

Changes in Strategies in Managing Motor and Non-Motor Symptoms in Parkinson's Disease

Rami G. Apelian, M.D., M.P.H.

Armenian American Medical Society

2019 AAMS CME

May 4, 2019

RAMI

APELIAN

MD, MPH

<http://ramiapelianmd.com>

Disclosures

- Serving as an active consultant with multiple pharmaceutical companies and device manufacturers across the spectrum of neurological disease
 - Parkinson's: Lundbeck, US World Meds
 - Epilepsy: Eisai, LivaNova, Pfizer, Sunovion, UCB
 - Migraine: Allergan, Lilly
 - Pseudobulbar Affect: Avanir
 - Pain: Pfizer

RAMI

APELIAN

MD, MPH

WHAT IS PARKINSON'S?

1M / US 5M / WORLD

TODAY, AN ESTIMATED **ONE MILLION** PEOPLE IN THE UNITED STATES AND MORE THAN **FIVE MILLION** WORLDWIDE ARE LIVING WITH PARKINSON'S DISEASE.

PARKINSON'S DISEASE AFFECTS **ONE IN 100 PEOPLE OVER AGE 60**. IN THE UNITED STATES, 60,000 NEW CASES WILL BE DIAGNOSED THIS YEAR ALONE.

1 / 100 OVER AGE 60 60,000 NEW

3 OUT OF 5 AMERICANS WILL SUFFER FROM A NERVOUS-SYSTEM DISEASE SUCH AS PARKINSON'S OR ALZHEIMER'S.

LESSER-KNOWN SYMPTOMS OF PARKINSON'S INCLUDE DEPRESSION, APATHY, FATIGUE, AND DEMENTIA.



RESEARCHERS ARE INVESTIGATING POTENTIAL EARLY SYMPTOMS, SUCH AS IMPAIRED SENSE OF SMELL, CERTAIN SLEEP DISORDERS, CONSTIPATION, AND UNUSUAL FATIGUE.



TODAY'S BEST PARKINSON'S DRUG WAS DISCOVERED IN 1967

LYNDON B. JOHNSON WAS PRESIDENT AND NEIL ARMSTRONG HAD NOT YET WALKED ON THE MOON.

PARKINSON'S DISEASE IS CAUSED BY THE DEATH OF DOPAMINE CELLS. 60 TO 80% OF THESE CELLS ARE ALREADY LOST BY THE TIME MOTOR SYMPTOMS APPEAR.



DYSKINESIA IS OFTEN MISTAKEN FOR A SYMPTOM OF PARKINSON'S DISEASE, BUT IT IS ACTUALLY A SIDE EFFECT OF PARKINSON'S TREATMENT. MANY PATIENTS REPORT DYSKINESIA TO BE AS DEBILITATING AS THE DISEASE ITSELF.



THE EXACT CAUSE OF PARKINSON'S DISEASE IS UNKNOWN BUT BOTH GENETICS AND ENVIRONMENT ARE CAUSES.



THERE IS NO TEST TO DIAGNOSE PARKINSON'S DISEASE. PEOPLE WITH PARKINSON'S VISIT MULTIPLE DOCTORS AND CAN WAIT YEARS BEFORE A CORRECT DIAGNOSIS.



THERE IS NO CURE FOR PARKINSON'S DISEASE TODAY. BUT THE MICHAEL J. FOX FOUNDATION IS WORKING URGENTLY TO CHANGE THAT.

LEARN MORE AT WWW.MICHAELJFOX.ORG

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

SOURCES: WWW.MICHAELJFOX.ORG/UNDERSTANDING-PARKINSONS/I-HAVE-GOT-WHAT.PHP | WWW.MICHAELJFOX.ORG/UNDERSTANDING-PARKINSONS/LIVING-WITH-PD.HTML

