

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

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Armenian American Medical Society

2019 AAMS CME

May 4, 2019



<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

WHAT IS PARKINSON'S?

Increases to 4% in patients above the age of 80

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

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

LESSER-KNOWN SYMPTOMS

OF PARKINSON'S INCLUDE DEPRESSION, APATHY, FATIGUE, AND DEMENTIA.



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.



THE EXACT CAUSE OF PARKINSON'S DISEASE IS UNKNOWN

BUT BOTH GENETICS AND ENVIRONMENT ARE CAUSES.



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

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.

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.



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.MICHAELFOX.ORG

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

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

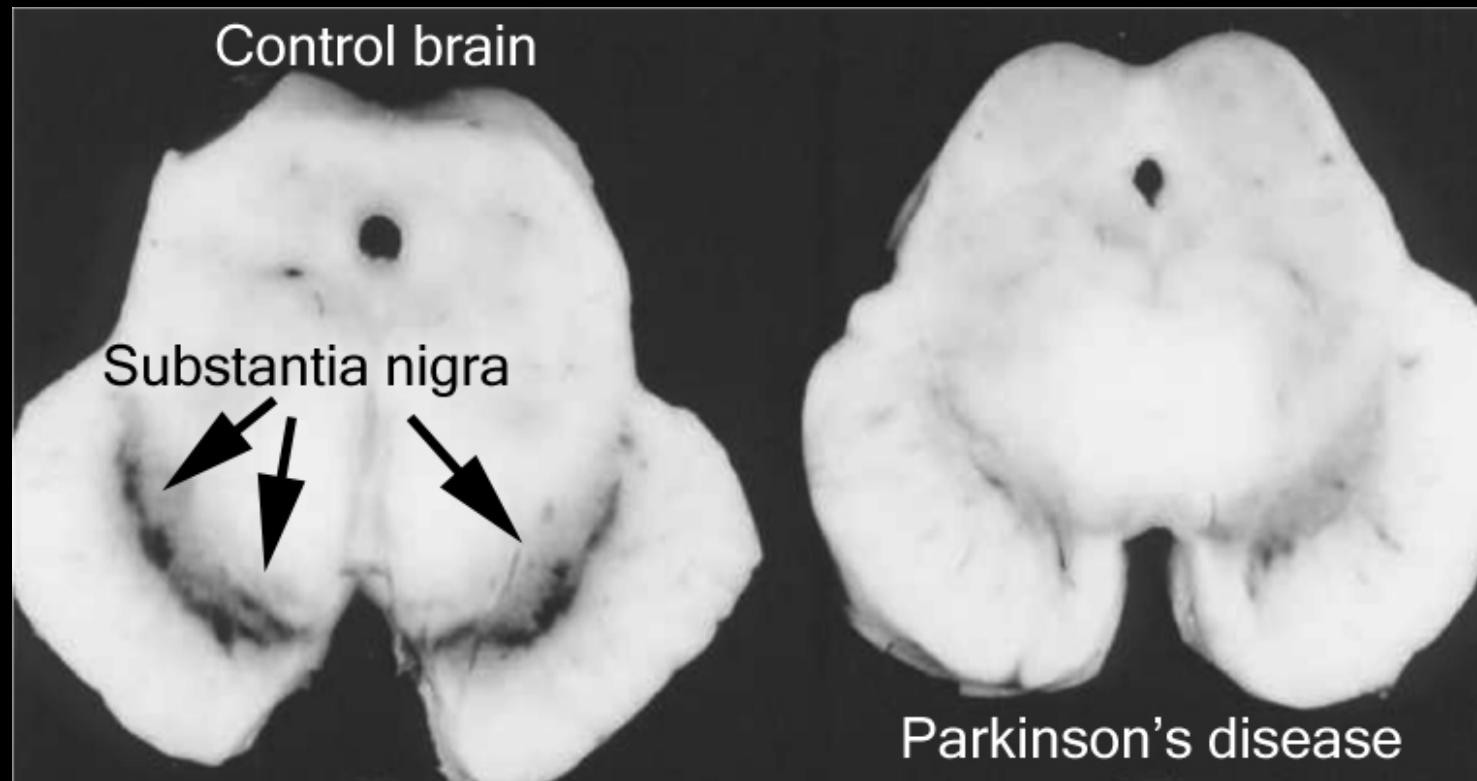
Levodopa therapy remains the “gold standard” for managing motor symptoms of PD

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What Causes PD?

