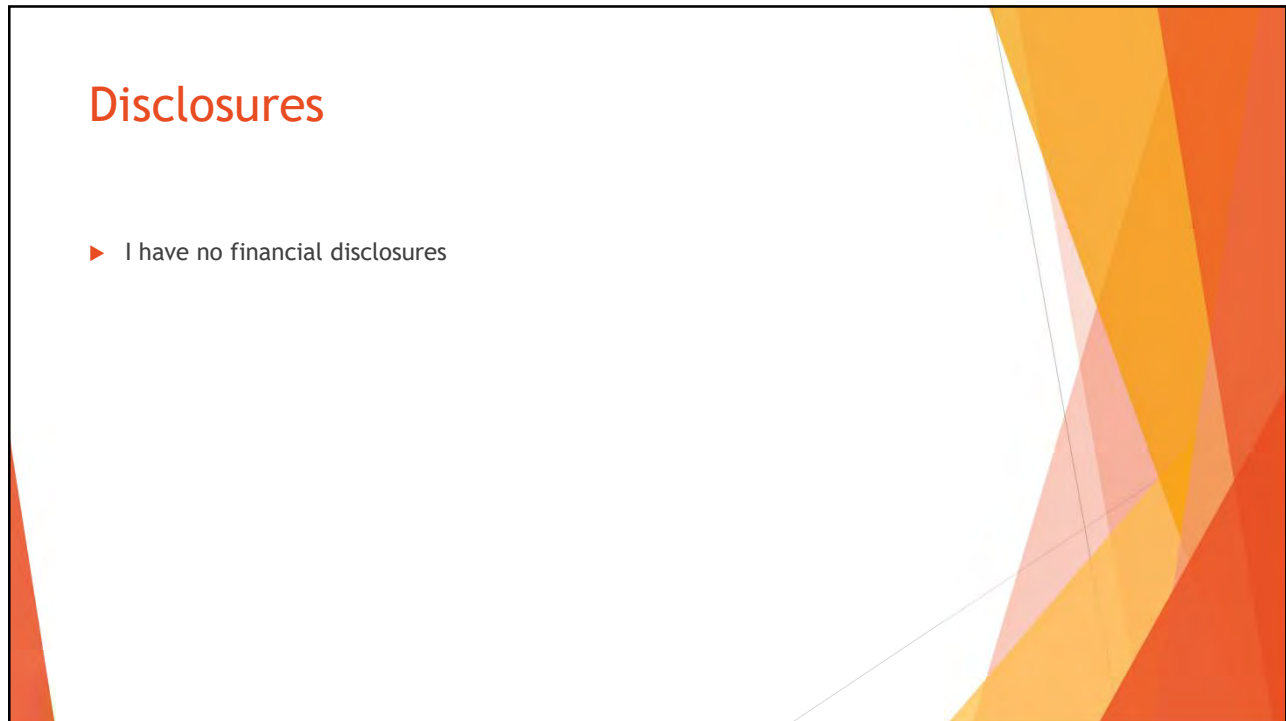


# Management of Moderate to Advanced PD

Mara Seier, MD  
Assistant Professor of Neurological Sciences  
Movement Disorder Division  
University of Nebraska Medical Center

1



## Disclosures

- ▶ I have no financial disclosures

2

## Objectives: Management of Moderate to Advanced PD



Discuss complications of chronic medical management of PD including motor fluctuations and dyskinesia



Recognize the importance of identifying motor complications and the indications for treating them



List medication management options for treatment of motor complications that occur in moderate and advanced PD

3

Things I will not cover:

