



PARKINSON'S DISEASE

SPOTLIGHT ON PARKINSON'S DISEASE: UNDERSTANDING DYSKINESIA

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WELCOME AND INTRODUCTIONS



Stephanie Paul

Vice President Development and Marketing
American Parkinson Disease Association



PRESENTATION



M. Maral Mouradian, MD

William Dow Lovett Professor of Neurology
Director, Center for Neurodegenerative and Neuroimmunologic Diseases
Rutgers - Robert Wood Johnson Medical School
Piscataway, NJ

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DOPAMINE NEURON LOSS IN PARKINSON'S DISEASE

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Normal Parkinson

By the time motor symptoms emerge 50% of dopamine neurons and 80% of striatal dopamine content are depleted

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DOPAMINE REPLACEMENT THERAPY IN PARKINSON'S DISEASE

Normal Dopamine Neuron

Parkinson's Disease

Dopamine Agonists:

- Ropinirole
- Pramipexole
- Rotigotine
- Apomorphine

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THE EVOLUTION OF THE RESPONSE TO L-DOPA IN PARKINSON'S DISEASE OVER TIME

- L-dopa is still the gold standard treatment for Parkinson's disease
- Initially, infrequent dosing three times per day provides a stable beneficial response throughout the day
- Over time, response complications emerge:
 - Wearing off fluctuations
 - On-off fluctuations
 - L-dopa induced dyskinesia

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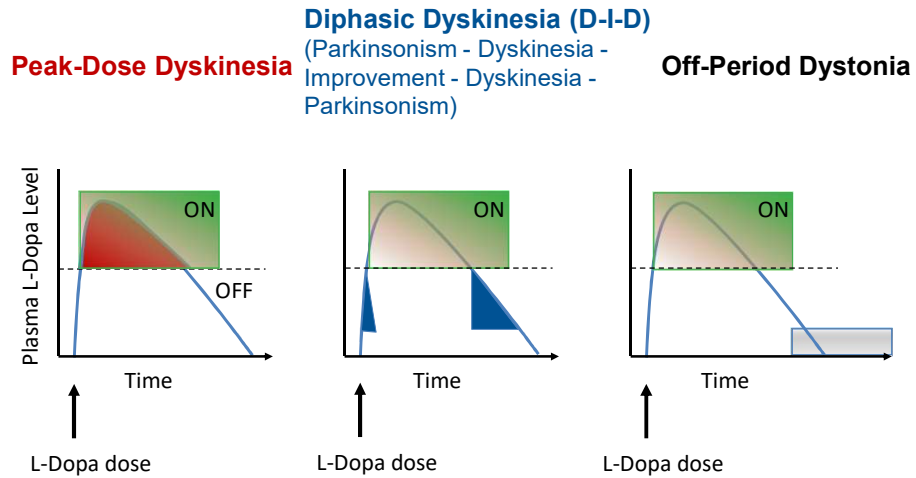
WHAT IS L-DOPA INDUCED DYSKINESIA?

- Involuntary, uncontrolled, purposeless movements
- Unlike tremor, dyskinesias are non-rhythmic
- Can be transiently or partially suppressed volitionally
- Affect various parts of the body including neck, face, limbs, shoulders, torso
- Start in mild form and become more noticeable over time
- Can interfere with walking, daily activities, and social life
- Stress and excitement can exacerbate dyskinesia

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TYPES OF L-DOPA INDUCED DYSKINESIA



HOW COMMON IS L-DOPA INDUCED DYSKINESIA?

- L-dopa induced dyskinesia is a common issue in the management of Parkinson's disease
- On average, about 50% of persons with Parkinson's disease develop this complication after 5-years of L-dopa therapy
- Around 90% by 10 years
- Can emerge within months or even weeks of starting L-dopa



FACTORS THAT INCREASE RISK FOR L-DOPA INDUCED DYSKINESIA

- Younger age of disease onset
- Female gender
- Low body weight
- More severe or advanced disease
- Higher L-dopa dose
- Akinetic-rigid dominant type of Parkinson's disease (compared to tremor-predominant type)

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WHAT CAUSES L-DOPA INDUCED DYSKINESIA? THE DISEASE OR TREATMENT?

Both:

- Progressive loss of dopamine neurons as the disease advances over time
- Long-term L-Dopa therapy
 - Intermittent L-dopa intake

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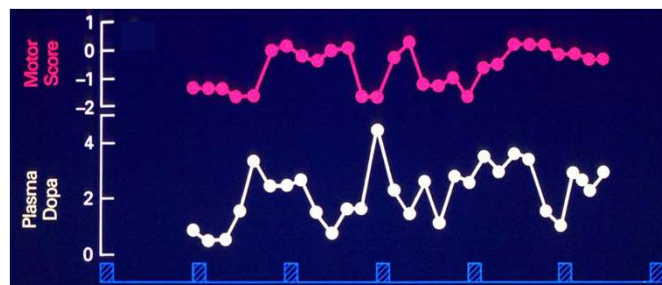
THE ROLE OF PARKINSON SEVERITY IN THE DEVELOPMENT OF L-DOPA INDUCED DYSKINESIA