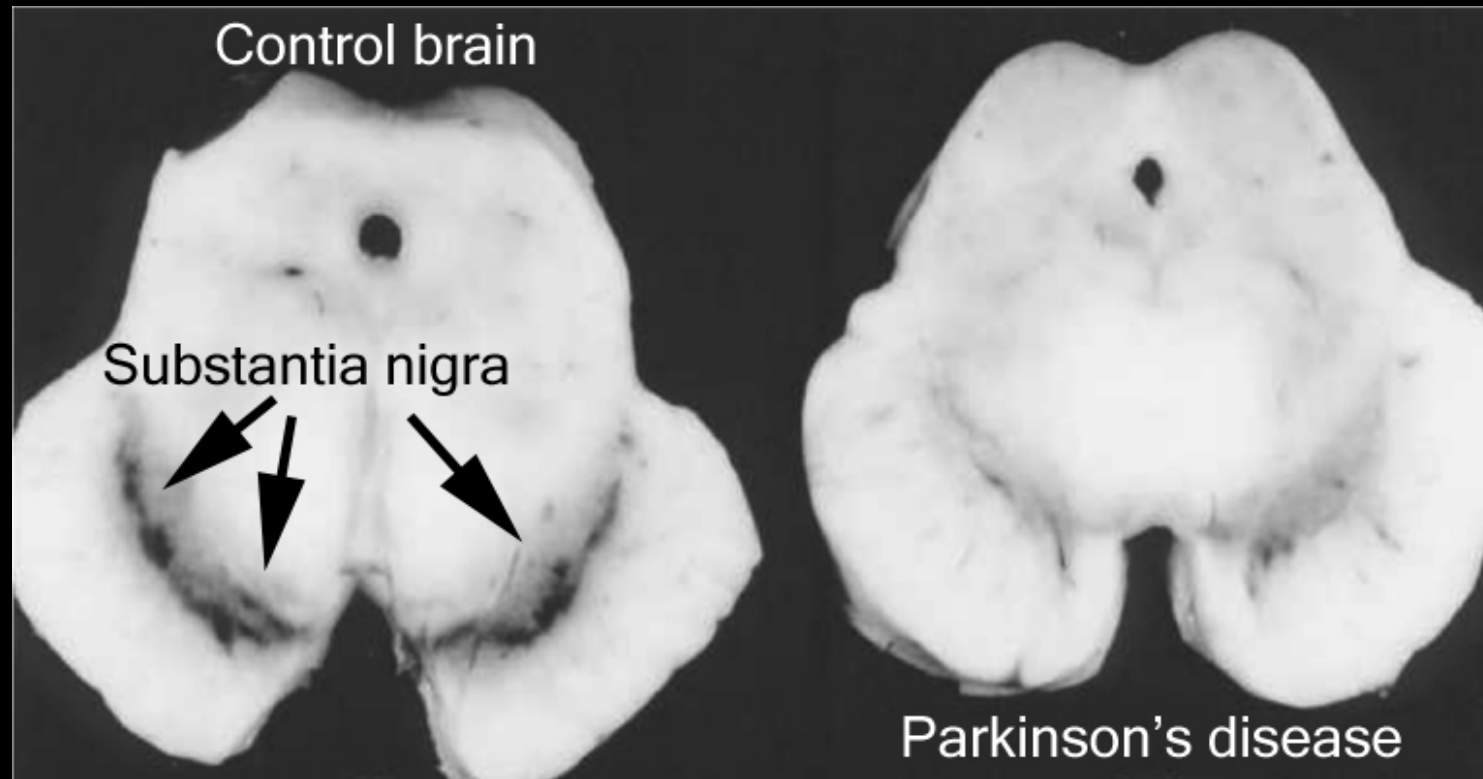
Increases to 4% in patients above the age of 80

Not mentioned: Sleep disturbances, constipation, autonomic instability, sexual dysfunction, psychosis, etc.

Levodopa therapy remains the "gold standard" for managing motor symptoms of PD

What Causes PD?

- Loss of nigral dopaminergic neurons and degeneration of nigrostriatal projections causes the cardinal motor features



What Causes PD?