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

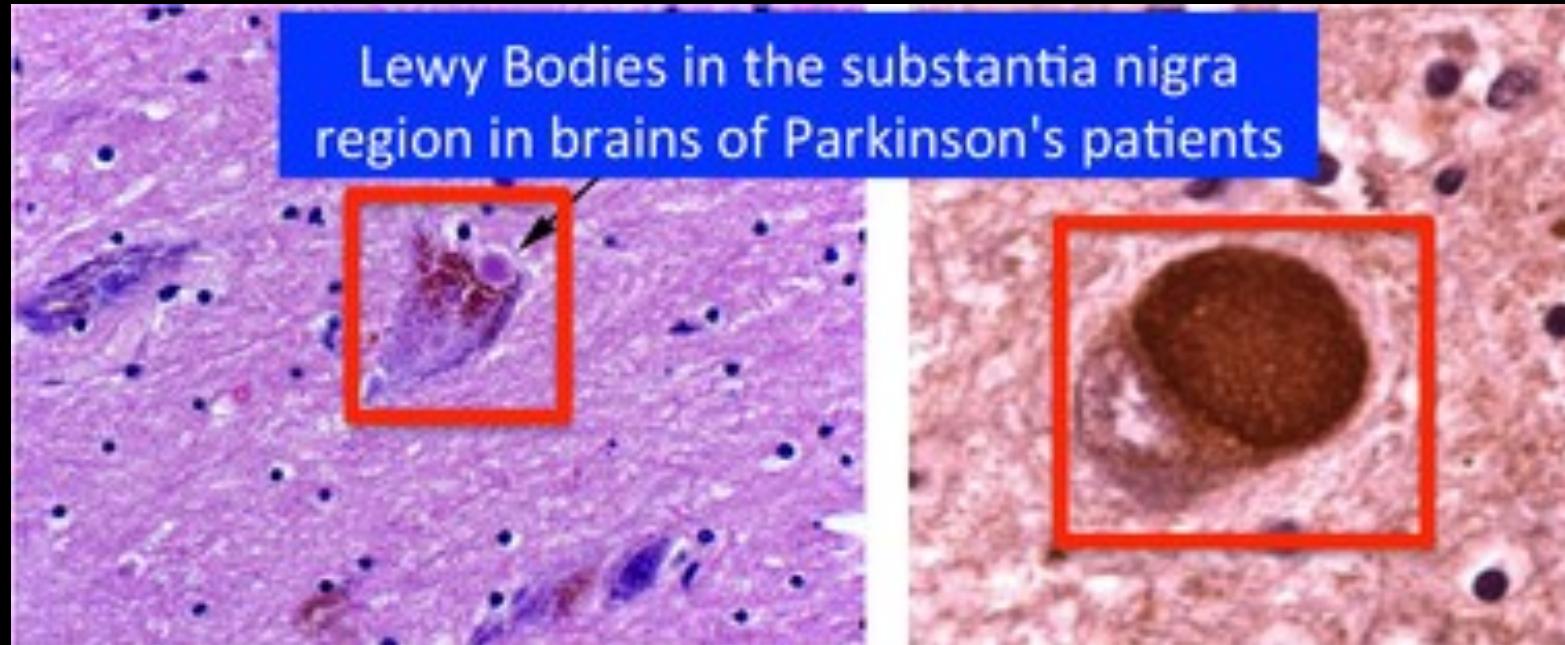


What Causes PD?

