Parkinson's Disease: An Overview

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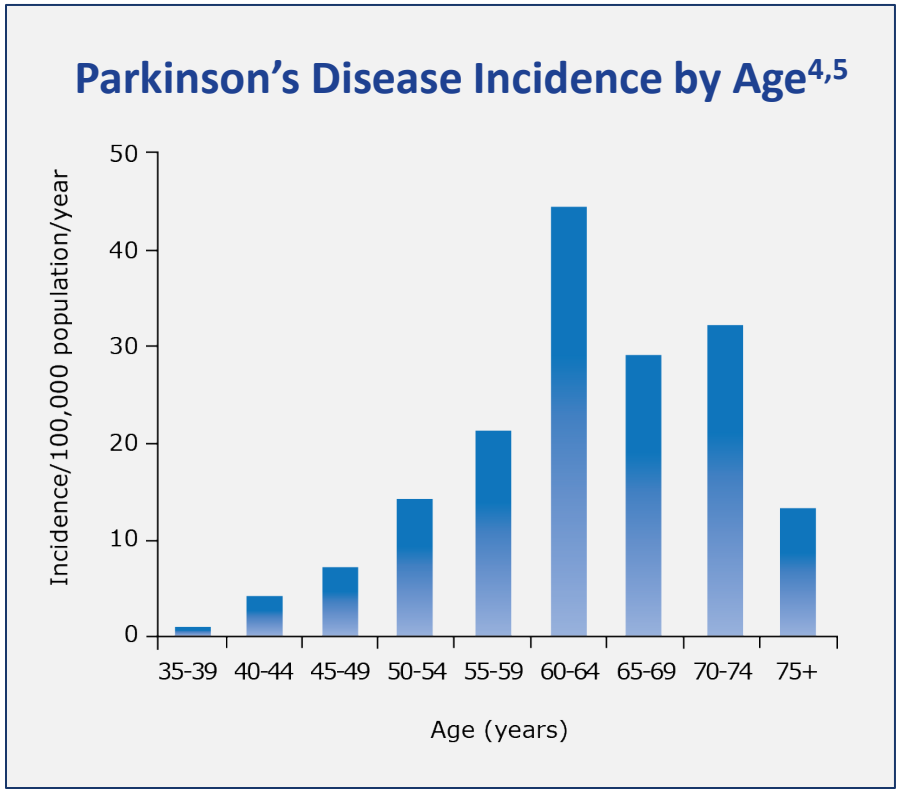
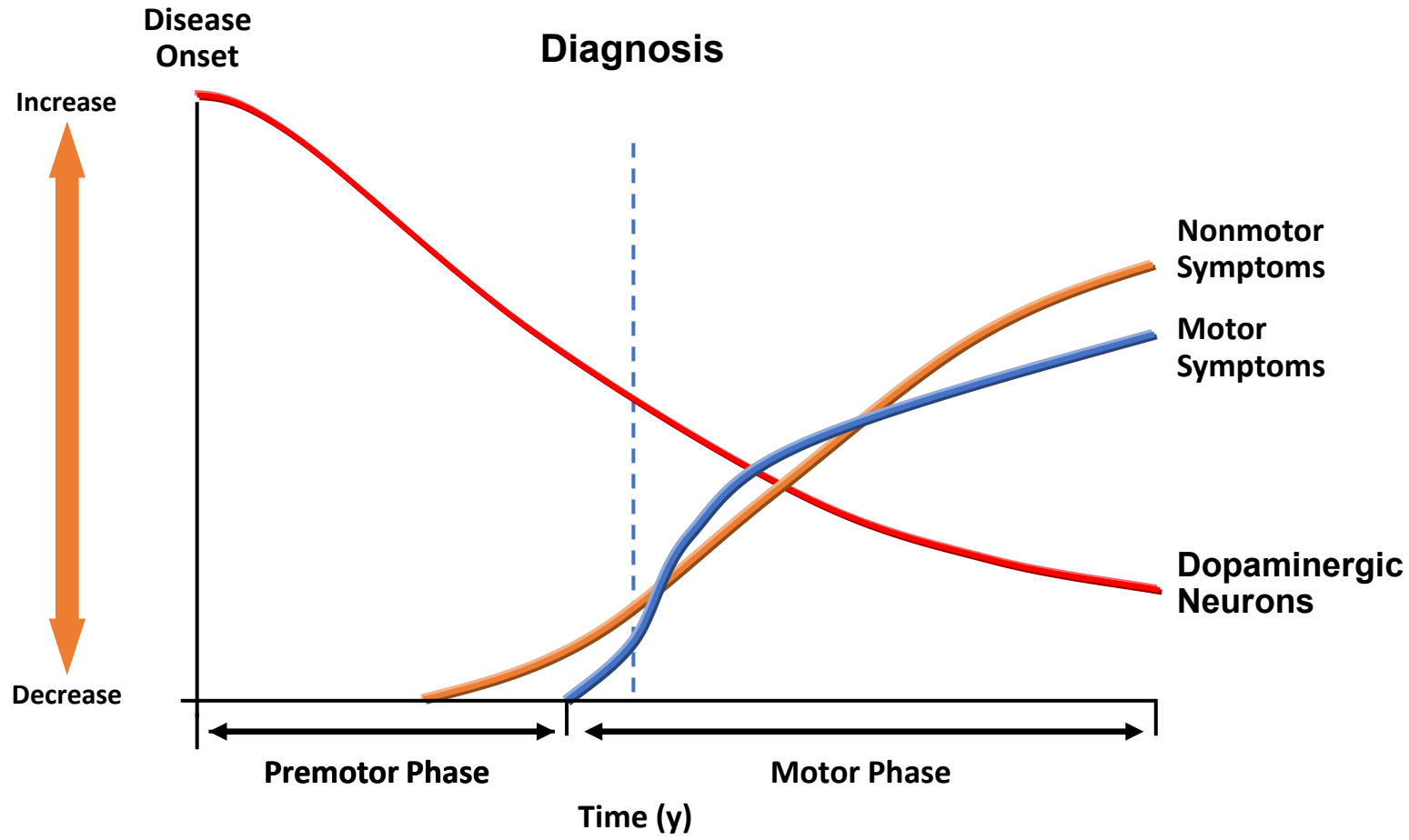
How Common Is PD?

- Second most common neurodegenerative disorder,[1] affecting
  - 7–10 million worldwide[2]
  - 1 million in US[2]
  - 0.3% in industrialized nations[3]
  - 60,000 new cases diagnosed annually in US[2]
    - Mean age at symptom onset ~60 years[4]
- Prevalence rises with age:
    - 1–2% of those >65 years[5]
    - 4–5% of those >85 years[5]



1. Nussbaum RL *et al*. N Engl J Med 2003; **348**: 1356-1364.
2. Parkinson's Disease Foundation, 2010.
3. de Lau LM *et al*. *Lancet Neurol* 2006; **5**: 525-535.
4. Twelves D *et al*. *Mov Disord* 2003; **18**: 19-31.
5. Weintraub D *et al*. *Am J Manag Care* 2008; **14**: S40-S48.