- Individuals with no Parkinson's disease and normal dopaminergic system do not develop L-dopa induced dyskinesia
- **Pre-LD** era patients: ~ 50% dyskinesia by 5 **months**
- In contrast, **Post-LD** era patients: 50% by 5 **years**
- Starting L-dopa therapy at moderately advanced stage is associated with a shorter time to dyskinesia than starting it at earlier stages
- Dyskinesia is more prominent on the side of the body most affected by Parkinson's disease

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PROPERTIES OF L-DOPA THAT CONTRIBUTE TO RESPONSE FLUCTUATIONS

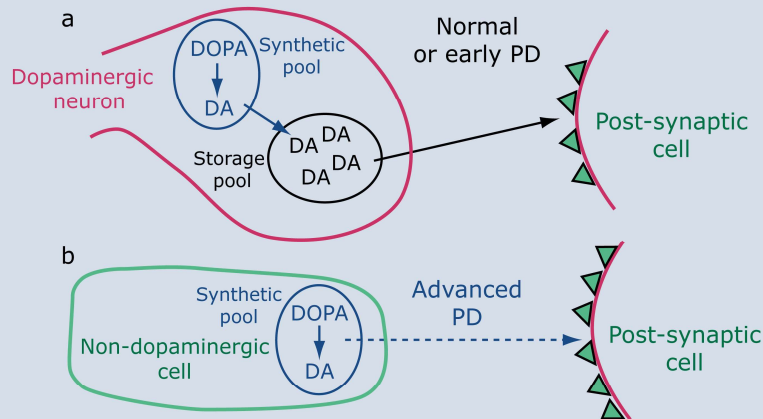
- L-dopa stays in blood for a relatively short time
- Erratic stomach emptying and food interfere with L-dopa absorption
- Dietary proteins interfere with L-dopa entry into the brain



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CHANGE FROM STEADY TO FLUCTUATING BRAIN DOPAMINE LEVELS IN ADVANCED DISEASE

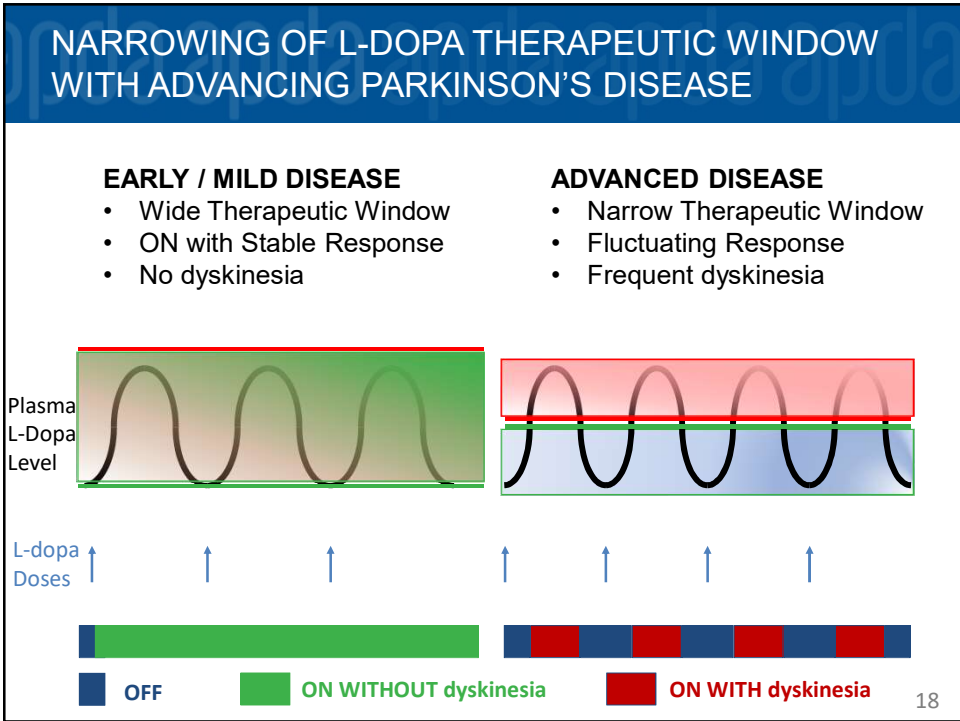
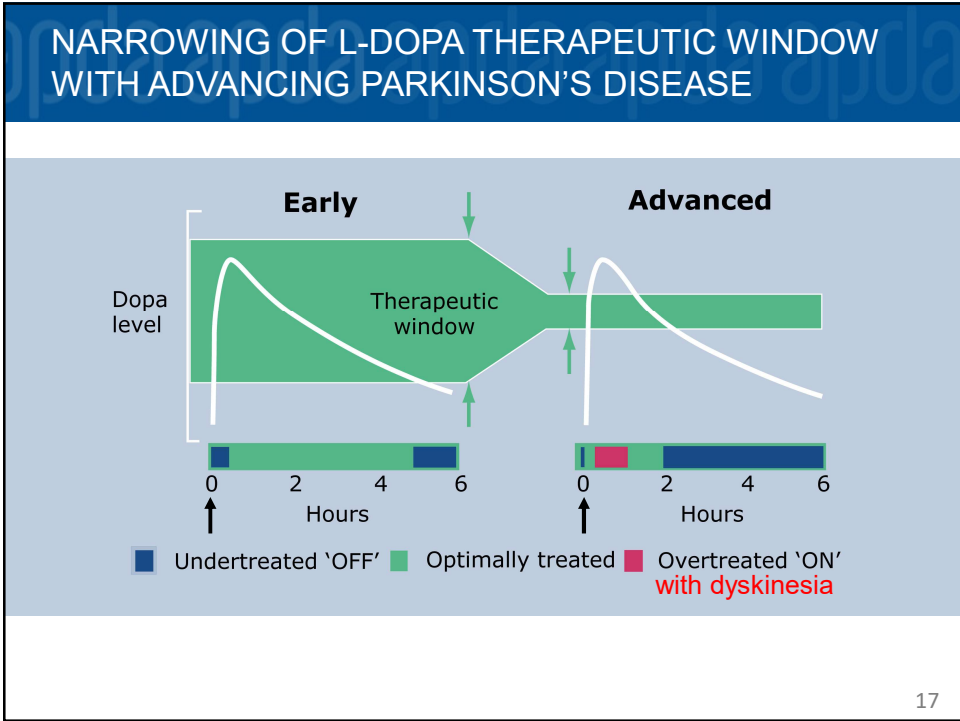