- Loss of nigral dopaminergic neurons and degeneration of nigrostriatal projections causes the cardinal motor features
- Etiology of PD is unknown
 - Likely multifactorial
 - Combination of environmental and genetic risk factors
- Environmental
 - Pesticides
 - Organic solvents
 - Well-water
 - Living in rural areas
- Genetic
 - Autosomal dominant and recessive genes
 - LRRK2, GBA, SNCA have similar phenotypes to idiopathic PD

RAMI

APELIAN MD, MPH

<http://ramiapelianmd.com>

Alpha-Synuclein and its Role

- Found in Lewy Bodies
- Lewy bodies are found in the surviving nigral neurons



Alpha-Synuclein and its Role

- Found in Lewy Bodies
- Lewy bodies are found in the surviving nigral neurons
- BUT Lewy bodies can also be found outside of the central nervous system

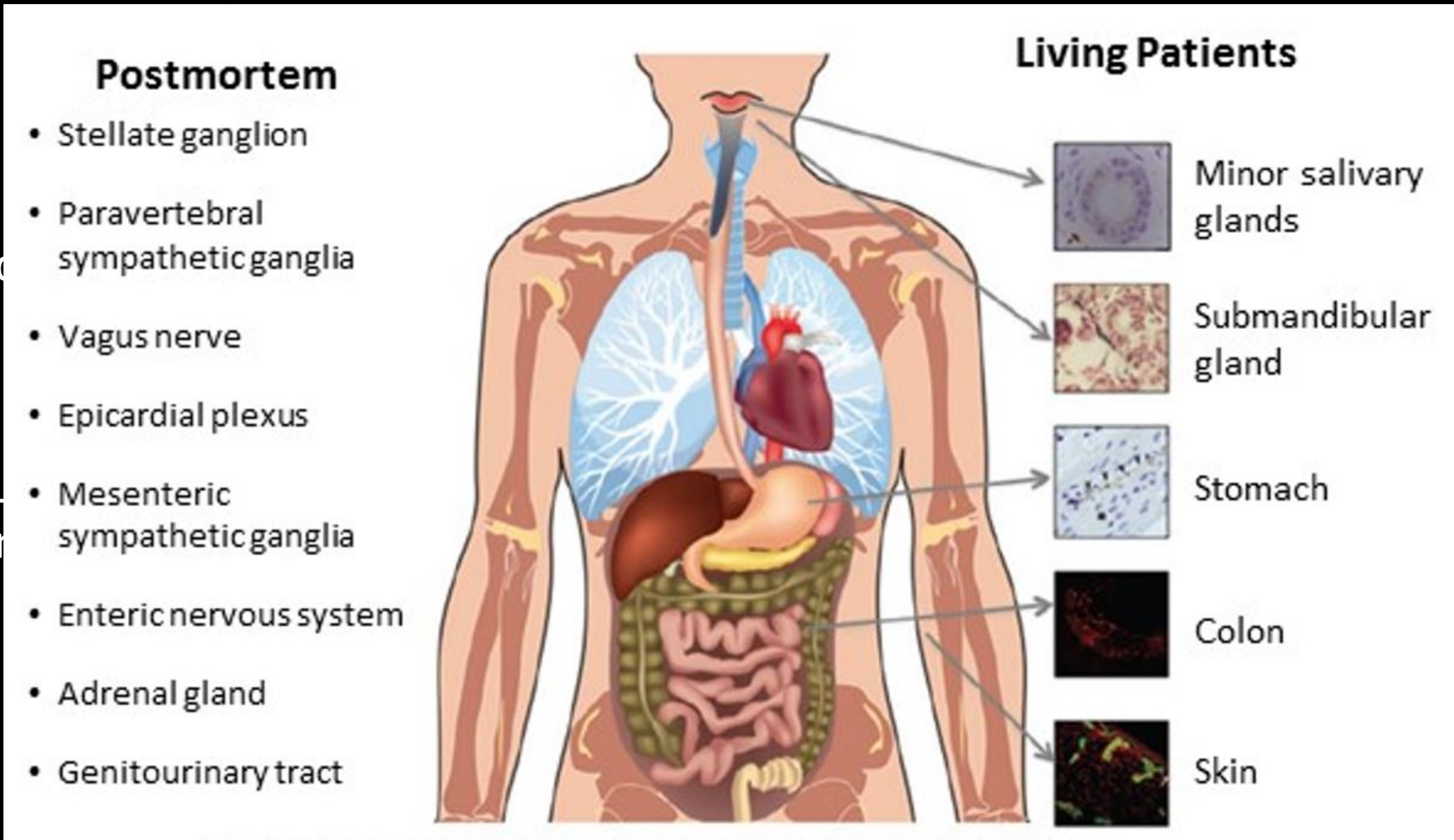
RAMI

APELIAN

MD, MPH

Alpha

- Found
- Lewy
- BUT L
- system



The Symptoms In PD

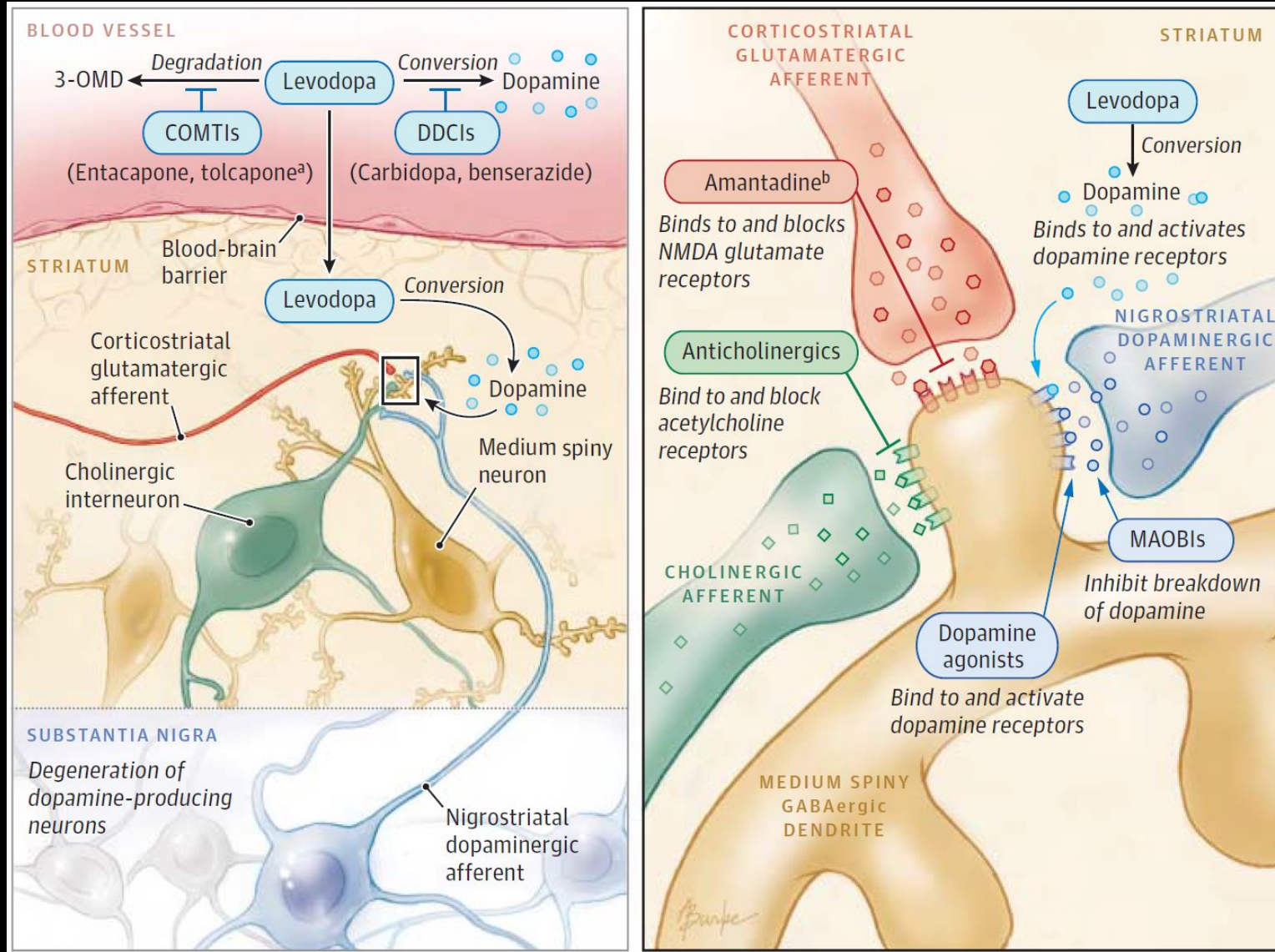
Motor

- Rigidity
- Tremor
- Bradykinesia
- Walking or Gait Disturbances
- Dystonia
- Vocal Symptoms
- Dyskinesia*