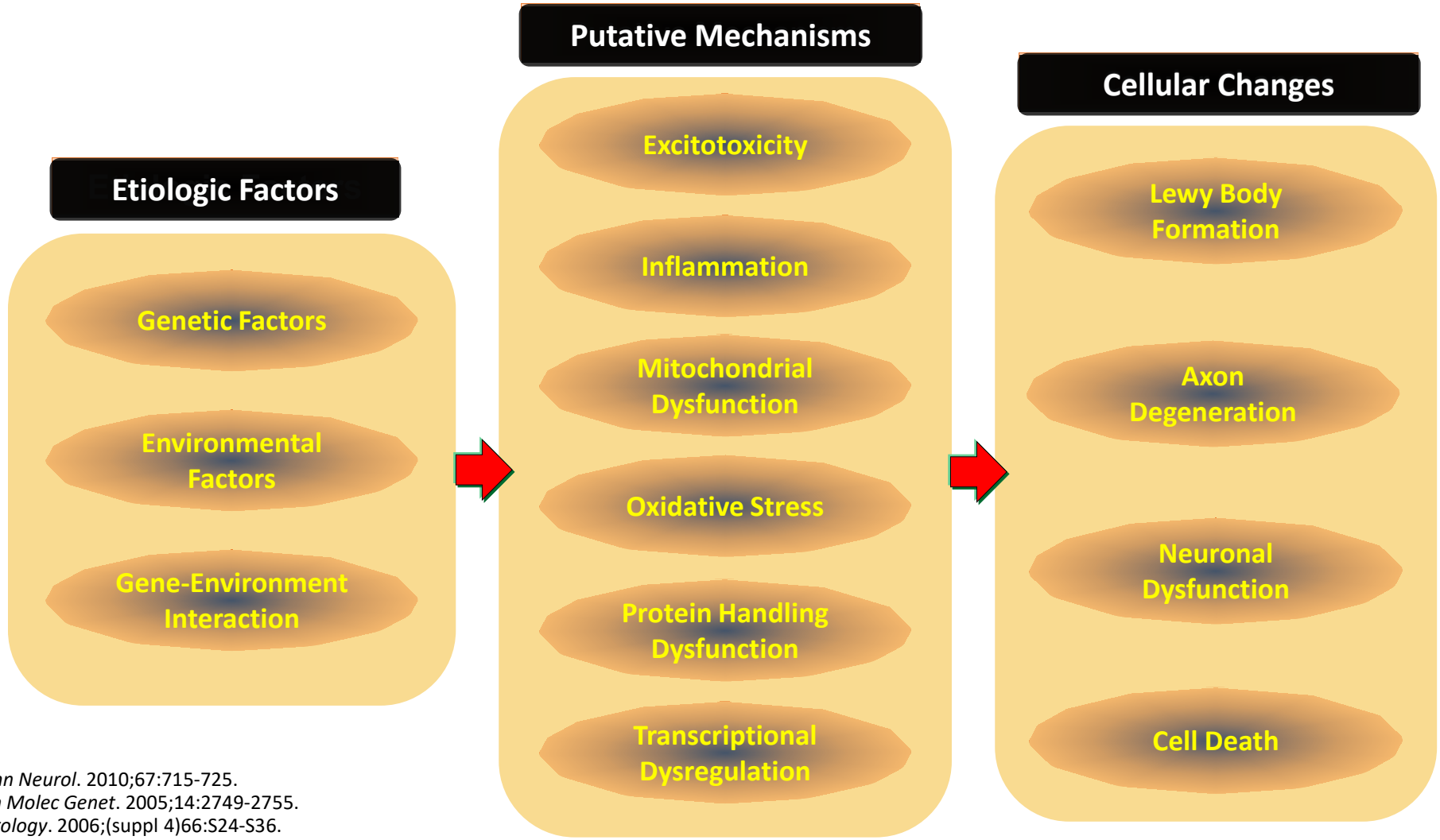
Conceptual Diagram of the Phases of PD



Schapira AH et al. *Nat Rev Neurol*. 2010;6:309-317.

Pathogenesis and Pathology of PD

Conceptual Diagram of the Pathogenesis of PD



Cheng H-C et al. *Ann Neurol*. 2010;67:715-725.
Gandhi S et al. *Hum Molec Genet*. 2005;14:2749-2755.
Jenner P et al. *Neurology*. 2006;(suppl 4)66:S24-S36.
Przedborski S. *Mov Disord*. 2010;25(suppl 1):S55-S57.
Tanner CM. *Mov Disord*. 2010;25(suppl 1):S58-S62.
Wider C et al. *Mov Disord.* 2010;25(suppl 1):S15-S20.

What's happening in PD?

- Propagation of abnormal aggregation of alpha-synuclein
  - Synuclein mutations
  - Too much synuclein
  - Problems with clearing abnormal synuclein
- Decreased energy state in neurons
- Inflammation

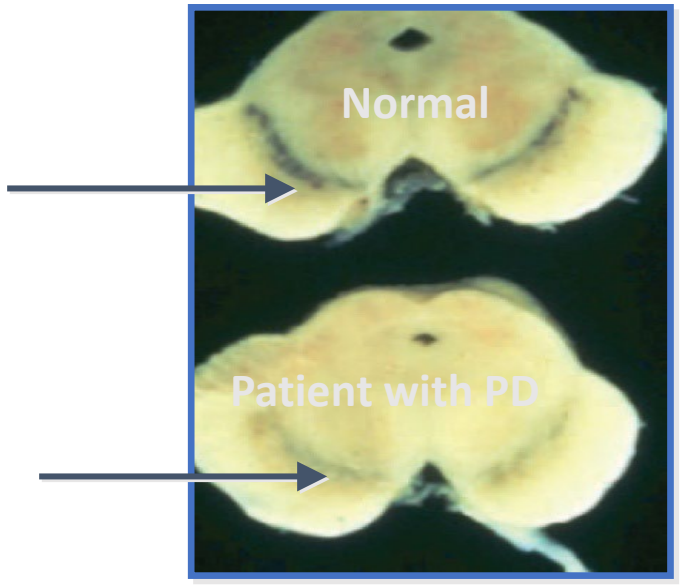
PD Pathogenesis: Genetics

- Over 90% of PD cases appear to be sporadic, due to some combination of genetic susceptibility (due to multiple genes) and environmental/lifestyle factors
- Less than 5% of cases of PD are due to single gene mutation, including:
  - *LRRK2*
  - *SNCA*
  - *PRKN*
  - *PINK1*
  - *DJ1*
  - *GBA1*
- Although molecular diagnostic testing is available for all 6 confirmed genes, results do not change clinical recommendations at this time;
- LRRK2 and GBA inhibitors in early clinical trials.

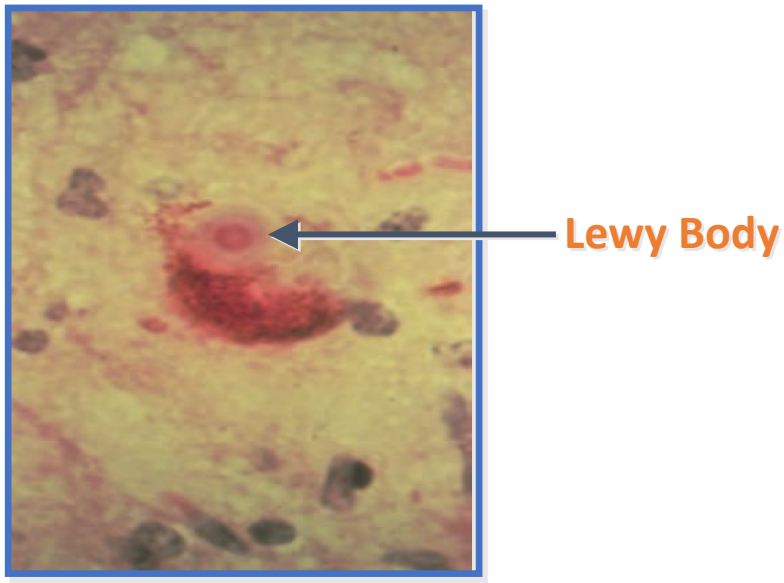
International Parkinson Disease Genomics Consortium. *Lancet*. 2011. DOI:10.1016/S0140-6736(10)62345-8.
Nicoletti A et al. *Neurol Sci*. 2010;31:47-52.
Wider C et al. *Mov Disord*. 2010;25:S15-S20.

