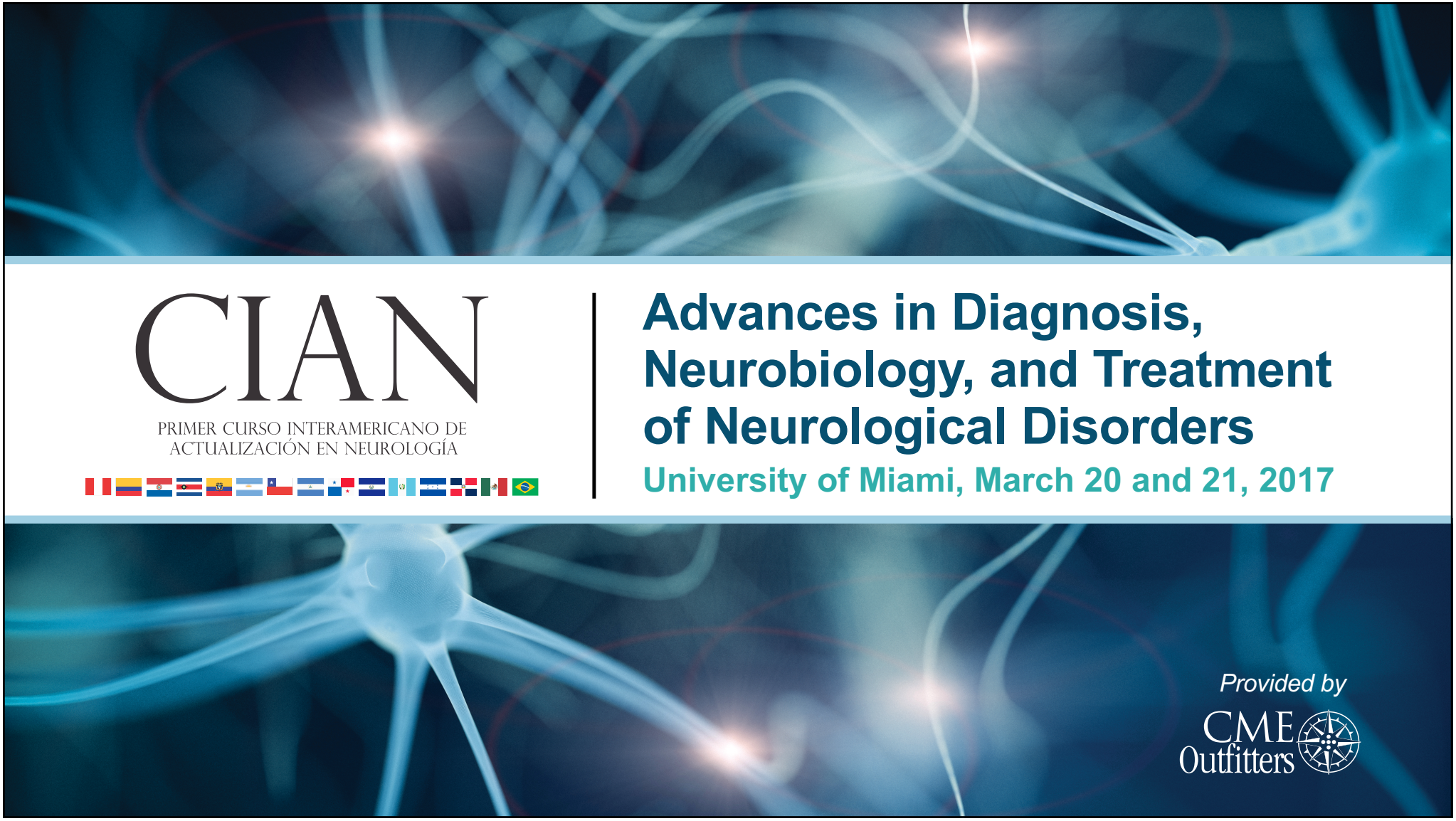

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PRIMER CURSO INTERAMERICANO DE ACTUALIZACIÓN EN NEUROLOGÍA

Advances in Diagnosis, Neurobiology, and Treatment of Neurological Disorders

University of Miami, March 20 and 21, 2017

Provided by

CME Outfitters

Corneliu Luca, MD, PhD

Assistant Professor of Neurology
Medical Director, Deep Brain Stimulation Program
University of Miami
Miller School of Medicine
Miami, FL

Corneliu Luca, MD, PhD

Disclosures

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- ***Consultant:*** Medtronic

Parkinson's Disease: Clinical Update, Comorbidities and Modern Management

Learning Objective 1

Review the latest advances in the management of Parkinson's Disease.

Outline/Objectives

- Clinical presentation and diagnosis
- Update on etiology; genetic and environmental factors
- Medical treatment: early, moderate and advanced stage
- Advanced treatments: deep brain stimulation and levodopa intestinal infusion

Clinical Diagnosis of Parkinson's Disease

- Parkinson's disease is a neurodegenerative disorders characterized by bradykinesia and tremors or rigidity or postural instability (UK Bank Criteria)
- Supportive criteria: unilateral, rest tremor, response to levodopa, presence of dyskinesia, progressive disorder

Hughes AJ, et al. *J Neurol Neurosurg Psychiatry*. 1992;55:181-184.

Clinical Diagnosis of Parkinson's Disease

- Exclusion criteria
  - History of repeated strokes,
  - Repeated head injury
  - History of definite encephalitis
  - Neuroleptic treatment at onset of symptoms
  - Sustained remission
  - Strictly unilateral features after 3 years
  - Supranuclear gaze palsy
  - Cerebellar signs
  - Early severe autonomic involvement

Hughes AJ et al. *J Neurol Neurosurg Psychiatry*. 1992;55:181-184.

Secondary Causes of PD

- Drug induced –neuroleptics and antiemetics
- Vascular parkinsonism- multi-infarct
- Infectious: post-encephalitic
- Metabolic: hypothyroid
- Toxic: manganese, CO, MPTP

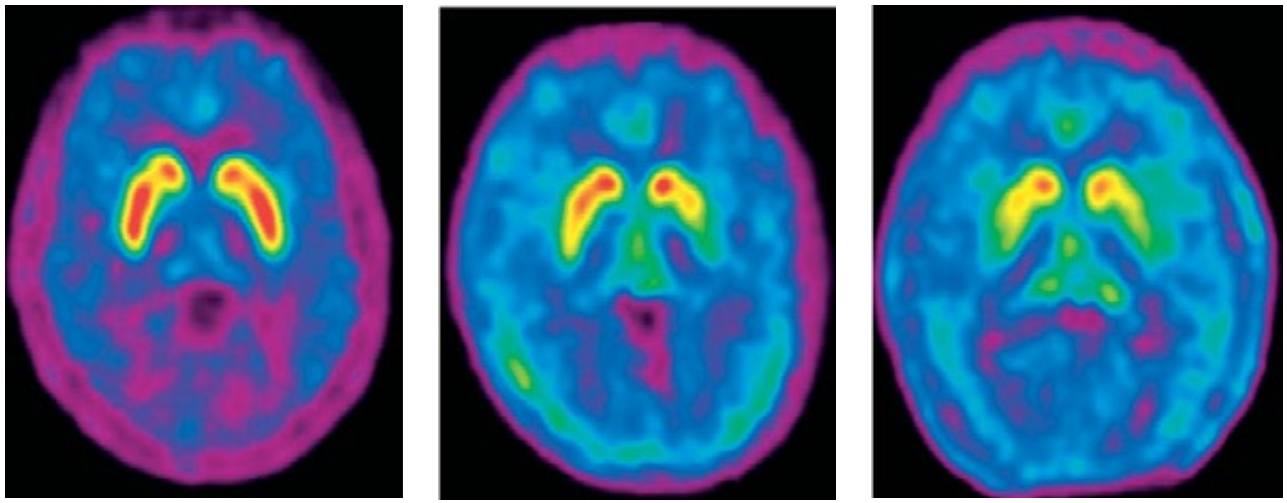
- Red flag suggesting atypical PD:
  - Early dementia,
  - Supranuclear gaze palsy
  - Hyperreflexia
  - Ataxia
  - Early postural instability severe dysautonomia

CO = carbon monoxide; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

Grant I, Adams KM. Neuropsychological Assessment of Neuropsychiatric and Neuromedical Disorders. 2009. Oxford University Press, New York; Massano J, et al. *Cold Spring Harb Perspect Med*. 2012;2(6):a008870.