Non-Motor

- Loss of smell
- Sleep disturbances
- Depression / Anxiety
- Psychosis and Hallucinations
- Fatigue
- Cognitive changes
- Constipation
- Sexual dysfunction
- Excessive drooling
- Melanoma
- Ocular dysfunction
- Orthostatic hypotension
- Urinary urgency and frequency
- Pain
- Pseudobulbar affect
- Impulse control disorders*

Managing Motor Symptoms



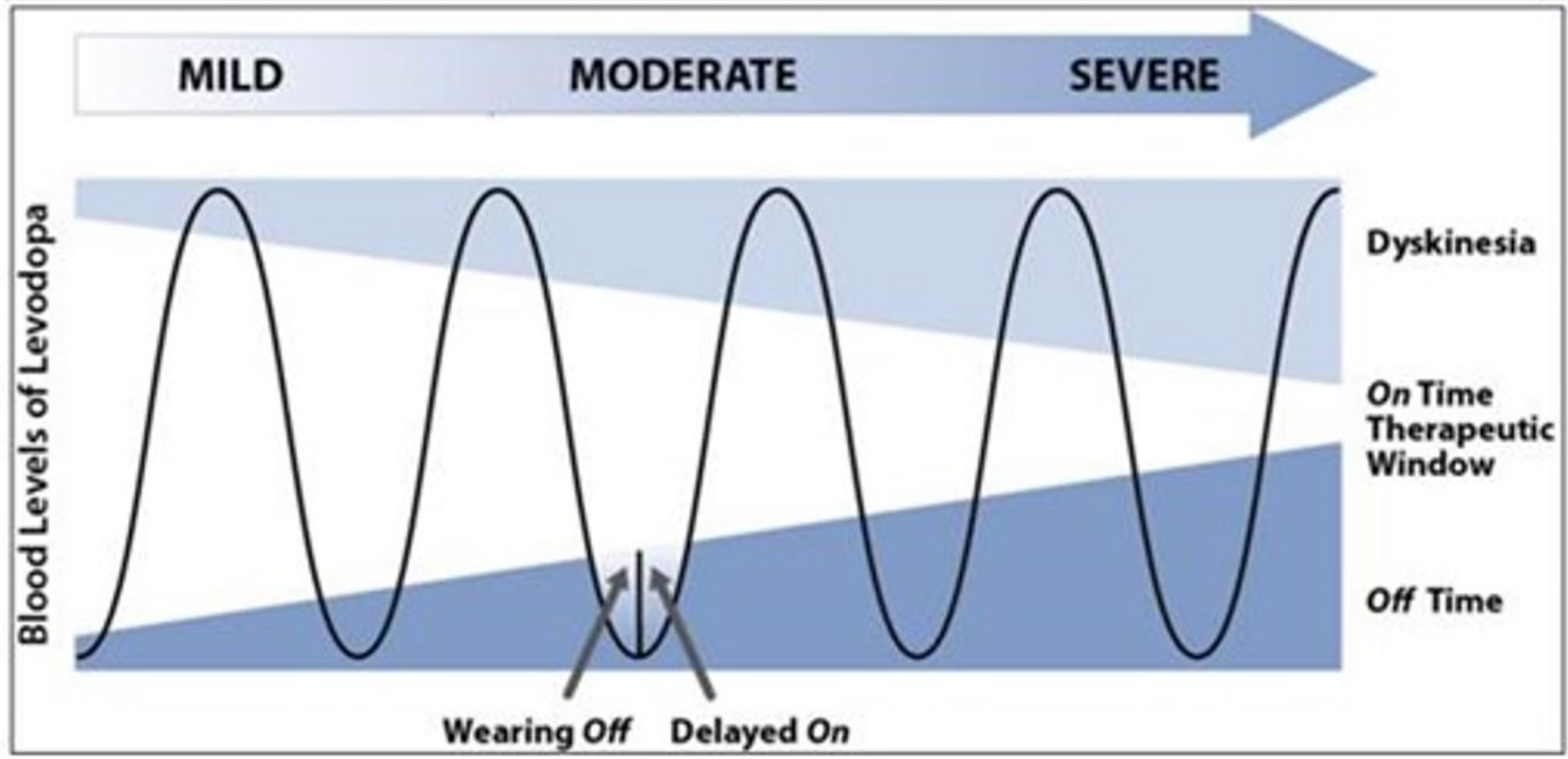
Motor Symptom Management

- Dopamine Replacement Therapy
 - Duopa (carbidopa-levodopa enteric), Inbrija (levodopa INH), Parcopa (carbidopa-levodopa ODT), Rytary (carbidopa-levodopa ER), Sinemet/Sinemet CR (carbidopa-levodopa IR/CR), Stalevo (carbidopa-levodopa-entacapone)
- Decarboxylase Inhibition
 - Lodosyn (carbidopa)
- Dopamine Agonists
 - Apokyn (apomorphine SC), Mirapex/Mirapex ER (pramipexole IR/ER), Neupro (rotigotine TD), Requip/Requip XL (ropinirole IR/ER)
- Monoamine Oxidase B (MAO-B) Inhibitors
 - Azilect (rasagiline), Eldepryl (selegiline), Zelapar (selegiline ODT), Xadago (safinamide)
- Catechol-O-Methyltransferase (COMT) Inhibition
 - Comtan (entacapone), Stalevo (carbidopa-levodopa-entacapone), Tasmar (tolcapone)