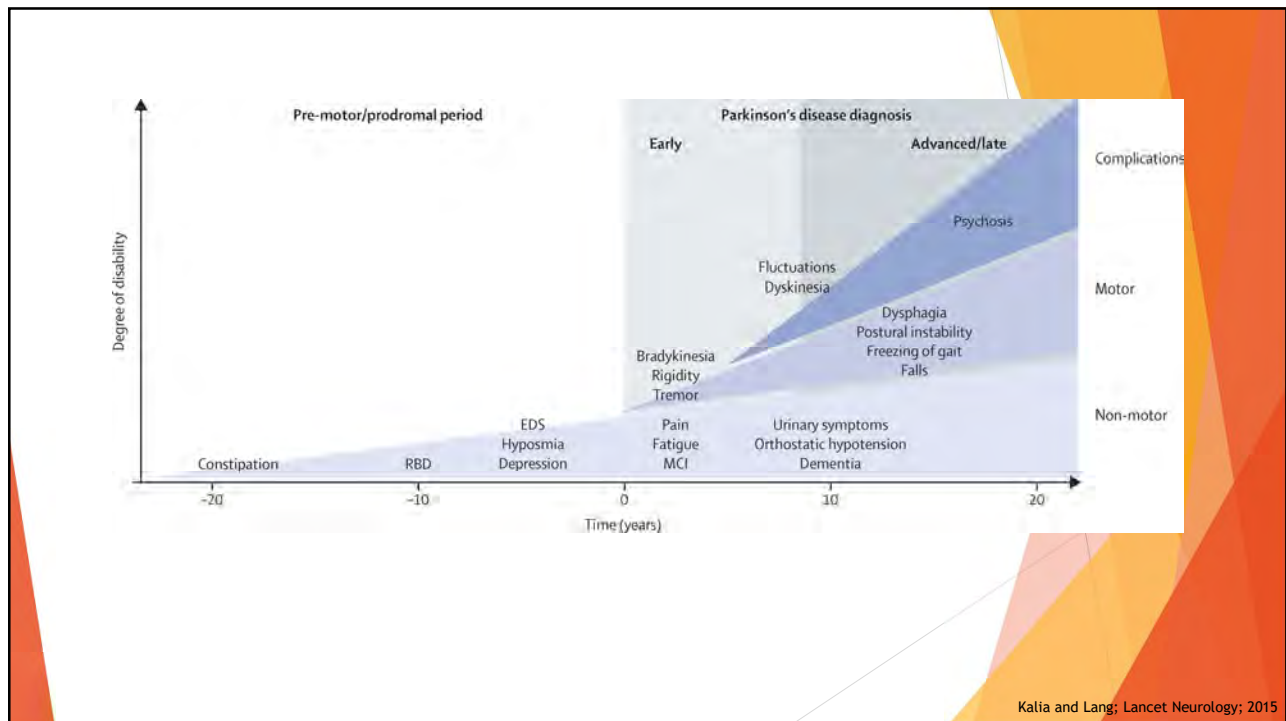
- ▶ DBS
- ▶ Exercise, PT, OT, SLP
- ▶ Non-motor symptoms management



4

## What is Moderate to Advanced PD?

5



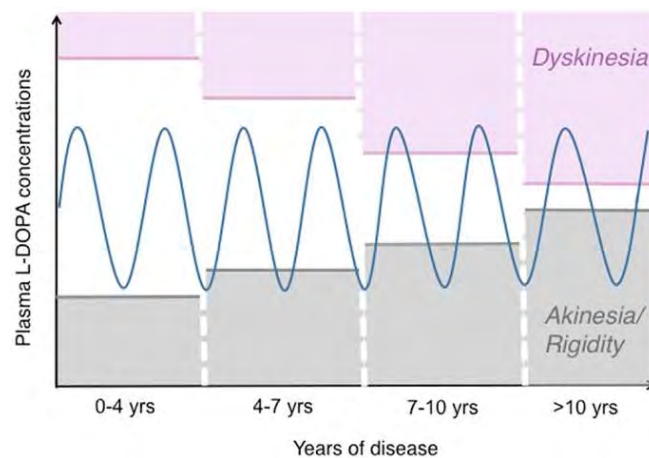
6

## Goals of Management

- ▶ Treatment has to be individualized
- ▶ Family and patient education is critical
  - ▶ Expectations, side effects, need for dose changes in the future, additional medications in the future
- ▶ “Team” decision
  - ▶ Patient and physician making choices together
- ▶ Goal: QOL