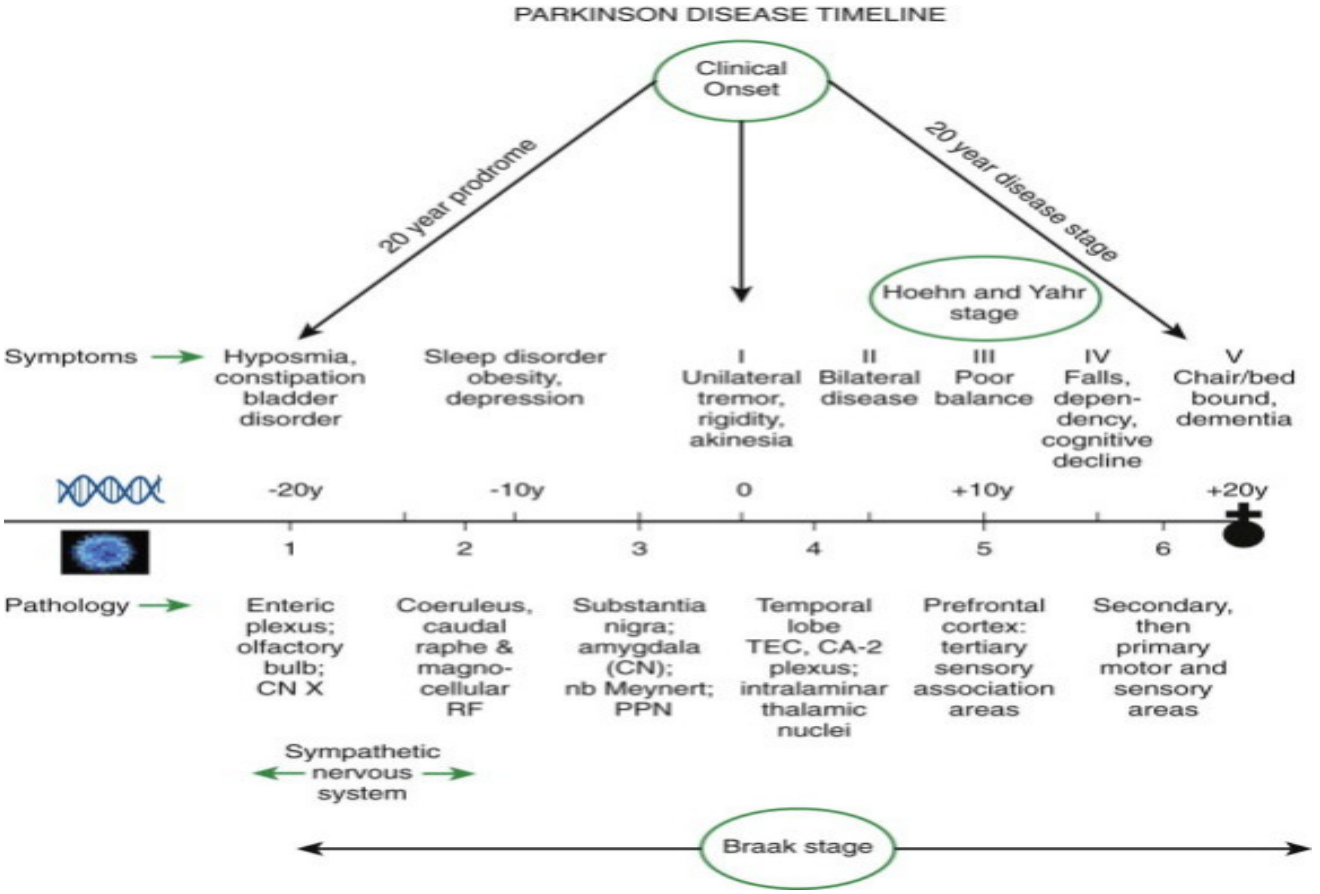
Dopamine Transporter Imaging

- PD motor manifestations begin focally, when dopamine concentrations fall below 60–70% in the contralateral striatum.



Rodriguez-Oros MC, et al. *Lancet Neurol*. 2009;8(12):1128-1139.

Natural History of Parkinson's Disease



Hawkes CH, et al. *Parkinsonism Relat Disord*. 2010;16(2):79-84

Non-Motor Symptoms of Parkinson's Disease

Behavioral/cognitive

- Mood
  - Apathy
  - Cognition and dementia
  - Hallucinations and psychosis
  - Impulse control disorders

Sleep

- Insomnia
  - REM behavior disorder
  - Excessive daytime somnolence

Autonomic function

- Gastrointestinal
- Genitourinary
- Cardiovascular
- Thermoregulatory
- Dysphagia

Sensory

- Olfaction
- Visual system
- Pain
- Skin
- Musculoskeletal

National Parkinson Foundation. Available at: http://www.parkinson.org/Understanding-Parkinsons/Non-Motor-Symptoms. Accessed March 14, 2017.

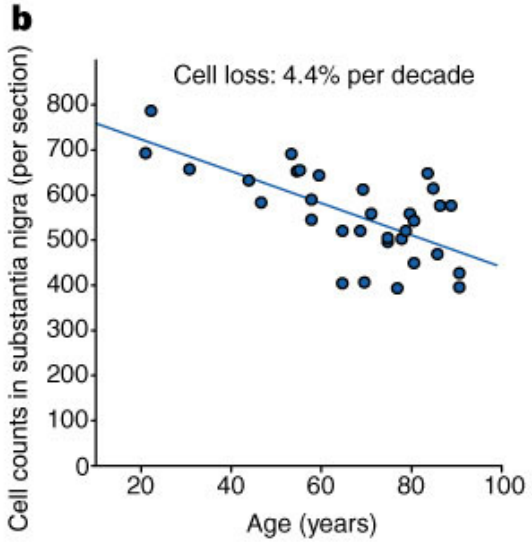
Preclinical Diagnosis

- REM behavioral disorder (RBD) is present in 50% of PD patients and precedes the motor symptoms
- Smell loss – early in PD
- Constipation – early in PD
- Anxiety and depression are comorbid with PD
- Biomarkers
  - Synuclein in gut
  - Salivary gland
  - Cerebrospinal fluid (CSF)

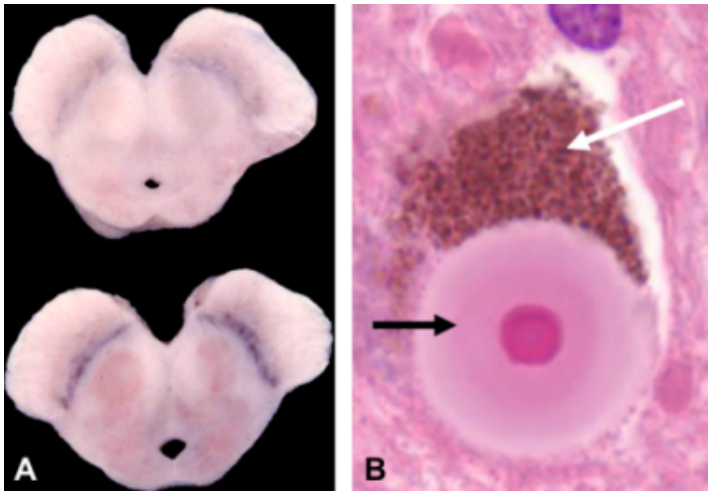
Palma J-A, et al. *Parkinsonism Relat Disord*. 2014;20:S94-S98.