- Anticholinergic Medications
 - Artane (trihexyphenidyl), Cogentin (benztropine)
- Anti-Glutamatergic Medications
 - Gocovri (amantadine ER), Osmolex ER (amantadine ER), Symmetrel (amantadine IR)

Motor Symptom Management

- Dopamine Replacement Therapy
 - **Duopa** (carbidopa-levodopa enteric), **Inbrija** (levodopa INH), Parcopa (carbidopa-levodopa ODT), **Rytary** (carbidopa-levodopa ER), Sinemet/Sinemet CR (carbidopa-levodopa IR/CR), Stalevo (carbidopa-levodopa-entacapone)
- Decarboxylase Inhibition
 - Lodosyn (carbidopa)
- Dopamine Agonists
 - Apokyn (apomorphine SC), Mirapex/Mirapex ER (pramipexole IR/ER), Neupro (rotigotine TD), Requip/Requip XL (ropinirole IR/ER)
- Monoamine Oxidase B (MAO-B) Inhibitors
 - Azilect (rasagiline), Eldepryl (selegiline), Zelapar (selegiline ODT), **Xadago** (safinamide)
- Catechol-O-Methyltransferase (COMT) Inhibition
 - Comtan (entacapone), Stalevo (carbidopa-levodopa-entacapone), Tasmar (tolcapone)
- Anticholinergic Medications
 - Artane (trihexyphenidyl), Cogentin (benztropine)
- Anti-Glutamatergic Medications
 - **Gocovri** (amantadine ER), **Osmolex ER** (amantadine ER), Symmetrel (amantadine IR)