- 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

Alpha-Synuclein and its Role

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



Alpha-Synuclein and its Role

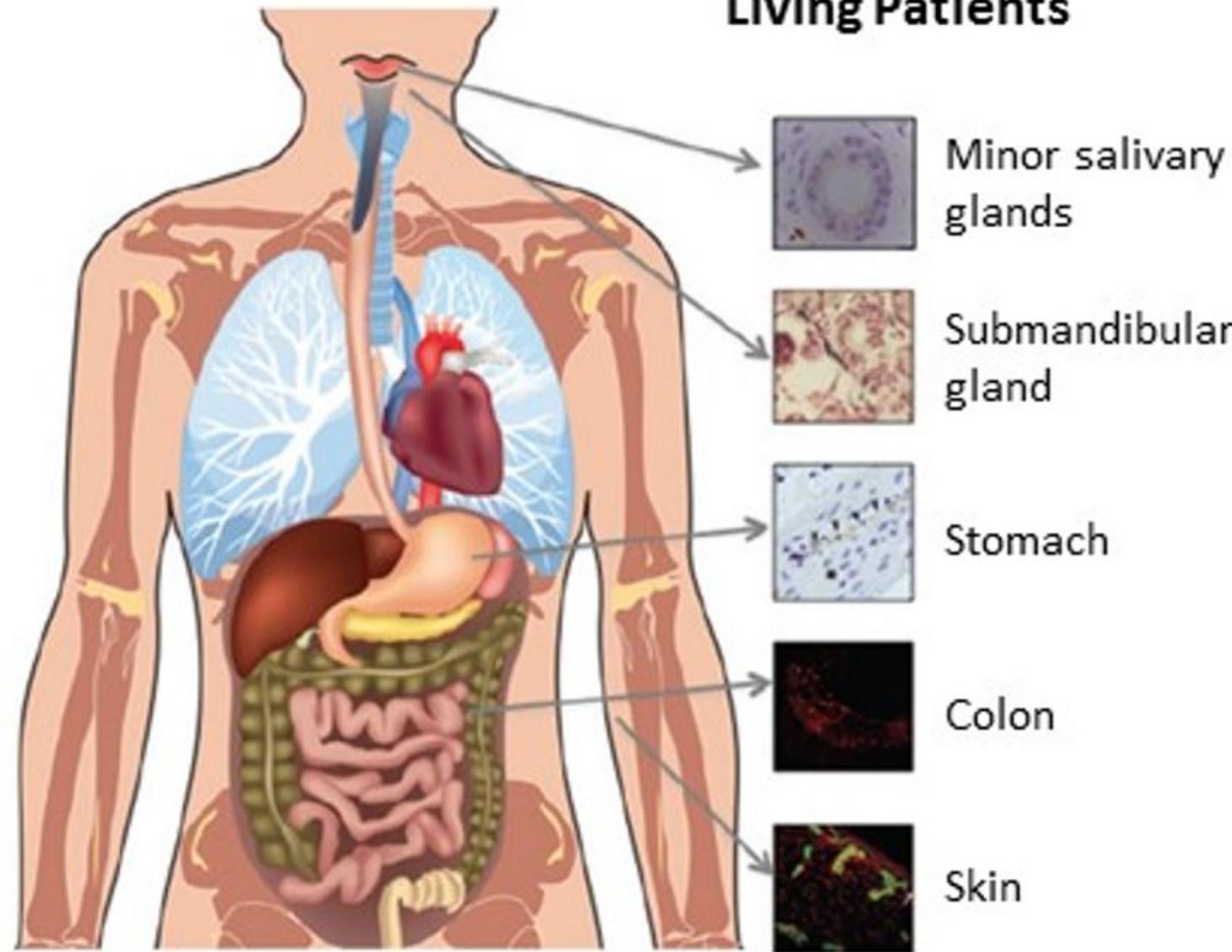
- Found in Lewy Bodies
- Lewy bodies are found in the surviving nigral neurons
- BUT Lewy bodies can also be found outside of the central nervous system

Alpha

Postmortem

- Stellate ganglion
- Paravertebral sympathetic ganglia
- Lewy bodies
- Vagus nerve
- Epicardial plexus
- BUT Lymphoid system
- Mesenteric sympathetic ganglia
- Enteric nervous system
- Adrenal gland
- Genitourinary tract