Pathology

- Degeneration of dopaminergic neurons -50% neuron loss in the substantia nigra (SN) at dx

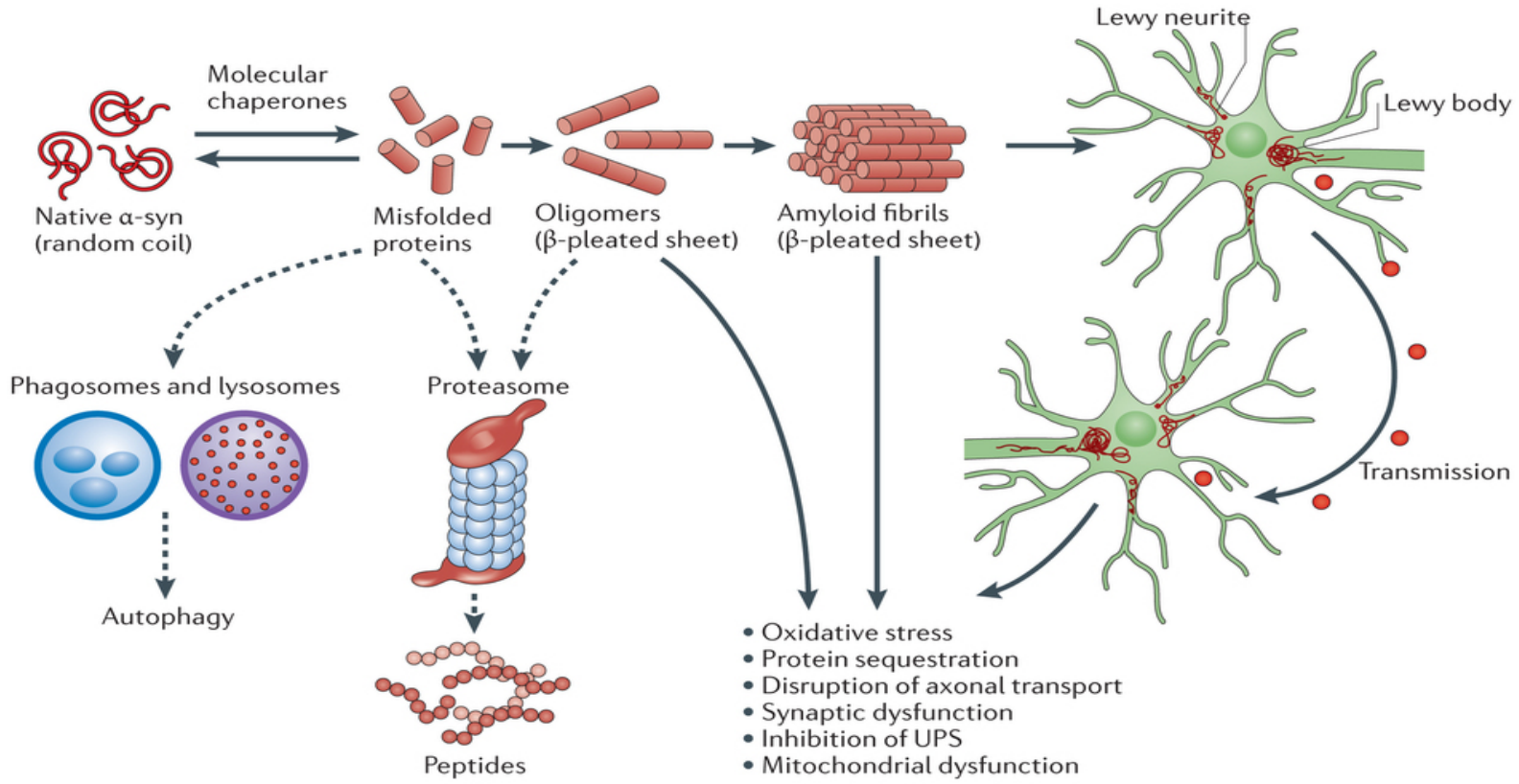


- Accumulation of synuclein aggregates- Lewy body
- Prion like aggregation



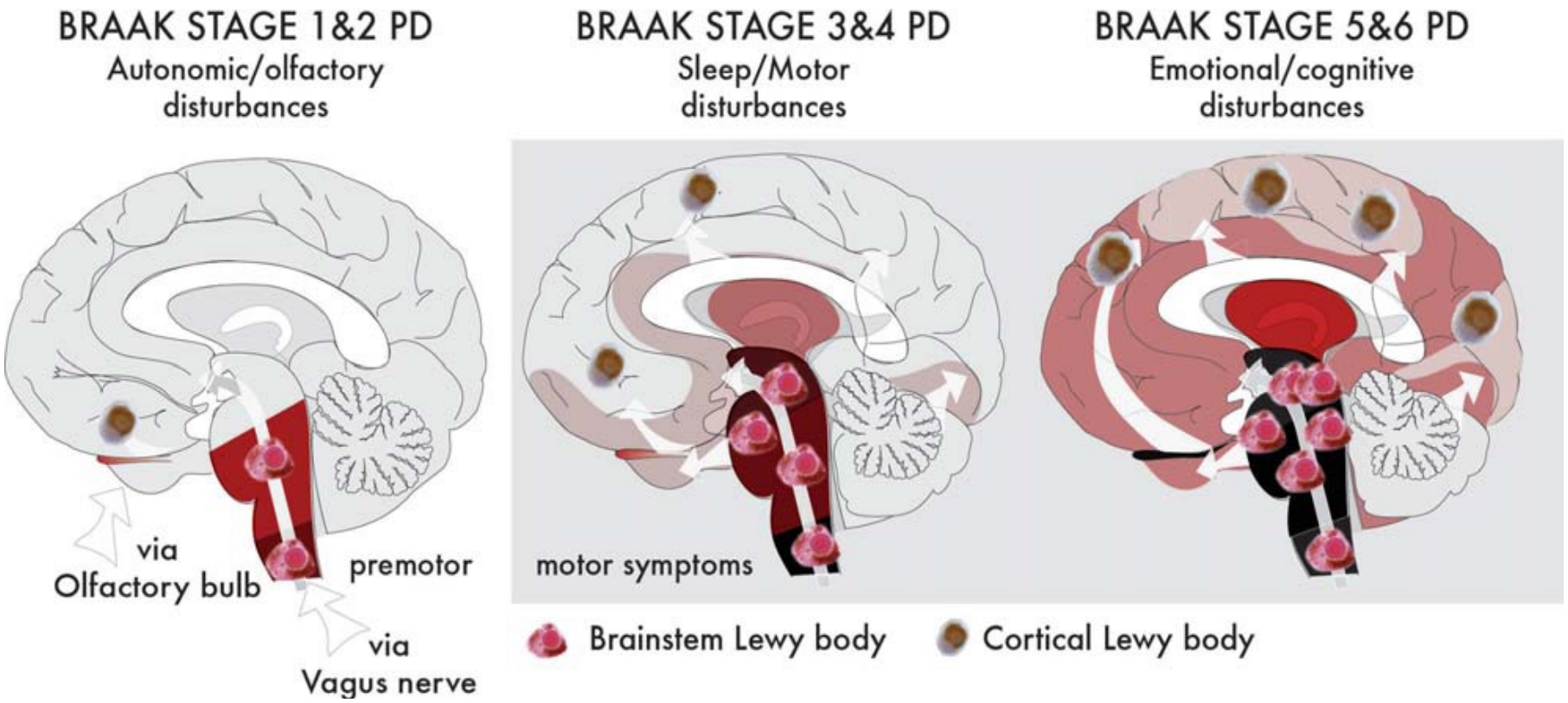
Dunnett SB, et al. *Nature*. 1999;399(6738):A32-A39.