7

## As PD advances - a narrowing of the therapeutic window occurs



Jankovic; Movement Disorders; 2005

8

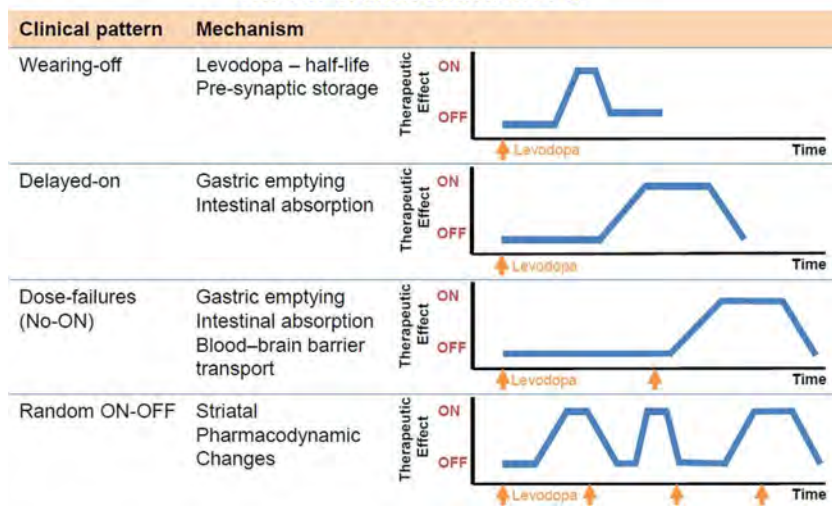
## Levodopa Induced Motor Complications

# Motor Fluctuations

# Dyskinesia

9

### Classification of levodopa-related motor fluctuations in PD



Chaudhuri et al; Movement Disorders; 2018

10

## Treatment of motor fluctuations

- Increasing frequency of levodopa dosing
- Extended release form of levodopa
- Addition of inhaled form of levodopa
- Addition of enzyme inhibitors
- Addition of dopamine agonist
- Addition of istradefylline - a new class
- Intestinal infusion of levodopa

11

## Treatment of motor fluctuations

- Increasing frequency of levodopa dosing
- Extended release form of levodopa
- Addition of inhaled form of levodopa
- Addition of enzyme inhibitors
- Addition of dopamine agonist
- Addition of istradefylline - a new class
- Intestinal infusion of levodopa

12

## Treatment of motor fluctuations

Increasing frequency of levodopa dosing

Extended release form of levodopa

Addition of inhaled form of levodopa

Addition of enzyme inhibitors

Addition of dopamine agonist

Addition of istradefylline - a new class

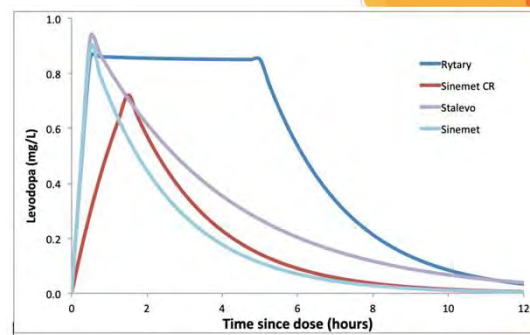
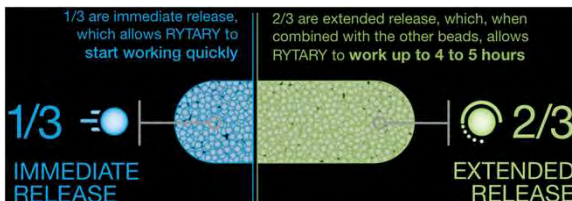
Intestinal infusion of levodopa

13

## Extended Release Carb/Levodopa (Rytary)



\*Carbidopa/levodopa. Capsules may not be representative of actual size.