Living Patients



The Symptoms In PD

Motor

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

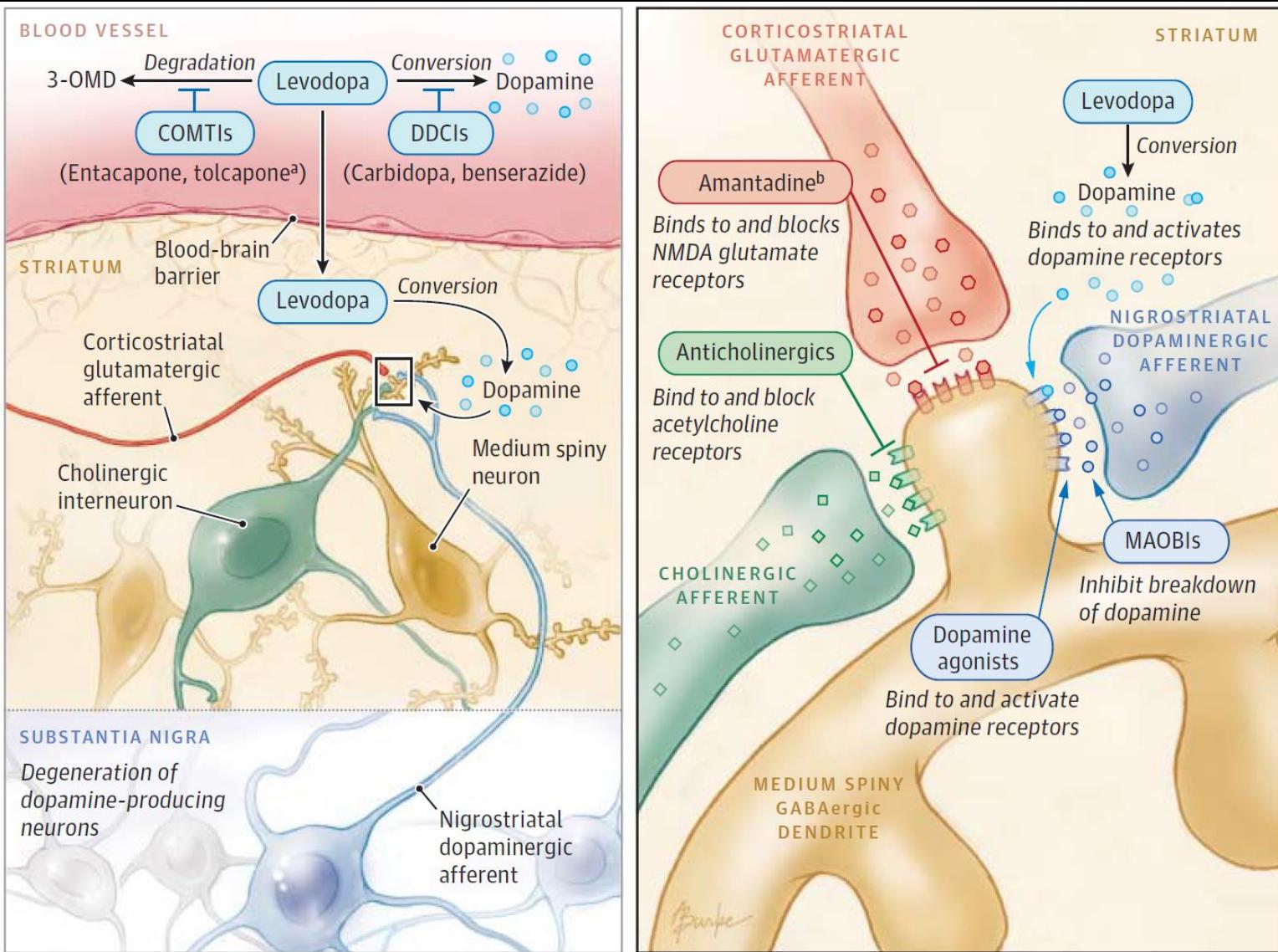
Non-Motor

- 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*

* Often secondary to medication side effects, not the disease state itself

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Managing Motor Symptoms



Connolly and Lang, JAMA. 2014;311(16):1670-1683

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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)