Classic Neuronal Pathology of PD

Nigrostriatal degeneration, primarily in the substantia nigra pars compacta (SNpc) and striatum, and α-synuclein aggregates are pathologic hallmarks of PD



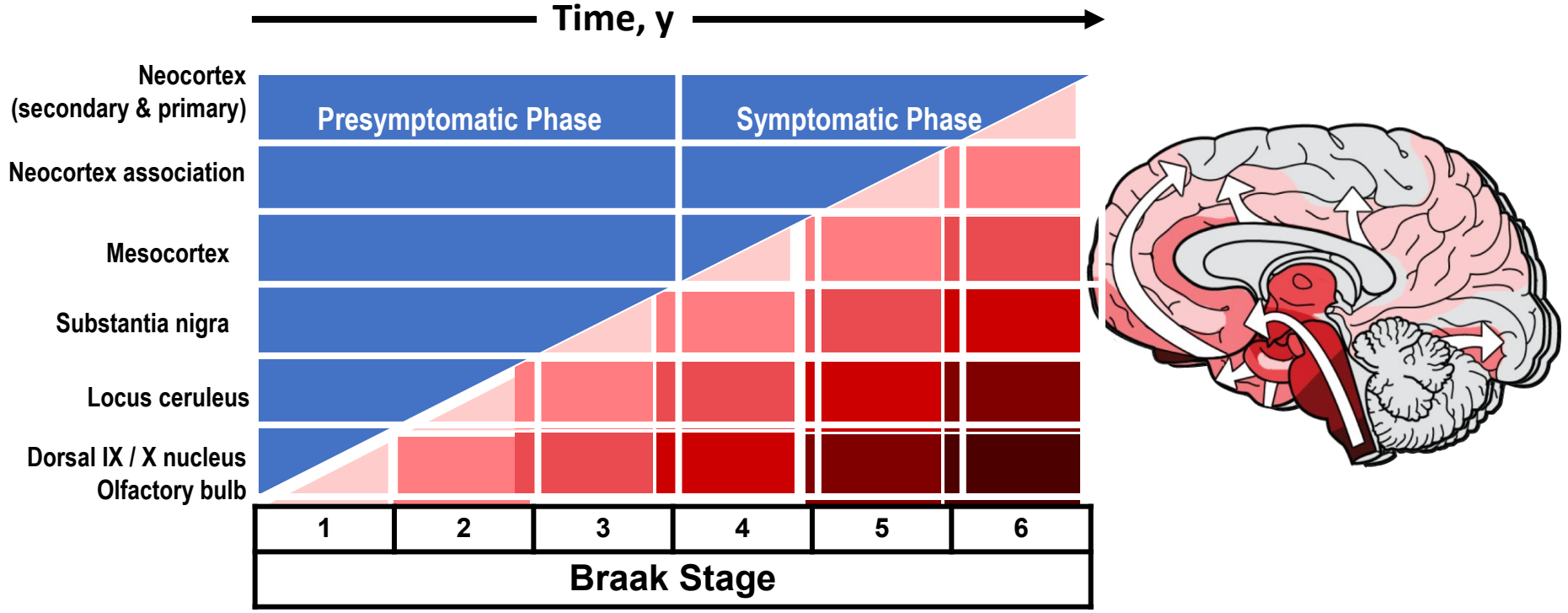
Significant nigral dopaminergic neuronal loss is marked by a reduction in neuromelanin pigment in the SNpc



Intraneuronal cytoplasmic inclusions, or "Lewy Bodies"

Images reprinted with permission from Olanow CW, Stern MB, Sethi K. The scientific and clinical basis for the treatment of Parkinson disease (2009). *Neurology*. 2009;72(21 suppl 4): S1-S136.
Farrer MJ. *Nat Review Genetics*. 2006;7:306-318.

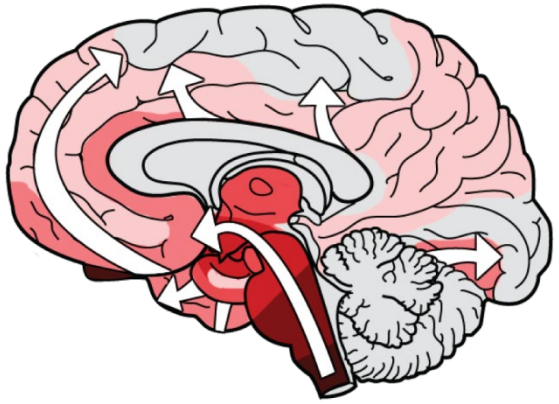
The Braak Hypothesis: An Evolving Concept of Disease Progression and Timing



Braak H et al. *Cell Tissue Res.* 2004;318:121-134.
Braak H et al. *J Neurol*. 2002;249(suppl 3):III/1-5.
Braak H et al. *Neurobiol Aging*. 2003;24:197-211.

What Is The Role of Abnormal α-Synuclein Aggregation in PD?

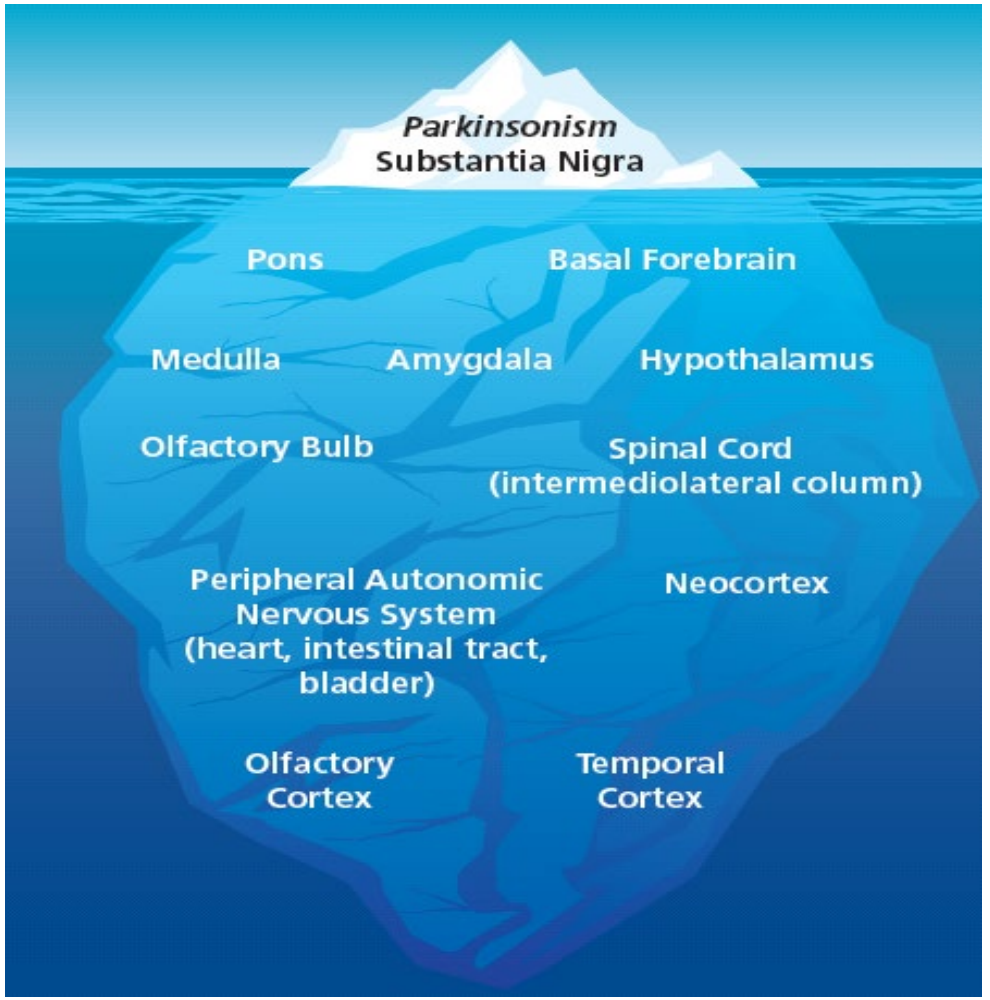
Braak Hypothesis
Spread of Lewy bodies as PD progresses



- Lewy bodies (abnormal aggregations of α-synuclein) are a prerequisite for postmortem PD diagnosis
- Braak and colleagues hypothesize that Lewy bodies spread throughout the brain in a predictable pattern as PD progresses
- Pathologic studies in PD patients have found Lewy pathology in brain, cardiac, and enteric autonomic nervous systems
- It is not known whether α-synuclein aggregation is a direct causative factor in the pathogenesis of PD or a protective mechanism against protein-induced cell toxicity

Braak H et al. *Cell Tissue Res.* 2004;318:121-134.
Fortin DL et al. *Mov Disord.* 2010;25(suppl 1):S21-26.
Hawkes CH et al. *Parkinsonism Relat Disord*. 2010;16:79-84.
Wider C et al. *Mov Disord*. 2010;25:S15-S20.