- ▶ Effective at “smoothing” the roller coaster of on/off times
- ▶ Also can reduce amount of dyskinesia

14

## Treatment of motor fluctuations

Increasing frequency of levodopa dosing

Extended release form of levodopa

**Addition of inhaled form of levodopa**

Addition of enzyme inhibitors

Addition of dopamine agonist

Addition of istradefylline - a new class

Intestinal infusion of levodopa

15

## Inhaled Levodopa (Inbrija)

- ▶ Inhaled levodopa (no carbidopa)
  - ▶ Taking oral medication can take 30-45 minutes to “kick in”
  - ▶ Absorbed directly into the blood system
    - ▶ Can work as quick as 10 minutes but with significant relief starting at 30 minutes
- ▶ **Used as a “Rescue” therapy for treatment of unpredictable off times, delayed on or dose failure**
  - ▶ Also some evidence that it can be used for early morning offs



Hauser et al; Parkinsonism and Relat Disord; 2019  
LeWitt et al; Lancet Neurology; 2017

16



## Treatment of motor fluctuations

Increasing frequency of levodopa dosing

Extended release form of levodopa

Addition of inhaled form of levodopa

**Addition of enzyme inhibitors**

Addition of dopamine agonist

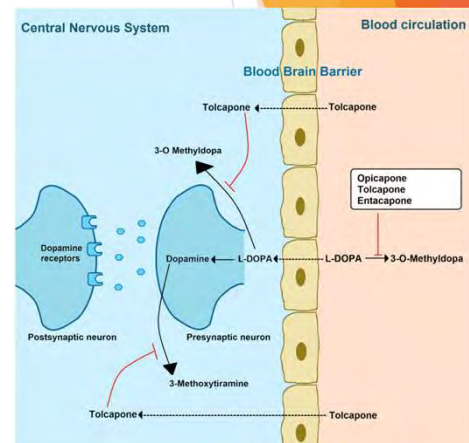
Addition of istradefylline - a new class

Intestinal infusion of levodopa

17

## Catechol-O-methyl Transferase Inhibitors (COMT inhibitors)

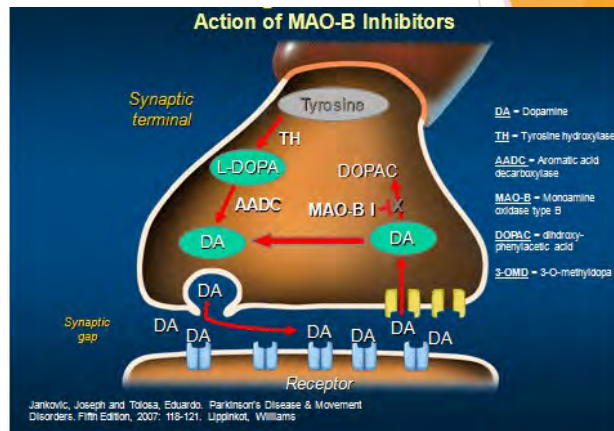
- ▶ Increases half-life of Levodopa, prevents it from being metabolized
  - ▶ Given with Levodopa to increase the duration of effect (increases “on” time)
- ▶ **Entacapone, Opicapone and Tolcapone**
  - ▶ Tolcapone more potent and crosses the blood brain barrier



18

## Monoamine oxidase-B inhibitors

- ▶ Selegiline
- ▶ Rasagiline
- ▶ Safinamide



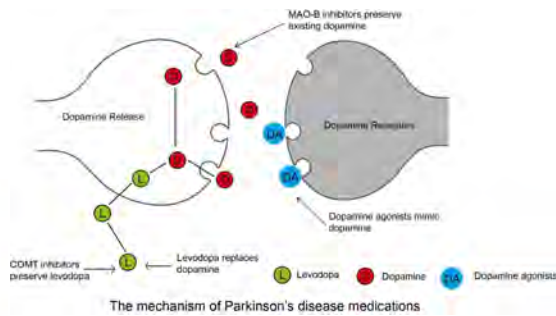
19

## Treatment of motor fluctuations

- Increasing frequency of levodopa dosing
- Extended release form of levodopa
- Addition of inhaled form of levodopa
- Addition of enzyme inhibitors
- Addition of dopamine agonist**
- Addition of istradefylline - a new class
- Intestinal infusion of levodopa