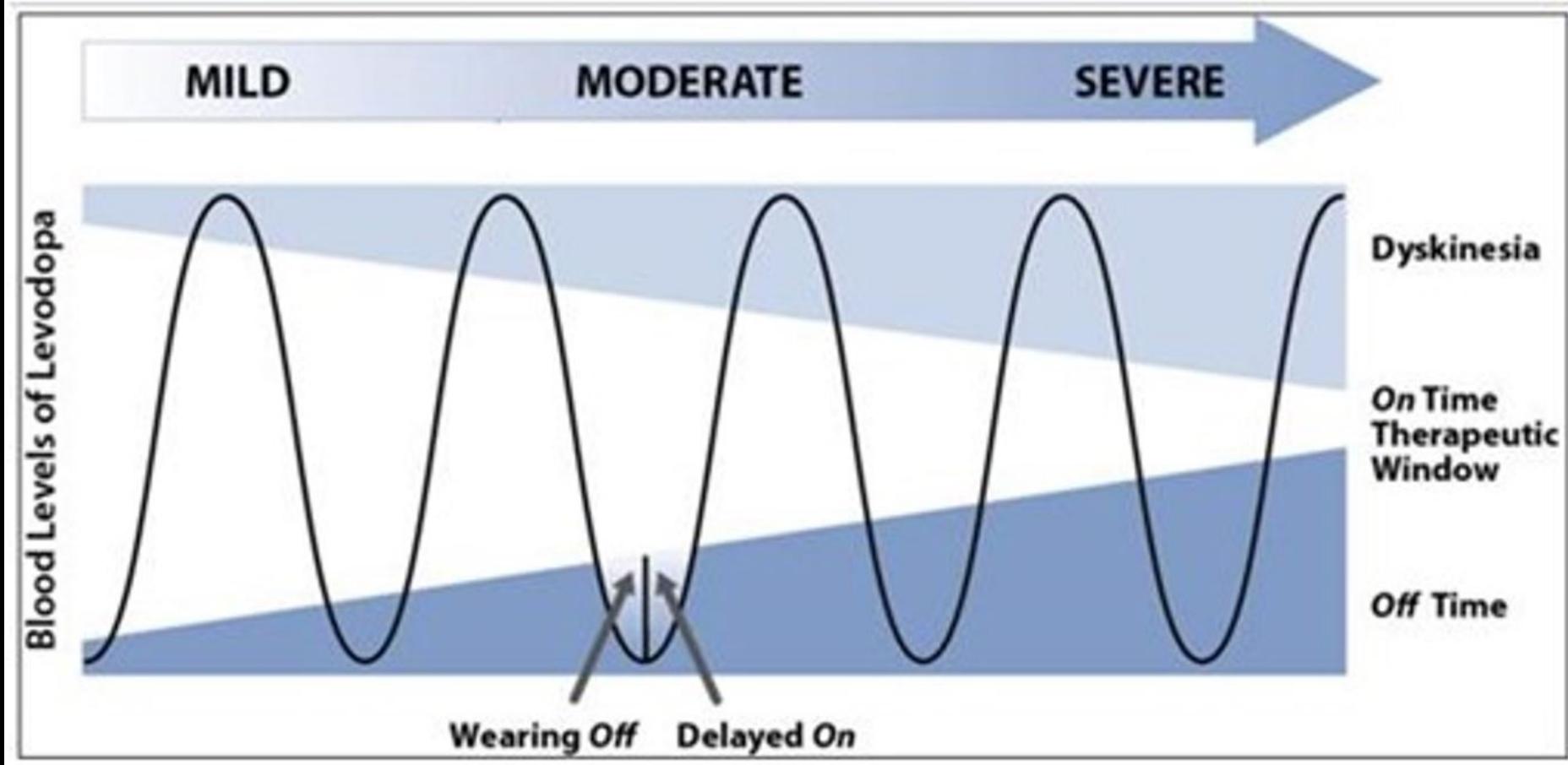
Motor Symptom Management

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Yellow text indicates FDA approval since 2015