The Parkinson's Complex



Langston JW. *Ann Neurol*. 2006;59:591-596.
Adapted with permission from Langston JW. The Parkinson's complex: Parkinsonism is just the tip of the iceberg. *Ann Neurol.* 2006;59(4):591-596.

Early Diagnosis of PD

- Up to 60% of nigrostriatal dopamine neurons are lost by the time PD motor symptoms are evident
- Premotor phase: 5–20 years
- Opportunity to test new medications and, ultimately, to treat patients during this phase requires reliable and well-validated biomarkers
- Potential strategies include:
  - Genetic testing
  - Nonmotor symptoms, eg, olfactory loss, RBD
  - Dopaminergic imaging

RBD, Rapid eye movement sleep behavior disorder

Marek K *et al*. *Neurology* 2009; **72** (7 Suppl): S21-26.

UKPDS Brain Bank: Clinical Diagnostic Criteria

Step 1: Diagnosis of parkinsonian syndrome	Step 2: Exclusion criteria for PD	Step 3: Supportive prospective positive criteria for PD
Bradykinesia plus ≥1 of the following: •Muscular rigidity •4–6 Hz rest tremor •Postural instability	• History of strokes, head injury or encephalitis • Oculogyric crises • Neuroleptic treatment or exposure to neurotoxins • >1 affected relative • Sustained remission • Strictly unilateral features after 3 years • Supranuclear gaze palsy • Cerebellar signs • Early severe autonomic involvement or dementia • Babinski signs • Cerebral tumor or communicating hydrocephalus • Negative response to levodopa	**≥3 of the following:** • Unilateral onset • Rest tremor • Progressive disorder • Persistent asymmetry • Excellent response to levodopa • Severe levodopa-induced chorea • Levodopa response for ≥5 years • Clinical course of ≥10 years

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

Nonmotor Symptoms Play an Important Role in Clinical Manifestations of PD

Nonmotor Symptoms

- Anxiety
- Constipation*
- Depression*
- Dementia
- Drooling
- Excessive daytime sleepiness
- Fatigue
- Hyperhidrosis
- Olfactory dysfunction*
- Orthostatic hypotension
- Pain
- Psychosis
- REM sleep behavior disorder (RBD)*
- Sexual dysfunction
- Urinary urgency

*Although nonmotor symptoms occur throughout the course of PD, certain nonmotor symptoms are considered "premotor" because onset may precede the emergence of motor symptoms by years

Jankovic J. *J Neurol Neurosurg Psychiatry*. 2008;79:368-376.
Morgan J et al. *Handbook of Parkinson's Disease*, 4th ed. New York, NY: Informa Healthcare USA, Inc; 2007:29-47. Tolosa E et al. *Neurology*. 2009;72(suppl 2):S12-S20.
Tysnes O-B et al. *Acta Neurol Scand*. 2010;122(suppl 190):72-77.

Tremor

- Distal parts of extremities and the lips at rest;
- 4 -6 Hz frequency resting tremor;
- Pill-rolling, flexion-extension, pronation-supination tremor;
- Tremor ceases upon active movement, but reemerges with posture against gravity;

Bradykinesia

- Hypomimia;
- Decreased frequency of blinking;
- Impaired upgaze and convergence of the eyes;
- Hypophonia;
- Aprosody;
- Drooling of saliva;
- Micrographia;
- Loss of spontaneous movements;
- Difficulty rising of the chair;
- Reduction of amplitude of movement

Rigidity

- Cogwheel rigidity;
- Lead pipe rigidity;
- Flexed extremities and trunk;
- Camptocormia.

Gait

- Short-stepped shuffling gait;
- Turning en-block;
- Decreased arm swing;
- Retropulsion and anteropulsion;
- Freezing with change of surface;
- Difficulty with initiation;
- Stooped posture.

Freezing

- Start-hesitation;
- Turning-hesitation;
- Destination-hesitation;
- Freezing when obstacle is encountered;
- Spontaneous sudden transient freezing;
- Palilalia or freezing of speech;
- Apraxia of eyelid opening;
- Freezing of limbs.

Differential Diagnosis of PD

Other Disorders	
Essential tremor	
Secondary Parkinsonism	
Drug-induced parkinsonism	Vascular parkinsonism
Toxin-induced parkinsonism	Posttraumatic parkinsonism • Dementia pugilistica
Infections • Creutzfeldt-Jakob disease	Structural parkinsonism • Normal pressure hydrocephalus • Subdural hematomas • Tumors
Metabolic parkinsonism • Hypo/hyperthyroidism • Hypoparathyroidism	
Neurodegenerative Disorders With Parkinsonian Features	
Multiple system atrophy Progressive supranuclear palsy	Corticobasal degeneration Diffuse Lewy body disease
Hereditary Disorders Associated With Parkinsonism	
Dentatorubral-pallidoluysian atrophy Huntington's disease	Machado-Joseph disease (spinocerebellar ataxia 3) Wilson's disease

Adler CH. *Med Clin North Am*. 1999;83:349-367.

Atypical Parkinsonian Syndromes at a glance

- May present with symmetrical limb signs or mainly axial involvement;
- May involve other systems (pyramidal, cerebellar, oculomotor, autonomic);
- May have prominent cognitive dysfunction early;
- Minimal to no response to levodopa;
- No sustained benefit from DBS;
- Greatest difficulty in differentiation: Multiple System Atrophy

Differential Diagnosis of PD

Distinguishing Features		*Common Misdiagnoses*
Tremor (action/postural) is the only feature; no response to PD drugs	→	Essential tremor (ET)
Early gait instability, supranuclear (downgaze) palsy, pseudobulbar affect, dysphagia	→	Progressive supranuclear palsy (PSP)
Autonomic disturbance, cerebellar signs, absence of tremor, early gait instability, dysphagia	→	Multiple system atrophy (MSA)
Limb apraxia, cortical sensory abnormalities, Coarse unilateral tremor, early dementia	→	Corticobasal degeneration (CBD)

Nutt JG, Wooten GF. *N Engl J Med*. 2005;353:1021-1027.

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

Differential Diagnosis of PD

Distinguishing Features	*Common Misdiagnoses*
Early dementia, psychosis (visual hallucinations and delusions), agitation	→ Dementia w/ Lewy Bodies (DLB)
Dementia is the primary symptom	→ Alzheimer's disease
Exposure to dopamine-blocking drugs; lack of asymmetry	→ Drug-induced parkinsonism
Severe chronic ischemic changes and/or multiple strokes on MRI; stepwise progression (if any); Lack of tremor	→ Vascular parkinsonism

NPH

- Ataxic, Parkinsonian gait;
- No evidence of upper body parkinsonism;
- Urinary incontinence;
- Progressive cognitive decline.
- Ventriculomegaly out of proportion to cortical atrophy and white matter disease
- Gait improves after high volume LP

Brain Imaging: Evolving Technology That May Aid in Diagnosis of PD

- DaTscan™ (Ioflupane I 123 Injection), is a radiopharmaceutical agent approved by the FDA for striatal dopamine transporter (DaT) visualization using single photon emission-computed tomography (SPECT) imaging
- DaTscan differentiates between patients with and without a dopaminergic deficit
- DaTscan is a potential adjunct in the diagnosis of Parkinsonian symptoms

FDA indicates United States Food and Drug Administration.