Prion like Aggregates



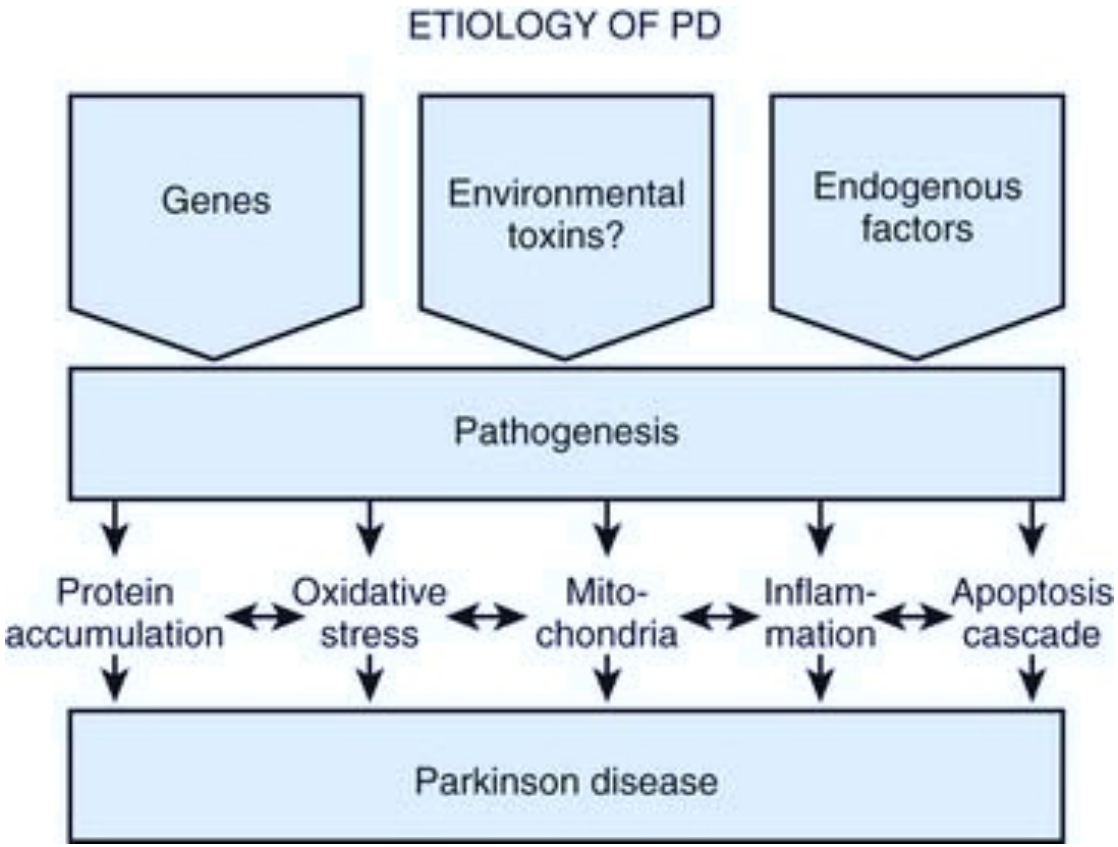
Irwin DJ, et al. *Nature Reviews Neuroscience. 2013;*14:626-636.

Braak Hypothesis



Halliday G. et al. *Mov Disord*. 2011;26:1015-1021.

Etiology of PD



Fahn S, et al. *Principles and Movement Disorders*. 2nd Edition. 2014.

Mechanisms of Dopaminergic Loss

- Lysosome dysfunction
- Ubiquitin-proteosomal dysfunction
- Oxidative stress
- Mitochondrial dysfunction
- Reactive oxygen species
- Inflammation
- Disturbances of calcium homeostasis
- Promotion of α-synuclein fibrillation
- Interference with dopamine transporter
- ↓ growth factor available
- ↓gene transcription

Fahn S, et al. *Principles and Movement Disorders*. 2nd Edition. 2014.

Risk Factors for PD

- Genetic and environment
- Age (dopaminergic loss with age)
- Increased risk
  - Traumatic brain injury,
  - Pesticides (rotenone, paraquat)
  - Industrial solvents
- Decreased risk
  - Cigarette smoke
  - Caffeine
  - Anti-inflammatories
  - Estrogen

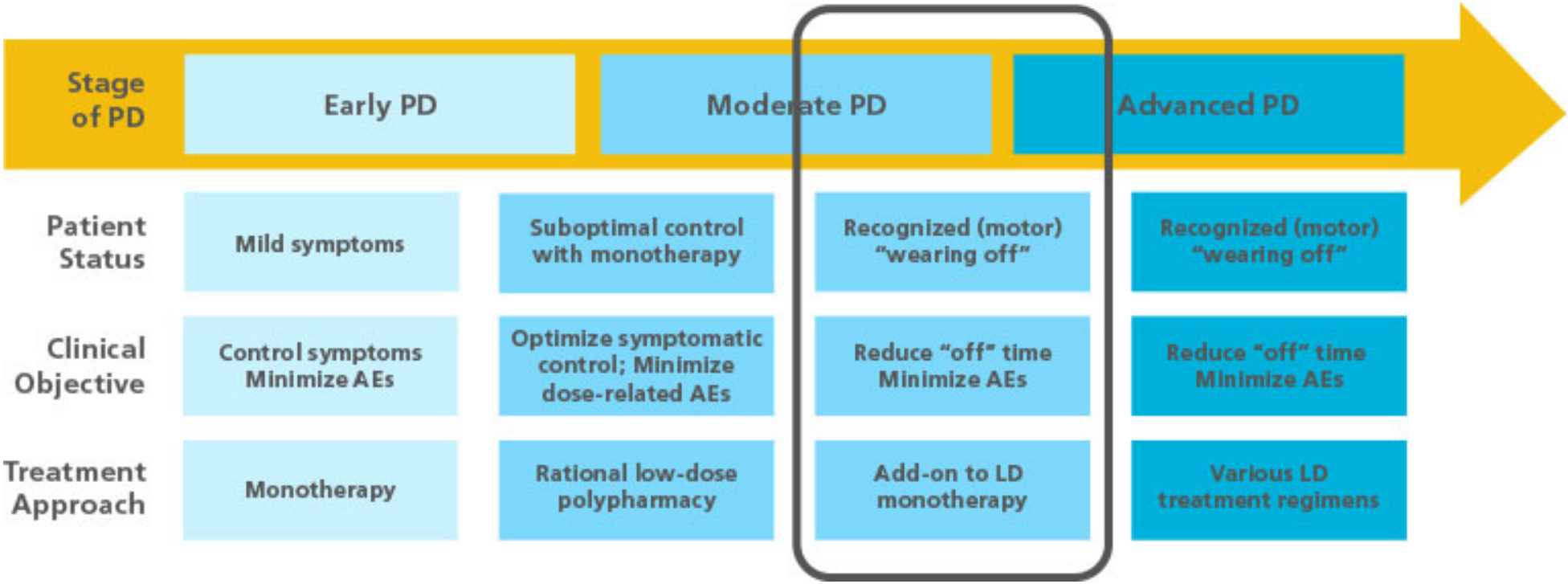
Mayo Clinic. Available at: http://www.mayoclinic.org/diseases-conditions/parkinsons-disease/basics/risk-factors/con-20028488. Accessed March 14, 2017.

Gene Mutations

PARK locus	Gene	Map position	Clinical phenotype	Pathology
PARK1/4	*SNCA*	4q21	Parkinsonism with common dementia	Lewy bodies
PARK2	*parkin*	6q25-q27	Early-onset, slowly progressing parkinsonism	Lewy bodies
PARK3	Unknown	2p13	Late-onset parkinsonism	Lewy bodies
PARK5	*UCHL1*	4p14	Late-onset parkinsonism	Unknown
PARK6	*PINK1*	1p35-p36	Early-onset, slowly progressing parkinsonism	One case exhibiting Lewy bodies
PARK7	*DJ-1*	1p36	Early-onset parkinsonism	Unknown
PARK8	*LRRK2*	12q12	Late-onset parkinsonism	Lewy bodies (usually)
PARK9	*ATP13A2*	1p36	Early-onset parkinsonism with Kufor–Rakeb syndrome	Unknown
PARK10	Unknown	1p32	Unclear	Unknown
PARK11	*GIGYF2*	2q36-q37	Late-onset parkinsonism	Unknown
PARK12	Unknown	Xq	Unclear	Unknown
PARK13	*Omi/HTRA2*	2p13	Unclear	Unknown
PARK14	*PLA2G6*	22q13.1	Parkinsonism with additional features	Lewy bodies
PARK15	*FBX07*	22q12-q13	Early-onset parkinsonism	Unknown
PARK16	Unknown	1q32	Late-onset parkinsonism	Unknown
FTDP-17	*MAPT*	17q21.1	Dementia, sometimes parkinsonism	Neurofibrillary tangles
SCA2	*Ataxin 2*	12q24.1	Usually ataxia, sometimes parkinsonism	Unknown
SCA3	*Ataxin 3*	14q21	Usually ataxia, sometimes parkinsonism	Unknown
Gaucher's locus	*GBA*	1q21	Late-onset parkinsonism	Lewy bodies

Fahn S, et al. *Principles and Movement Disorders*. 2nd Edition. 2014.