20

## Dopamine Agonists

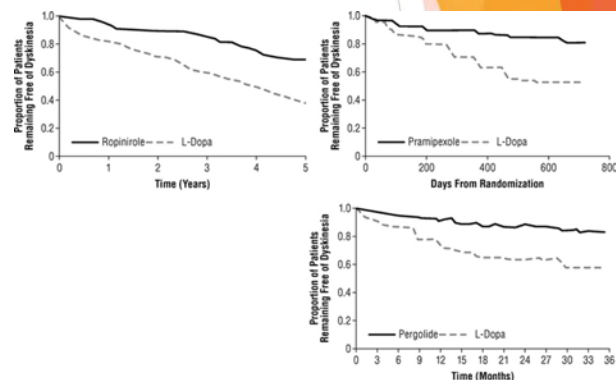


- ▶ Ropinirole (IR and ER)
- ▶ Pramipexole (IR and ER)
- ▶ Rotigotine (dermal patch, long acting)
- ▶ Apomorphine (injection and sublingual formulation)

21

## Dopamine agonists - Advantages

- ▶ Do not require metabolic conversion into active product
- ▶ No dietary concerns with protein for absorption into the gut and brain
- ▶ Have a longer half life than IR levodopa
- ▶ Levodopa "sparing"
  - ▶ Levodopa doses can be reduced or maintained lower while still keeping symptoms under control
  - ▶ Reduce risk of motor complications (dyskinesia and wearing off)



Survival analyses demonstrating time to develop dyskinesia in three separate trials

22

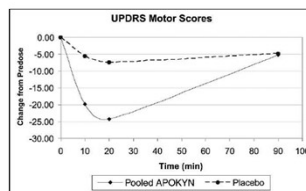
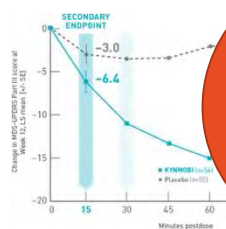
## Dopamine Agonists - Disadvantages

- ▶ Not as potent as Levodopa
- ▶ Side effects
  - ▶ Similar to Levodopa: nausea, vomiting, hypotension
  - ▶ **Hallucinations** (especially in older patients)
  - ▶ **Excessive daytime sleepiness** (“sleep attacks”)
  - ▶ Lower leg edema
  - ▶ **Impulse Control Disorders** (ICD): pathologic gambling, hypersexuality, and compulsive eating and shopping - up to 40% of patients
  - ▶ Difficulty with withdrawal symptoms in up to 15-20% (anxiety, panic, irritability, sweating, pain)

23

## Sublingual or Subcutaneous Apomorphine

- ▶ Treatment of Off times; “Rescue” medication
  - ▶ Morning off, early wearing off, delayed on, unpredictable off, dose failure
- ▶ Side effects
  - ▶ Significant for **nausea/vomiting (30%)**; so started in conjunction with an anti-emetic
  - ▶ Hypotension
  - ▶ Drowsiness