DaTscan [package insert]. Arlington Heights, IL: GE Healthcare; January 2011.
Hauser RA et al. *J Neuroimaging*. 2011; DOI: 10.111/j.1552-6569.2011.00583.x

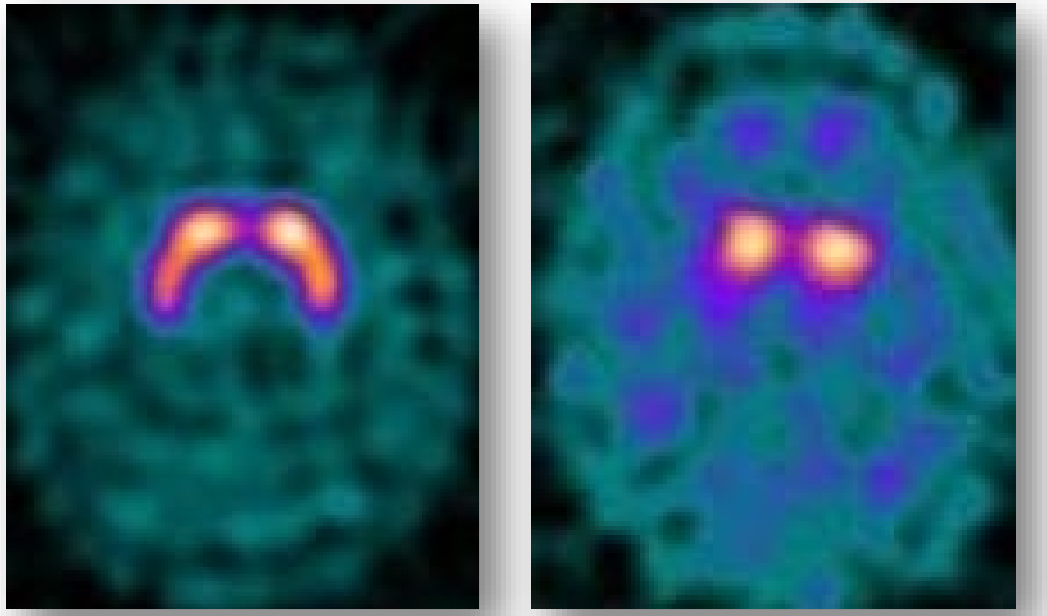
DaTscan (Ioflupane I 123 Injection) Indications

- DaTscan is a radiopharmaceutical indicated for striatal dopamine transporter visualization using SPECT brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS)
- In these patients DaTscan may be used to help differentiate essential tremor (ET) from tremor due to Parkinsonian Syndrome
  - DaTscan cannot differentiate between different forms of PS (eg, PD, MSA, and PSP)
  - DaTscan is an adjunct to other diagnostic evaluations
  - The effectiveness of DaTscan as a screening or confirmatory test and for monitoring disease progression or response to therapy has not been established

DaTscan™ prescribing information, 2011

How Does DaTscan (Ioflupane I 123 Injection) Aid Diagnosis in Suspected Parkinsonian Syndrome?

Conserved striatal DaT activity



Marked reduction in striatal DaT activity

Images courtesy of Birmingham City Hospital, UK

DaT: dopamine transporter

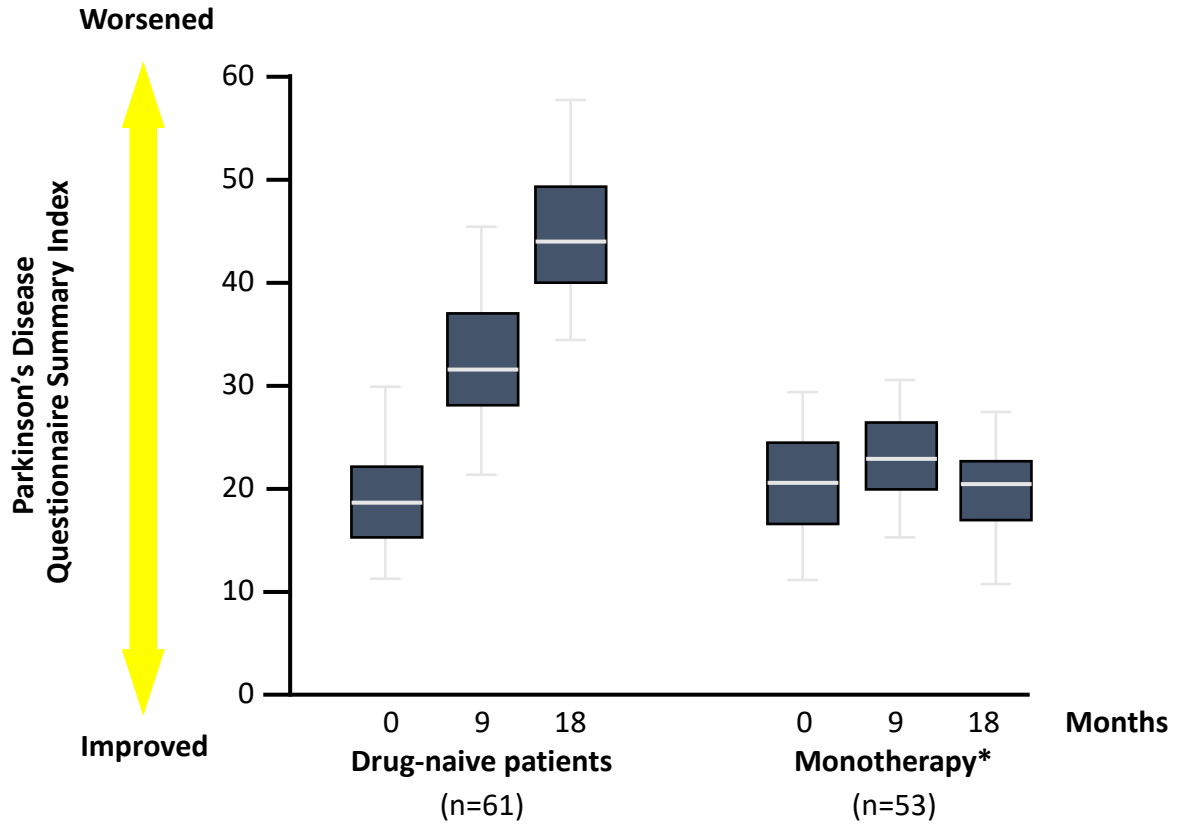
DaTscan™ prescribing information, 2011

Current Treatments for Parkinson's Disease

Types of Treatments

- Pharmacologic Treatments (drugs)
- Non-pharmacologic Therapies
- Surgical Therapies