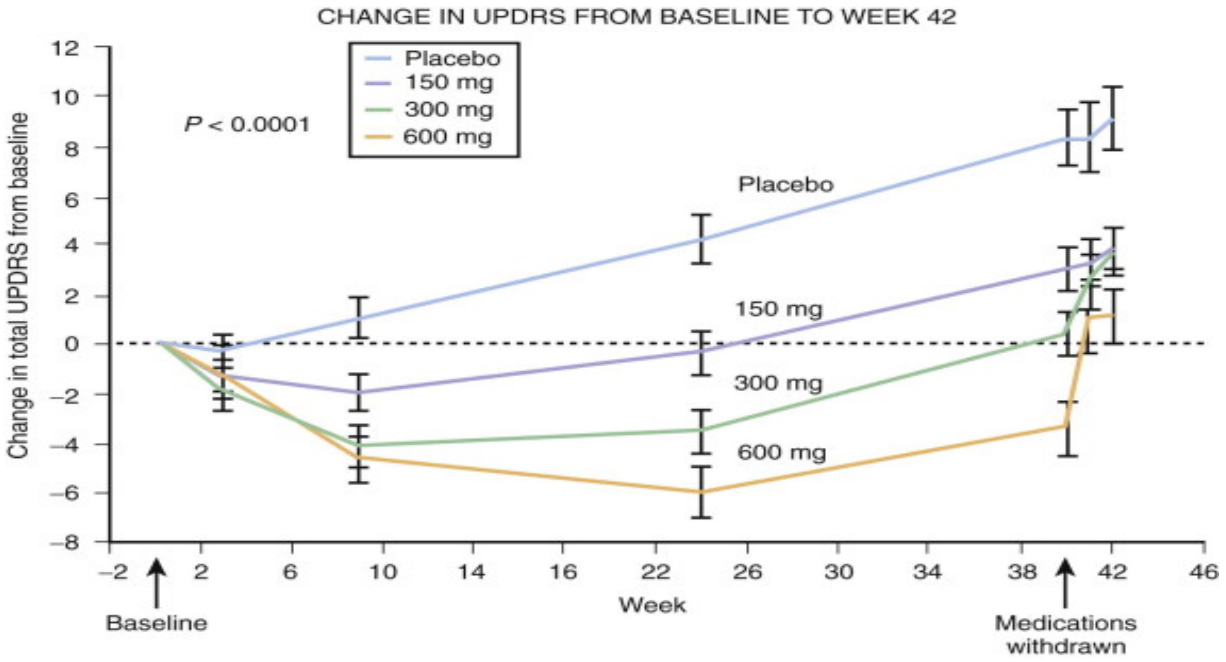
Medical Treatment



Schapira AH. *Arch Neurol*. 2007; 64.1083-1088.

Medical Treatment

- Carbidopa-Levodopa is the gold standard



Fahn S, et al. *N Engl J Med.* 2004;351:2498-2508.

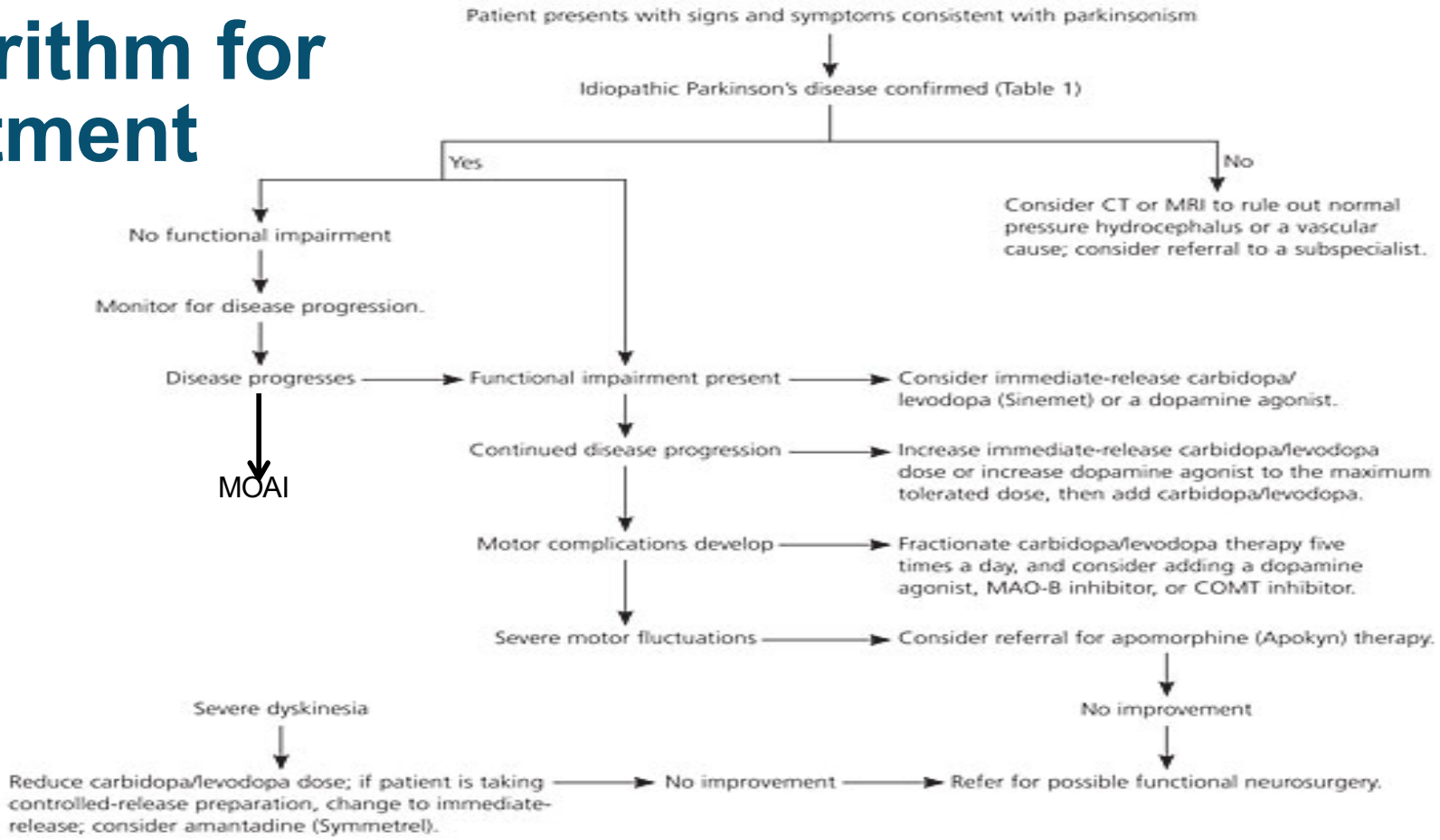
Levodopa Formulations

- Immediate release carbidopa /levodopa- (use 25/100)
- Benserazide/levodopa
- Sublingual carbidopa/levodopa
- Sustained release levodopa and combination of IR and CR
- Carbidopa/levodopa/entacapone
- Jejunal infusion
- Inhaled levodopa-phase 3 trial