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THE ROLE OF INTERMITTENT DRUG DELIVERY IN THE DEVELOPMENT OF DYSKINESIA

- In laboratory experiments, repeated injections of a dopaminergic drug produces dyskinesia, whereas continuous delivery of the same drug does not
- In individuals with Parkinson's disease, dyskinesia is more commonly induced by L-dopa than by dopamine agonist drugs
- Dopamine agonists generally:
 - Stay in blood for a longer time than L-dopa
 - Less effective than L-dopa as anti-Parkinson drugs

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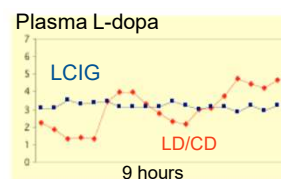
MANAGEMENT OF L-DOPA INDUCED PEAK-DOSE DYSKINESIA

- Peak-dose dyskinesia is treated mainly by:
 - Reducing individual doses of L-dopa and adjusting inter-dose interval
 - Adding amantadine
 - Known for 20 years to have anti-dyskinesia effect
 - Also has mild anti-Parkinson effect
 - Extended release capsule now available (once at bedtime)
 - Compared to placebo, 25-30% reduction in dyskinesia severity
 - Increases ON time without troublesome dyskinesia
 - Deep brain stimulation (DBS)

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MANAGEMENT OF L-DOPA INDUCED DIPHASIC DYSKINESIA

- Diphasic dyskinesias are the most difficult to treat:
 - Adjust L-dopa dosage and schedule
 - Add amantadine
 - Deep brain stimulation
 - L-Dopa Carbidopa Intestinal Gel infusion to maintain plasma L-dopa levels above a certain threshold



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MANAGEMENT OF L-DOPA INDUCED OFF-PERIOD DYSTONIA

- Off-period dystonia is managed by:
 - Adjusting L-dopa dose and schedule to minimize OFF times
 - Extended release L-dopa capsules
 - L-Dopa Carbidopa Intestinal Gel
 - For abrupt off-period dystonia, apomorphine subcutaneous injection
 - Botulinum toxin injections

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ADDITIONAL CONSIDERATIONS FOR THE MANAGEMENT OF LID

- Continuous Dopaminergic Drug Delivery:
 - L-dopa Carbidopa Intestinal Gel
 - Increases ON time without troublesome dyskinesia
 - Decreases OFF time
 - Carbidopa/levodopa extended release capsules
 - More ON time without troublesome dyskinesia
 - Decreases OFF time
 - Apomorphine infusion may reduce dyskinesia
- Safinamide as an adjunct to L-dopa: Increases ON time without worsening dyskinesia

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WHEN TO START L-DOPA THERAPY?

- Individualize treatment
- Generally, L-dopa is needed when symptoms interfere with daily activities, job performance, exercise or quality of life
- Other medications are available for milder symptoms

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WHAT'S ON THE HORIZON FOR LID? DRUGS

- New compounds that target various neurotransmitters / receptors in the brain
- New ways to deliver L-dopa continuously
- Subcutaneous infusion of apomorphine
- Disease modifying treatments for PD

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WHAT'S ON THE HORIZON FOR LID? NON-DRUG TREATMENTS

- Optimize Deep Brain Stimulation
 - Transcranial MR Guided Focused Ultrasound for Unilateral Pallidotomy
 - Creates a lesion
 - Not adjustable
 - Transcranial Static Magnetic Field Stimulation (tSMS)
- Non-invasive:**
No holes in the skull
No implanted device or battery

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QUESTION & ANSWER



M. Maral Mouradian, MD

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CLOSING REMARKS



Stephanie Paul

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