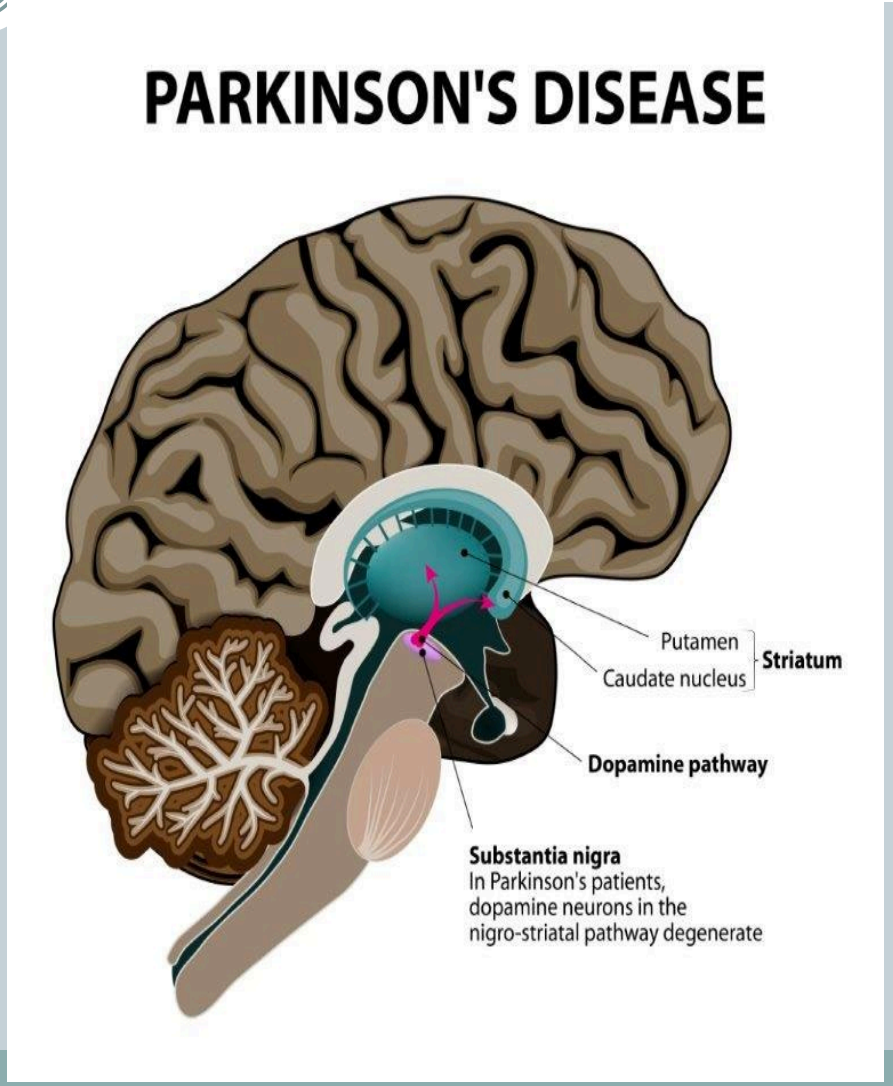
QOL Health Status Deteriorates in Untreated Parkinson's Patients Over 18 Months



*Initial treatment included levodopa (51% of patients), dopamine agonists (43%), and other (6%).
Horizontal line within box=median value; box edges=lower and upper quartiles; whiskers display range.
Grosset D et al. *J Neurol Neurosurg Psychiatry*. 2007;78:465-469.

How do Parkinson's meds work??

- In PD, there are loss of dopamine cells
- PD meds can:
  - Replace dopamine
  - Stimulate dopamine receptors
  - Encourage cells to make more dopamine
  - Stop the breakdown of dopamine

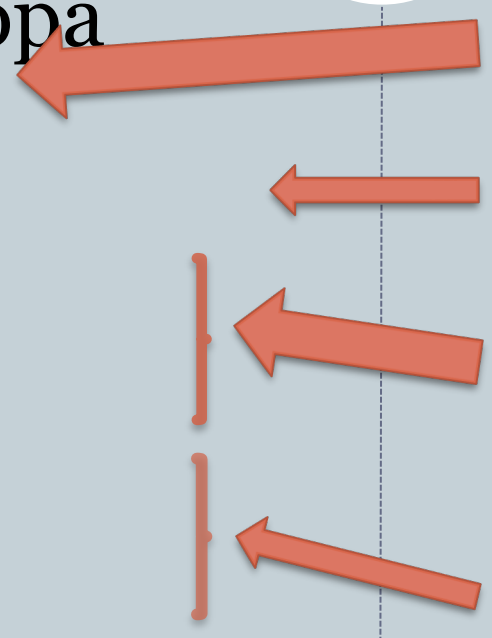


PD meds side effects

- ALL Parkinson's meds can cause these side effects, because of dopamine stimulation:
  - Nausea
  - Sleepiness
  - Dizziness (low blood pressure)
  - Confusion
  - Vivid dreams / hallucinations

Pharmacologic Treatments (for motor symptoms)

- Carbidopa / Levodopa
- Dopamine Agonists
- MAO Inhibitors
- COMT Inhibitors
- Amantadine
- Anticholinergics



Replace dopamine

Stimulate dopamine receptors

Stop the breakdown of dopamine

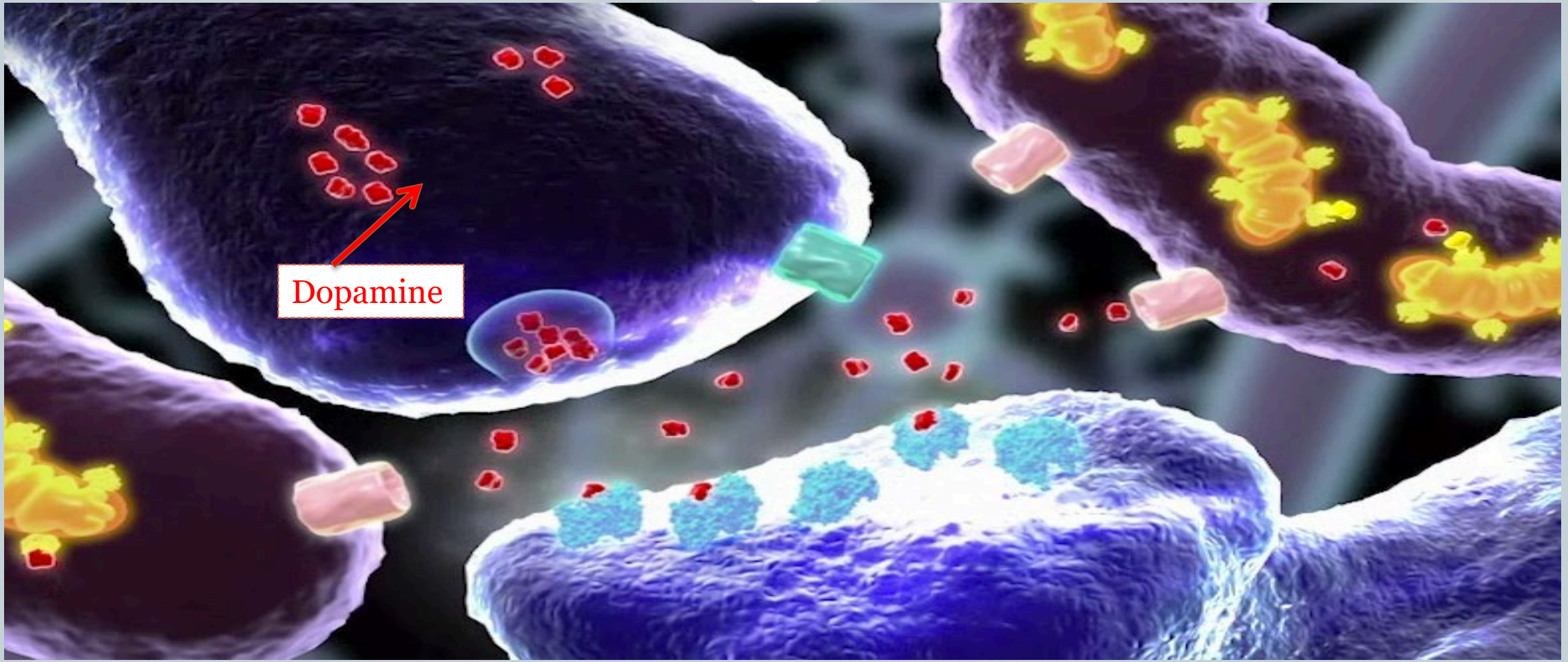
Affects mostly non-dopamine receptors

*many other drugs for non-motor symptoms (ex: antidepressants)

Carbidopa / Levodopa

- Replaces Dopamine (it IS dopamine!)
- Levodopa is active ingredient
  - Most powerful PD medicine by far!
  - One of the cheapest meds
  - Converted by body to Dopamine

How does Levodopa work?