24

## Treatment of motor fluctuations

Increasing frequency of levodopa dosing

Extended release form of levodopa

Addition of inhaled form of levodopa

Addition of enzyme inhibitors

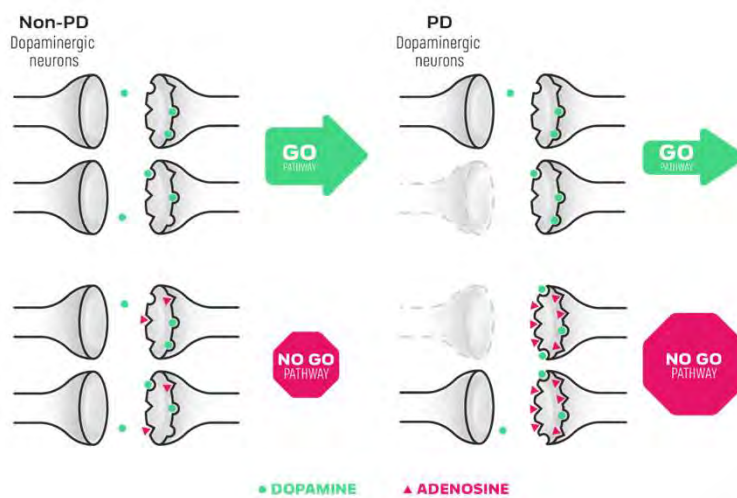
Addition of dopamine agonist

**Addition of istradefylline - a new class**

Intestinal infusion of levodopa

25

## Istradefylline: adenosine receptor antagonist



26

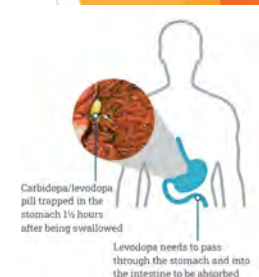
## Treatment of motor fluctuations

- Increasing frequency of levodopa dosing
- Extended release form of levodopa
- Addition of inhaled form of levodopa
- Addition of enzyme inhibitors
- Addition of dopamine agonist
- Addition of istradefylline - a new class
- Intestinal infusion of levodopa

27

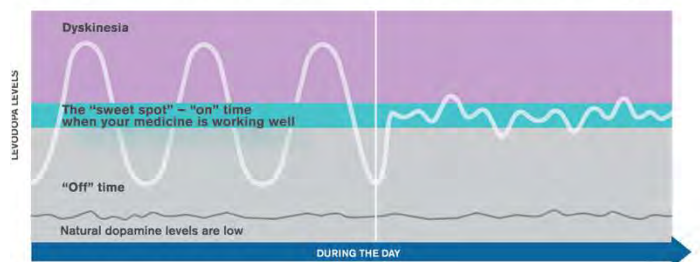
## Continuous Intestinal Carbidopa/Levodopa (Duopa)

- ▶ Levodopa is absorbed in the jejunum (the 2<sup>nd</sup> portion of the small intestine)
  - ▶ PD can slow transit time in the GI tract, thus pills can become trapped in the stomach or upper intestine which will delay on time and/or can cause unpredictable on times
  - ▶ “Dial” in on correct dose



LEVODOPA LEVELS are often too low or too high in advanced Parkinson's

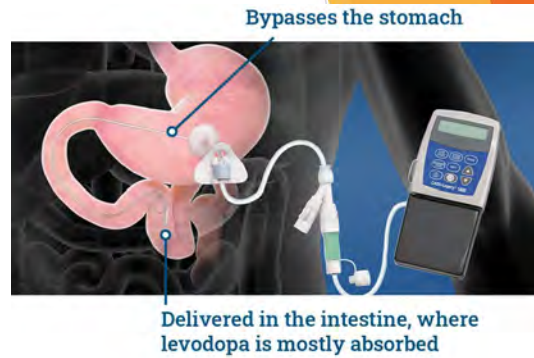
THE GOAL OF THERAPY is to keep levodopa levels within the "sweet spot"



28

## Continuous Intestinal Carb/Levodopa (Duopa)

- ▶ Increases On time by 2 hours compared to oral immediate release C/L
  - ▶ Also can increase On time without bothersome dyskinesia
- ▶ Runs for 16 hours during the day



29

## **\*\*NEW Levodopa Formulation!\*\***

Safety and efficacy of continuous subcutaneous foslevodopa-foscarbidopa in patients with advanced Parkinson's disease: a randomised, double-blind, active-controlled, phase 3 trial

- ▶ Subcutaneous 24-hour infusion of levodopa-based therapy
  - ▶ Foscarbidopa/foslevodopa - approved for use in European Union
  - ▶ Awaiting FDA approval in the US!!!