Adjunct Therapy

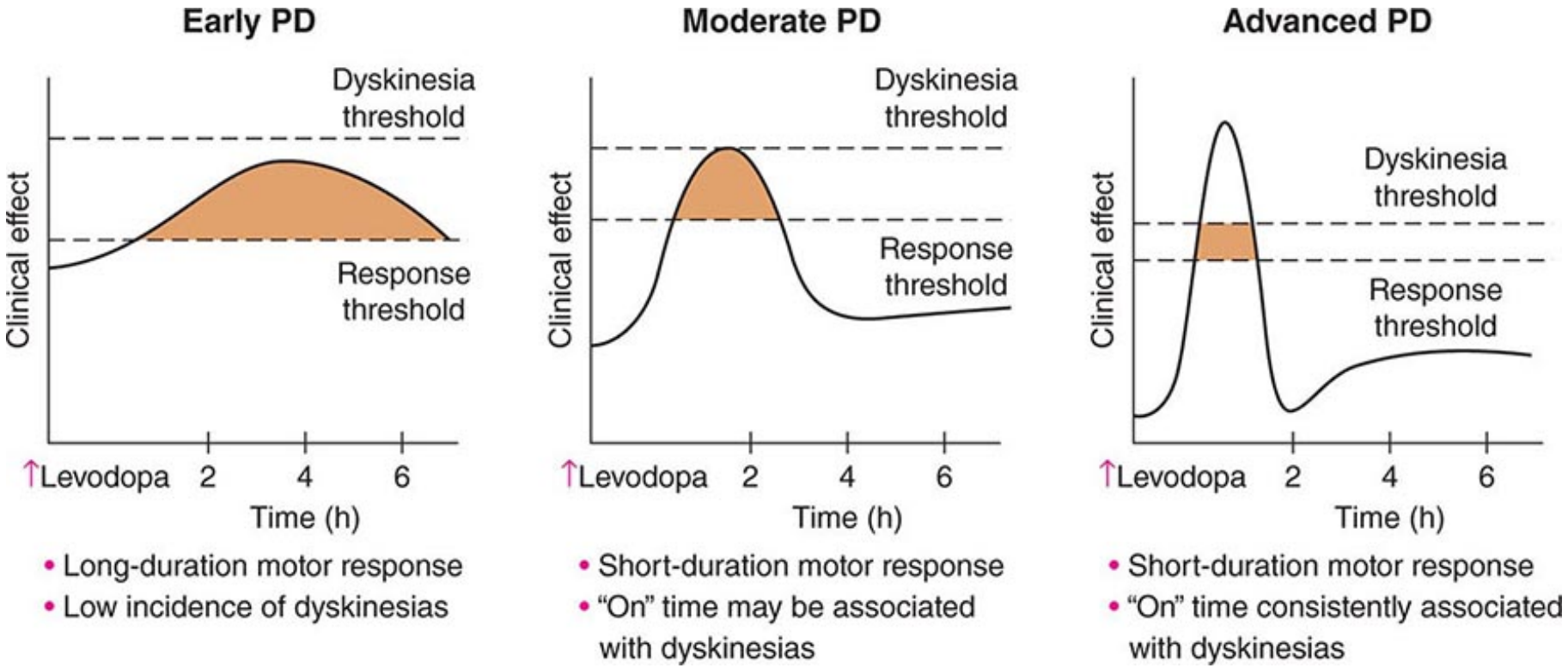
- Anticholinergics-benztropine, trihexyphenidyl
- Dopamine agonists- pramipexole, ropinirole, rotigotine patch, apomorphine injection, bromocriptine, pergolide
- MAO-B inhibitors-selegiline, rasagiline
- COMT inhibitors-entacapone, tolcapone
- Antiglutaminergic agents-amantadine, amantadine ER

Algorithm for Treatment



Rao SS, et al. *Am Fam Physician*. 2006;74(12):2046-2054.

Complications of Levodopa Therapy

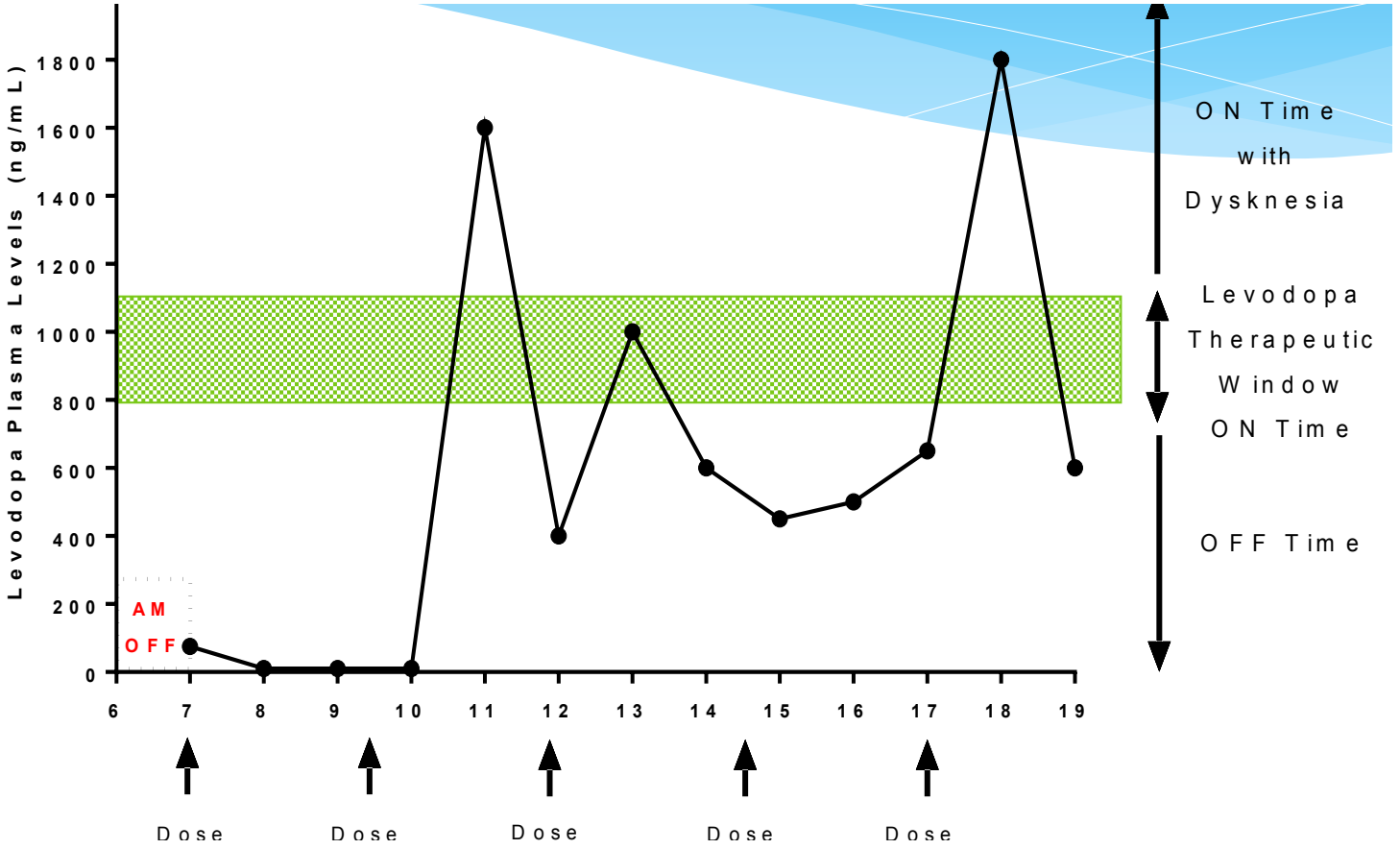


Fahn S, et al. *Principles and Practice of Movement Disorders.* 2nd Edition. 2014.

Managing Wearing Off

- Increase frequency of levodopa administration
- Consider adjunctive oral therapies
- Night time dose for nocturnal symptoms
- Avoid heavy protein meals before levodopa dose
- Subcutaneous apomorphine
- For patients that continue to have fluctuations consider advanced therapies