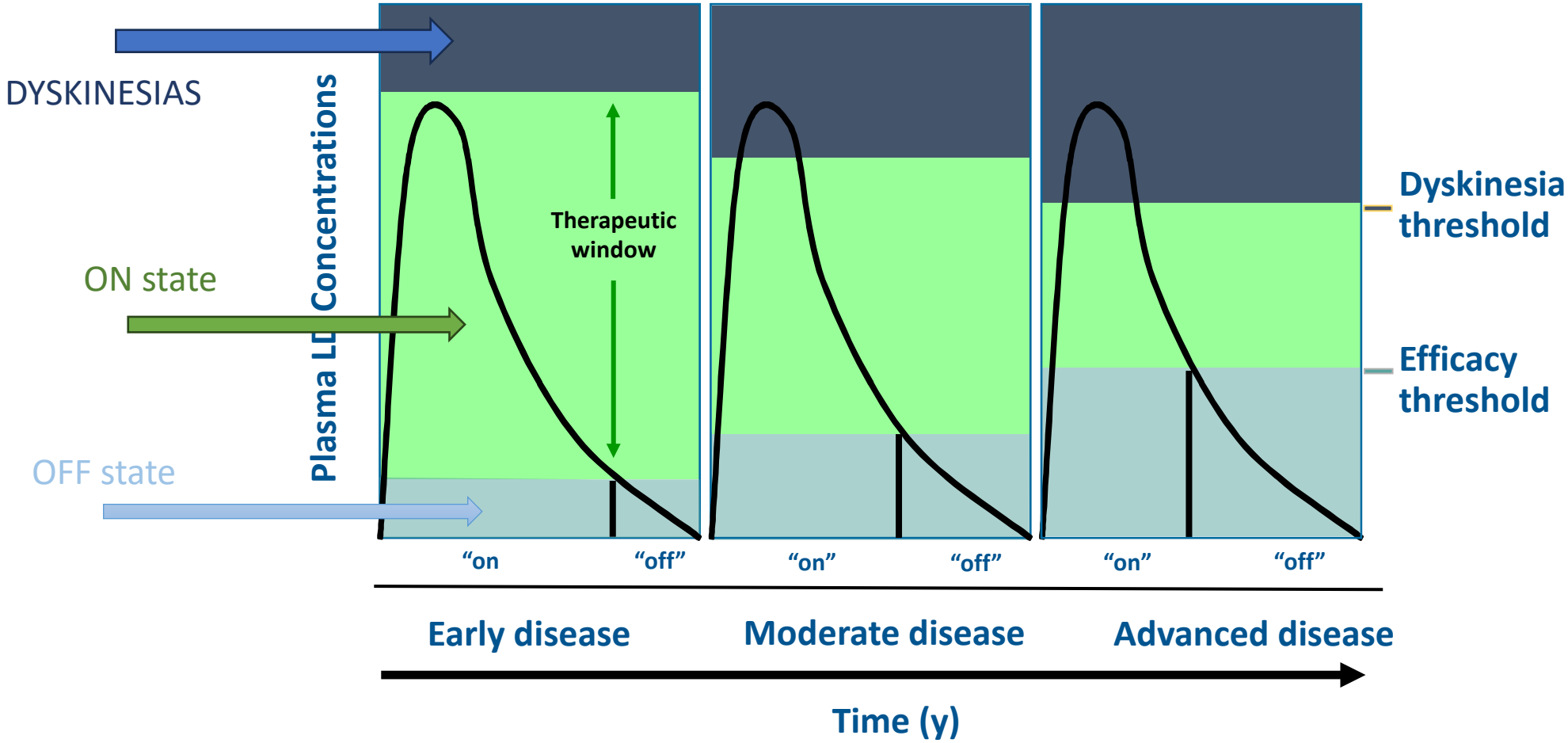
Carbidopa / Levodopa

- Carbidopa always given with Levodopa to treat nausea caused by Levodopa
  - Extra carbidopa can be given separately if needed for refractory nausea
- Almost all PD patients eventually should be on Levodopa
  - most should be on levodopa within few years of diagnosis
  - Many movement disorder neurologists almost exclusively use levodopa!

Carbidopa / Levodopa variants

- Oral
  - Carbidopa / Levodopa (regular) 1968
  - Carbidopa / Levodopa CR 1992
  - Carbidopa / Levodopa/Entacapone (Stalevo) 2003
  - Carbidopa / Levodopa extended-release capsules (Rytary) 2015
- Duodenal (infused into intestines via pump)
  - In USA, known as Duopa (2015)
  - In Europe, known as Duodopa (2005)
- Inhalational (Inbrija), for rescue therapy only, for severe OFF spell

Chronic LD Therapy Is Associated With End of Dose “Wearing Off” and Peak Dose Dyskinesia



Adapted by permission from Macmillan Publishers Ltd: *Nat Clin Pract Neurol*., Olanow CW, Obeso JA, Stocchi F. Drug insight: Continuous dopaminergic stimulation in the treatment of Parkinson's disease. *Nat Clin Pract Neurol*. 2006;2:382-392. copyright 2006.

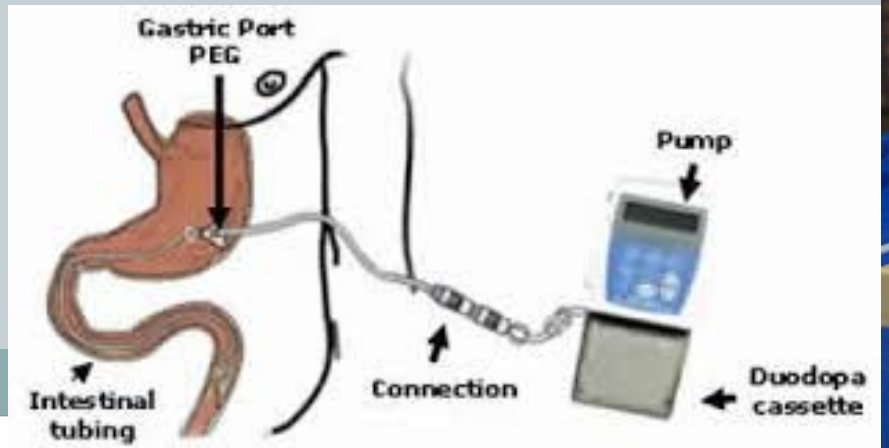
Early Signs of Wearing Off Vary Among Patients

Motor	Nonmotor
Bradykinesia	Abdominal discomfort
Difficulty getting out of a chair	Akathisia (uncontrollable motor restlessness)
Dystonia	Anxiety
Imbalance	Cloudy mind, dullness of thinking
Muscle cramping	Drenching sweats
Reduced dexterity	Drooling
Slowness in early morning/during the night	Dysphagia
Stiffness	Dyspnea
Tremor	Facial flushing
Weakness	Fatigue
	Irritability
	Mood changes
	Numbness
	Pain
	Tightening sensations
	Tingling sensations

Stacy M et al. *Mov Disord*. 2005;20:726-733.
Witjas T et al. *Neurology*. 2002;59:408-413.