The pattern of motor response to levodopa changes during the progression of PD



Managing Dyskinesia

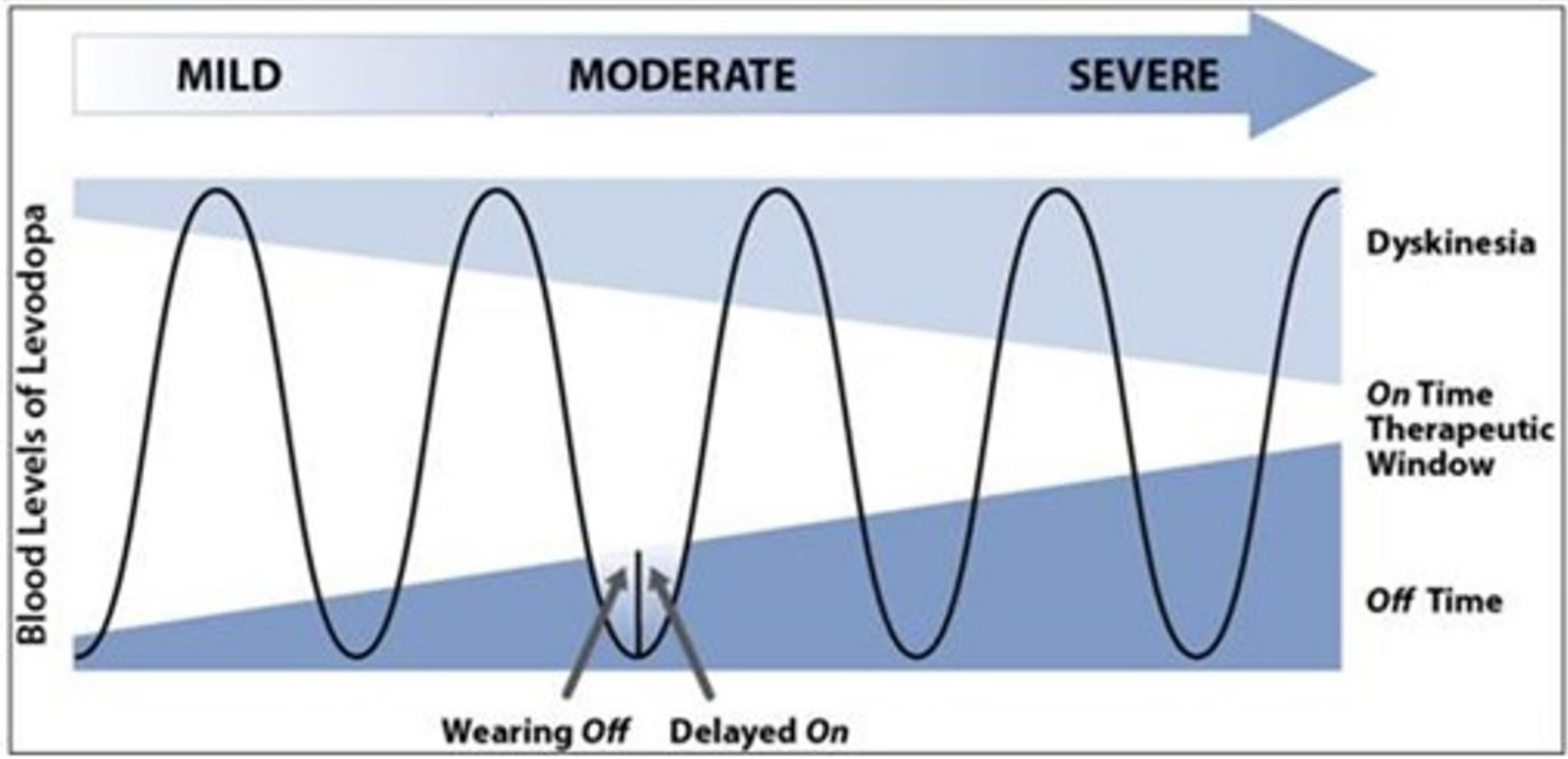
- Dyskinesia occurs as a complication of long-term dopamine replacement
- More likely to occur with:
 - Levodopa doses > 400-600mg daily
 - Longer disease duration
 - Greater disease severity
 - Earlier age of onset
- 40% of patients with PD develop motor fluctuations by 5 years
 - Increases to 70% by 10 years

RAMI

APELIAN

MD, MPH

The pattern of motor response to levodopa changes during the progression of PD



Managing Dyskinesia (and its converse – “OFF”)

- Only one pharmacological therapy indicated for management of levodopa induced dyskinesias
 - Gocovri (amantadine ER)
- Another drug on the market has been shown to improve “ON” time without troublesome dyskinesia
 - Xadago (safinamide)
- Traditionally, therapy has been aimed at reducing levodopa doses and increasing the frequency of administration to prevent high “peaks” and low “troughs”.
- Deep Brain Stimulation for PD
 - Not an option for all patients
 - Can worsen cognitive dysfunction or mood disorders
 - Neuropsychological testing prior to implantation is necessary