Wearing Off and Dyskinesia

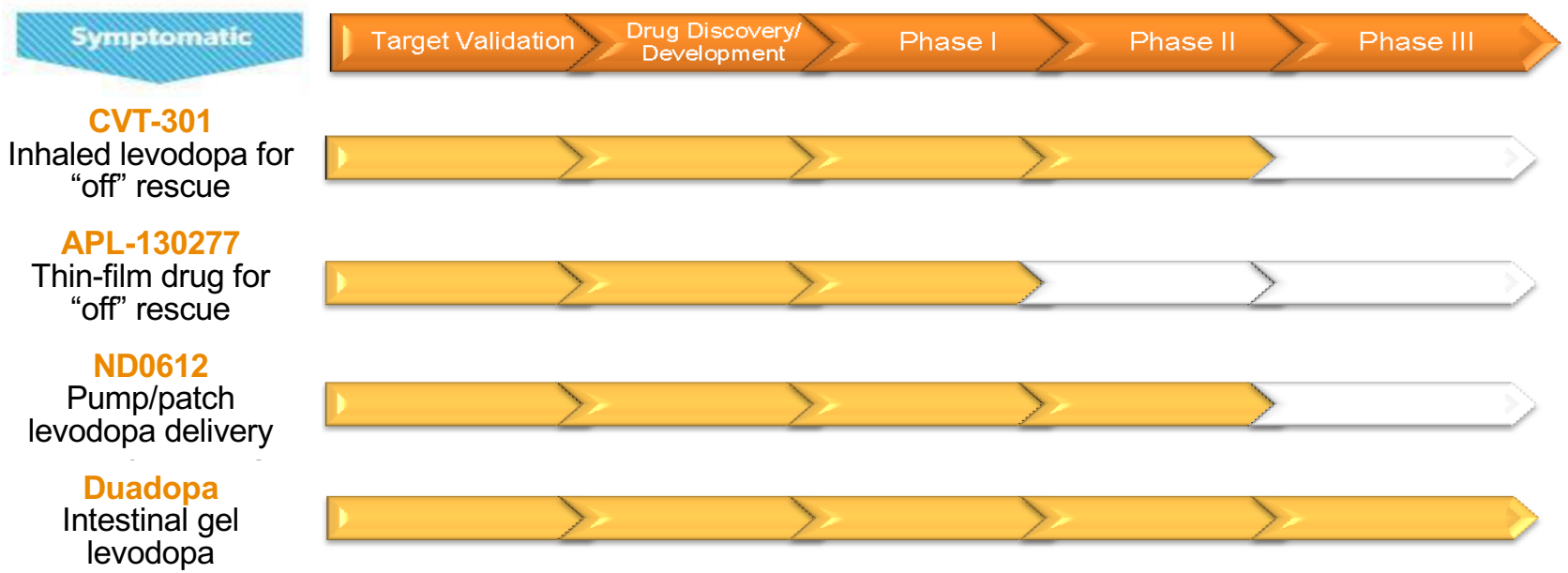


Managing Dyskinesia

- Reduction in individual dose of L-dopa and more frequent administration.
- Add a dopamine agonist and reduce dose of levodopa
- Amantadine 100 mg tid or more as tolerated (sustained release under development)
- Propranolol, clozapine and valproate have some efficacy
- Infusion therapies-apomorphine or jejunal levodopa
- Surgery-DBS GPI or STN

New Drugs for PD

We're on the verge of breakthrough treatments for motor fluctuations.



These drugs are expected to be available in the next one to three years.

Michael J. Fox Foundation. Available at: https://www.michaeljfox.org/understanding-parkinsons/living-with-pd/topic.php?therapies-in-development&navid=therapies-in-development. Accessed March 14, 2014.

Non-motor Symptoms

- Depression and anxiety
  - SSRIs citalopram, escitalopram, sertraline
  - SNRIs venlafaxine, desvenlafaxine and atomoxetine
  - TCAs amitriptyline, nortriptyline
- Psychosis
  - Typical: clozapine
  - Atypical: quetiapine, pimavanserin
- Cognitive impairment
  - Cholinesterase inhibitors rivastigmine, donepezil
  - NMDA anatagonist-memanatine

SSRI = selective serotonin reuptake inhibitor; SNRI – selective norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; NMDA = N-methyl-D-aspartate.

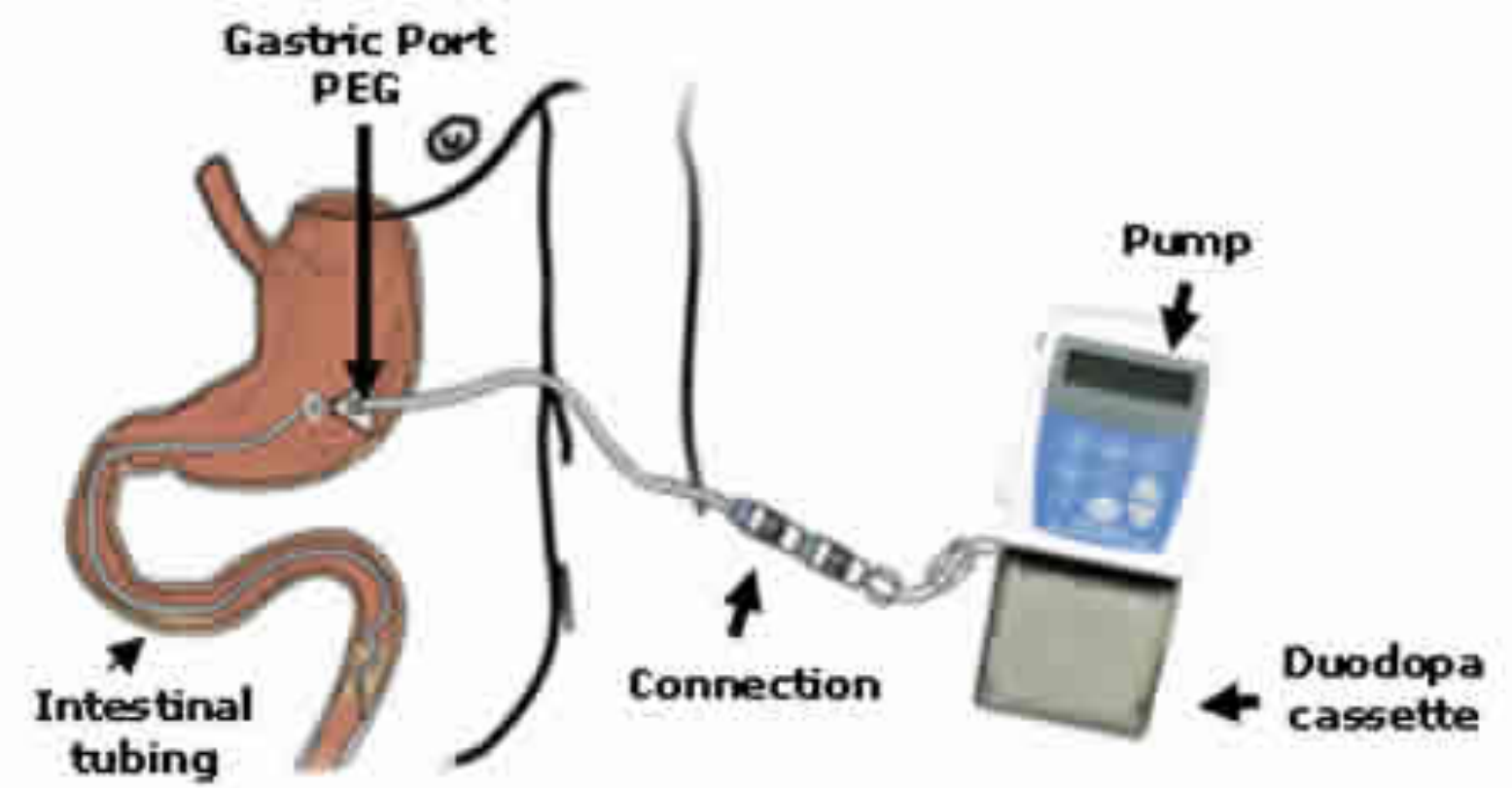
Non-motor Symptoms

- Sleep: behavioral therapy, sleep hygiene, bright light therapy, melatonin, hypnotics, waking-promoting agents, and CPAP
  - Benzodiazepines, zolpidem, eszopiclone, suvorexant, trazodone, mirtazapine, gabapentin, ramelteon