30

Adjusting medications to  
treat motor fluctuations is  
not done in a vacuum

31

Levodopa Induced Motor Complications

Motor Fluctuations

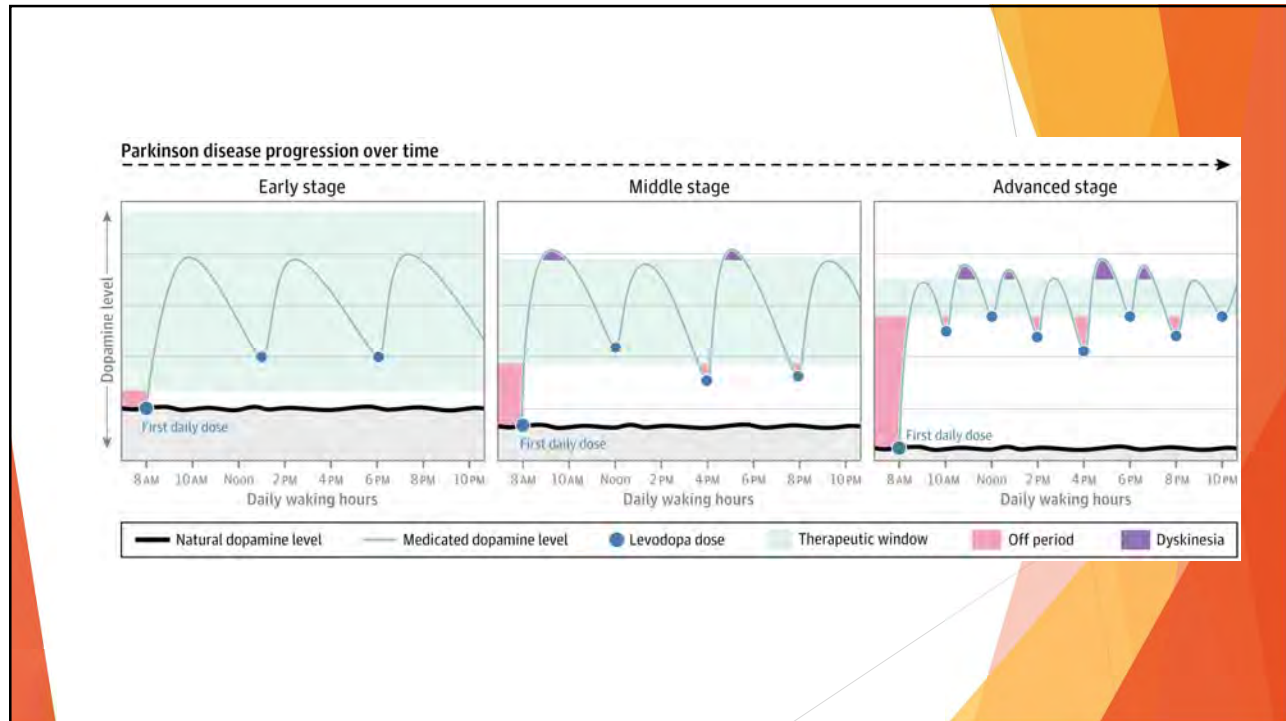
Dyskinesia



Zesiewicz; Continuum; 2019

32





33

## Treatment of dyskinesia

Identifying its occurrence in relation to the levodopa dosing

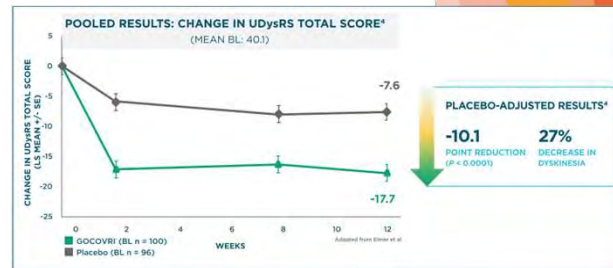
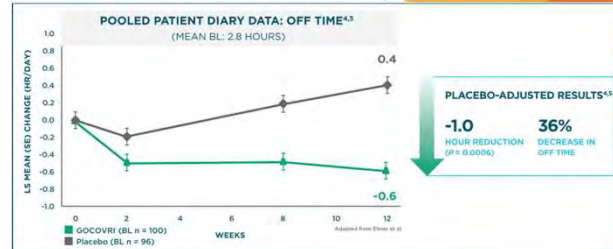
Redistribution or lowering doses; consideration of long-acting formulation

Addition of amantadine

34

## Extended Release Amantadine (Gocovri; Osmolex)

- ▶ **Amantadine** is an NMDA antagonist:
  - ▶ Increases dopamine release and inhibits dopamine reuptake
  - ▶ Reduces glutamate hyperactivity which may contribute to both **improved Off time** and **reduction of Dyskinesia**



35

## Conclusions

- ▶ Motor fluctuations and Dyskinesia are common manifestations of disease progression in PD
- ▶ Medical adjustments and additional medications can help relieve these complications
- ▶ Combined decision making between patient and medical team is necessary



36