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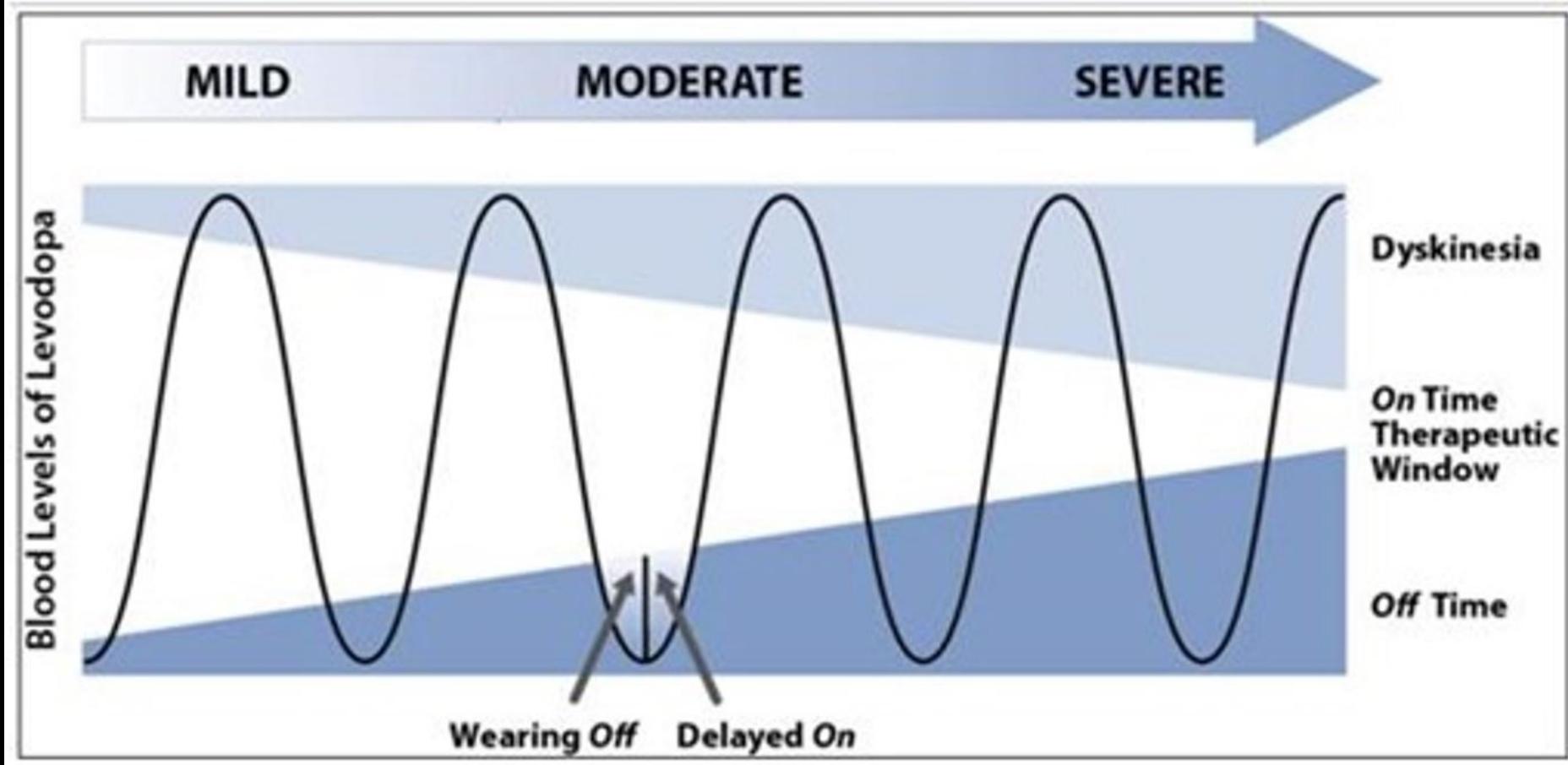
The pattern of motor response to levodopa changes during the progression of PD



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

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

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.

Non-Motor Symptom Management

- Loss of smell
- Sleep disturbances
- Depression / Anxiety
- Psychosis and Hallucinations
- Fatigue
- Cognitive changes
- Constipation
- Sexual dysfunction
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- Melanoma
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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

Thank You!

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