RAMI

APELIAN MD, MPH

<http://ramiapelianmd.com>

Deep Brain Stimulation for PD

- Criteria for candidacy:
 - PD for at least 4 years
 - No significant cognitive impairment or mood disorder
 - Experiencing fluctuations or dyskinesia despite therapeutic doses of levodopa+
 - Must be levodopa responsive!
- Two cerebral targets:
 - Subthalamic nucleus
 - Globus pallidus interna
- Electrical stimulation provided at a controlled rate determined by the programming physician
- Theoretically attempts to regulate abnormal cerebral electrical signals
- Multiple device manufacturers:
 - Medtronic
 - Abbot
 - Boston-Scientific
- Goal of therapy
 - Reduce pharmacological support and maintain an “ON” state with reduced “OFF” time and reduced dyskinesia.

RAMI

APELIAN

MD, MPH

Non-Motor Symptom Management

- Loss of smell
- Sleep disturbances
- Depression / Anxiety
- Psychosis and Hallucinations
- Fatigue
- Cognitive changes
- Constipation
- Sexual dysfunction
- Excessive drooling
- Melanoma
- Ocular dysfunction
- Orthostatic hypotension
- Urinary urgency and frequency
- Pain
- Pseudobulbar affect
- Impulse control disorders*

Non-Motor Symptom Management

- Loss of smell
- Sleep disturbances
- Depression / Anxiety
- **Psychosis and Hallucinations**
- Fatigue
- **Cognitive changes**
- Constipation
- Sexual dysfunction
- **Excessive drooling**
- Melanoma
- Ocular dysfunction
- **Orthostatic hypotension**
- Urinary urgency and frequency
- Pain
- **Pseudobulbar affect**
- Impulse control disorders

Non-Motor Symptom Management (FDA Approved)

- Psychosis and Hallucinations
 - Only one FDA approved medication – Nuplazid (pimavanserin)
 - Drugs used off-label include Clozaril (clozapine) and Seroquel (quetiapine)
- Cognitive changes
 - Only one FDA approved medication for Parkinson’s Dementia – Exelon (rivastigmine)
 - Drugs used off-label include Aricept (donepezil), Razadyne (galantamine) and Namenda (memantine)
- Excessive drooling
 - Botulinum toxin – Only Xeomin is FDA approved for sialorrhea.
 - Use of Botox and Mybloc is common
 - Off-label use of Artane (trihexyphenidyl), Elavil (amitriptyline), Robinul (glycopyrrolate) common
- Orthostatic hypotension
 - Northera (droxidopa) is the only FDA approved medication for Neurogenic OH
 - Common off-label uses include Florinef (fludrocortisone) and ProAmatine (midodrine)
- Pseudobulbar affect
 - Nuedexta (dextromethorphan-quinidine) is the only FDA approved medication for this condition
 - Commonly patients are treated with SSRIs or atypical antipsychotics for the emotional outbursts

Non-Motor Symptom Management (Winging It!)

- REM Sleep Behavior Disorder
 - No FDA approved therapy
 - Klonopin (clonazepam) or melatonin OTC have evidence to help
- Insomnia
 - Typical treatments including short or long acting sleep aids
 - Benzodiazepines, non-benzo sedatives, etc
- Urinary Disturbances
 - Typically requires the consultation of a urologist
 - Detrol (tolterodine), Ditropan (oxybutynin), Myrbetriq (mirabegron)
 - Botox (onabotulinumtoxin A)
- Sexual Dysfunction
 - Men: PDE5 inhibitors
 - Women: Hormonal therapy, lubrication
- Fatigue
 - No FDA approved therapy
 - Commonly used drugs include amphetamine salts and wakefulness promoting agents
 - Amantidine and MAO-B inhibitors may also decrease daytime fatigue
- Depression / Anxiety
 - Standard therapy including SSRIs, SNRIs, etc
 - Often requires the consultation of a psychiatrist with geriatric experience
- Constipation
 - Prune juice 1st line
 - OTC stool softeners, laxatives
 - Prescription pharmacologic therapy commonly used includes drugs for IBS-C

RAMI

APELIAN

MD, MPH

Thank You!



RAMI

APELIAN

MD, MPH

<http://ramiapelianmd.com>