Non-motor Symptoms

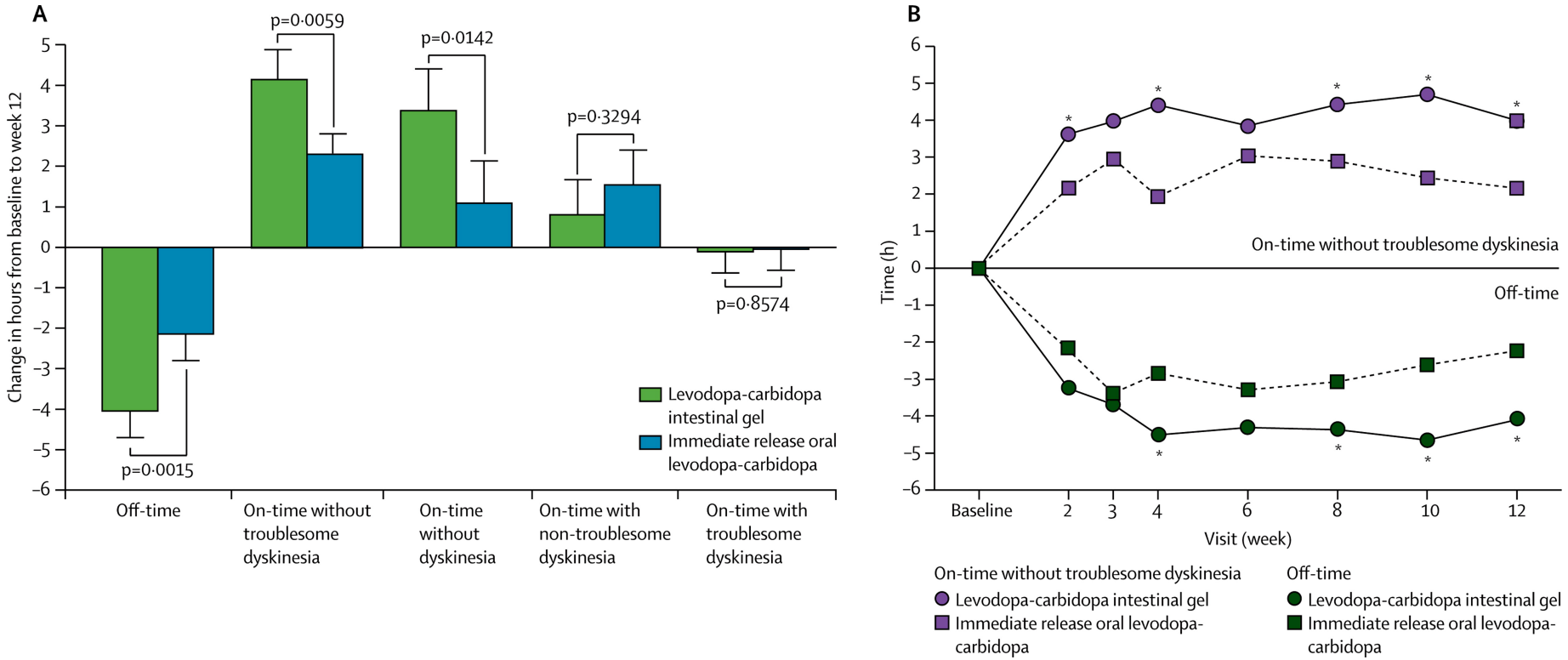
- Orthostatic hypotension: salt intake, compressive stocking, fludrocortisone, midodrine, droxidopa
- GI
  - Gastroparesis: H-pylori eradication, domperidone
  - Constipation: fiber, linaclotide, probiotics
- Bladder: urgency oxybutynin, mirabegron, botulinum toxin

Levodopa Intestinal Gel Pump



Olanow CW, et al. *Lancet Neurol*. 2014;13(2):141-149.

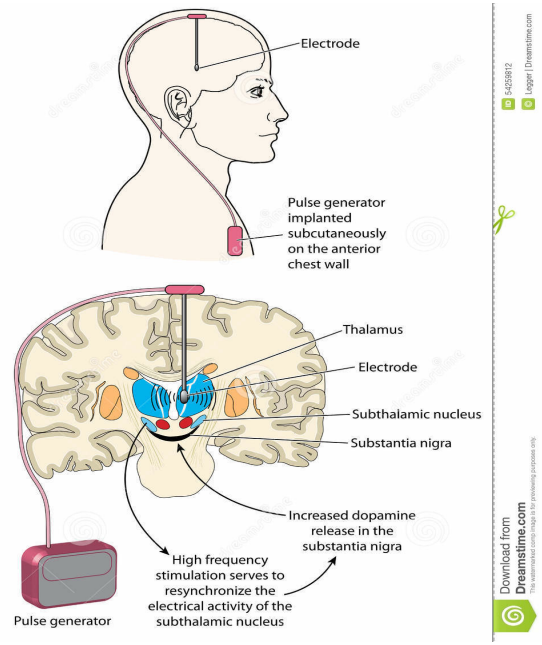
Levodopa Intestinal Gel Pump



Olanow CW, et al. *Lancet Neurol*. 2014;13(2):141-149.

Deep Brain Stimulation (DBS)

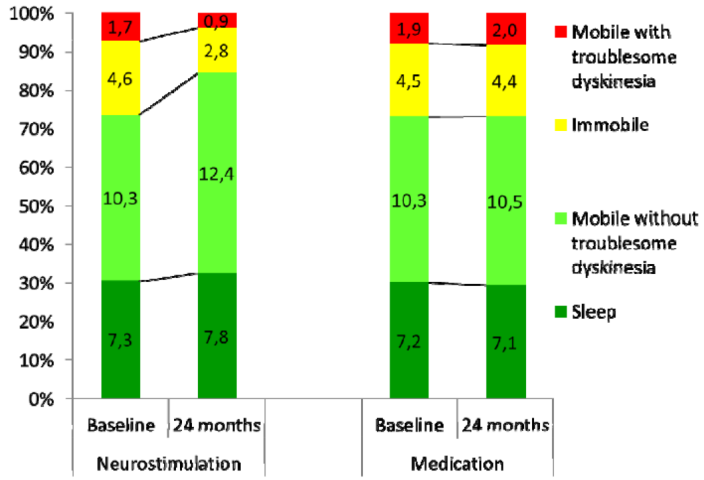
- Use of electrical current to modulate dysfunctional brain networks.
- High frequency DBS of subthalamic nucleus is indicated in patients with motor fluctuations (wearing off and dyskinesias)- approved by FDA in 2002
- Neurostimulation is usually done after 10-13 years of disease- improves motor symptoms and quality of life.
- Recently clinical trials showed that early use of DBS increases quality of life

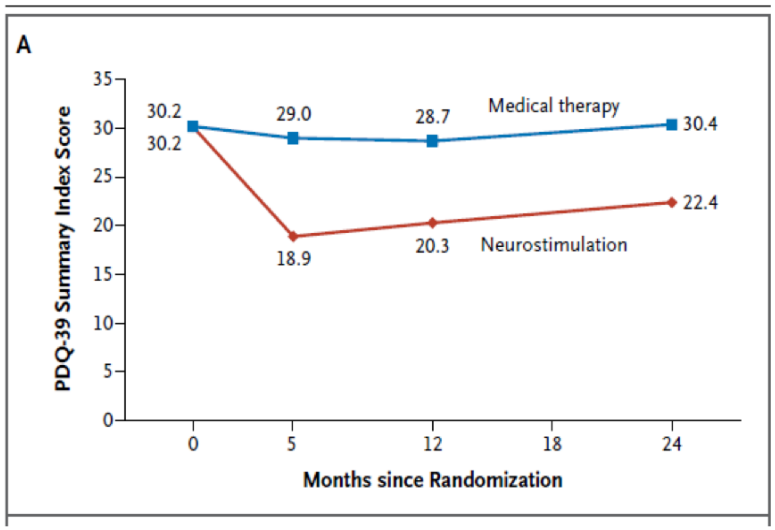


Dreamstime. Available at: https://www.dreamstime.com/stock-illustration-deep-brain-stimulation-using-implanted-pulse-generator-especially-as-relates-to-parkinson-s-disease-image54259812. Accessed March 14, 2017.

Deep Brain Stimulation

- On time increased with 2.1 hours in DBS group vs 0.2 hours in the medical therapy group.
- Quality of Life significantly increased in DBS group.





Schuepback WM, et al. *N Engl J Med*. 2013;368(7):610-622.

Deep Brain Stimulation

- DBS is superior to best medical therapy in patients with early motor complications (wearing off and dyskinesia)
- Improves significantly levodopa responsive symptoms: tremor, rigidity and bradykinesia, on-off fluctuations, and allows significant reduction in medication.
- Shortcomings: does not improve axial symptoms: gait/freezing, balance, speech, cognition

Schuepback WM, et al. *N Engl J Med*. 2013;368(7):610-622.

Take Home Message

- PD is a neurodegenerative disorders with motor and nonmotor symptoms
- PD is comorbid with depression and anxiety
- Etiology is multifactorial: genetic and environmental
- Medical treatment is tailored to patient symptoms both motor and non motor
- Advanced treatment: DBS and DUOPA.

Questions & Answers

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