Duopa

- Carbidopa / Levodopa Enteral Suspension
- Pump / Cartridge system
- Indicated for the treatment of motor fluctuations in PD patients
- Gastric tube must be placed by a gastroenterologist or surgeon



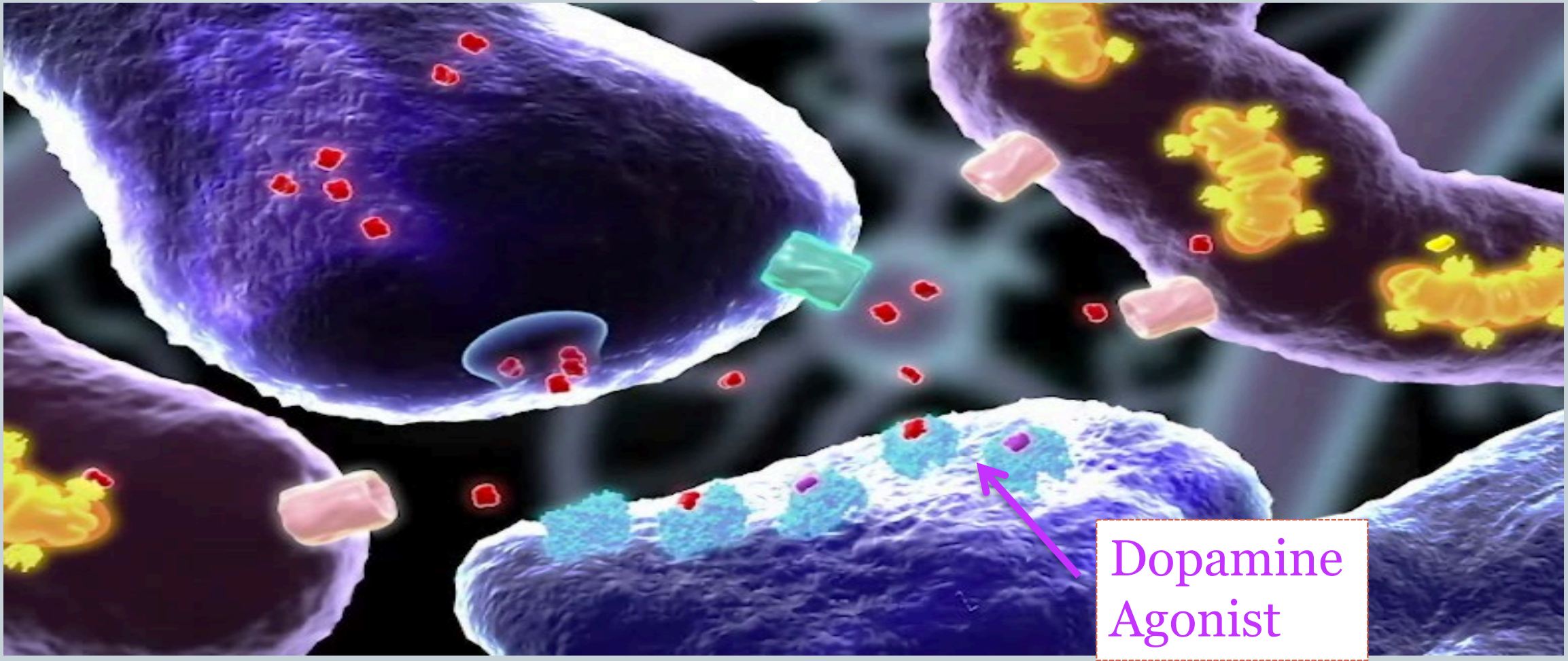
Future Carbidopa/Levodopa variants?

- Subcutaneous Pump (in clinical trials)

Dopamine Agonists

- Stimulate dopamine receptors
- “fake” dopamine
- Not as strong as “real” dopamine
- 2nd strongest PD meds (levodopa is #1)

How do Dopamine Agonists work?



Dopamine Agonists

- 3 dopamine agonists (DAs) commonly used for PD
  - 2 pills
  - 1 patch
- 2 other DAs much less commonly used
- Older DAs removed from market due to side effects

Dopamine Agonists

- Mirapex (Pramiprexole) 1997
  - Immediate-release pills (3 times a day)
  - Extended-release pills (once a day)
- Requip (Ropinirole) 1997
  - Immediate-release pills (3 times a day)
  - Extended-release pills (once a day)
- Neupro (Rotigotine) 2007
  - Once-daily patch

Dopamine Agonists

- Apokyn (Apomorphine) 2004
  - Subcutaneous injection
  - Intended as rescue therapy for OFF periods
  - Clinical trials looking at apomorphine pump

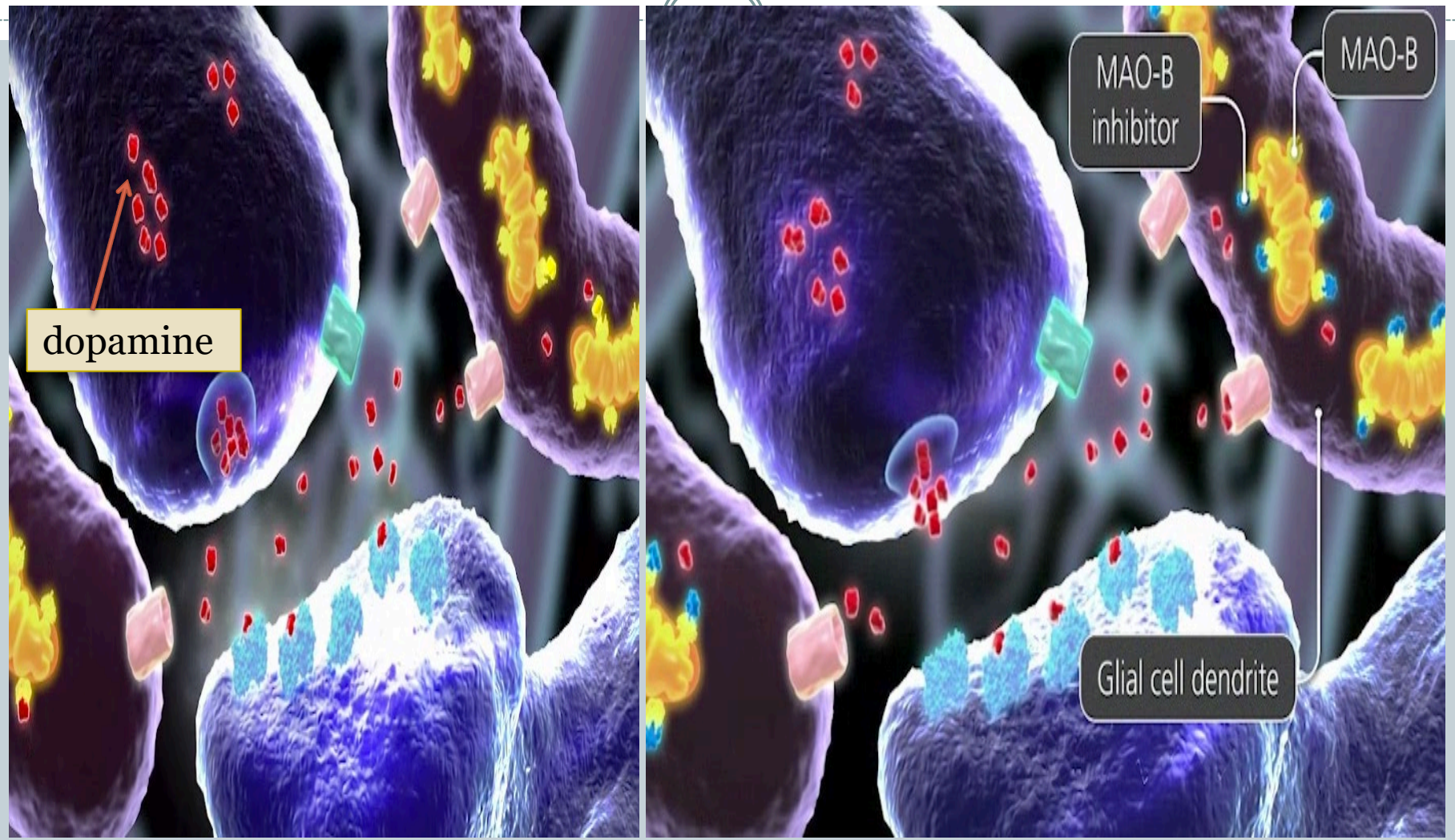
Dopamine Agonists Unique Side Effects

- Impulse Control Disorders (ICDs)
  - Compulsive behaviors such as gambling, shopping, eating, or sexual compulsions
- Ankle swelling
- Falling asleep at the wheel

MAO Inhibitors

- MAO (Monoamine Oxidase) is an enzyme in the brain
- This enzyme breaks down dopamine
- MAO Inhibitors prevent breakdown of dopamine, so more dopamine is around for the brain to use

How do MAO Inhibitors work?



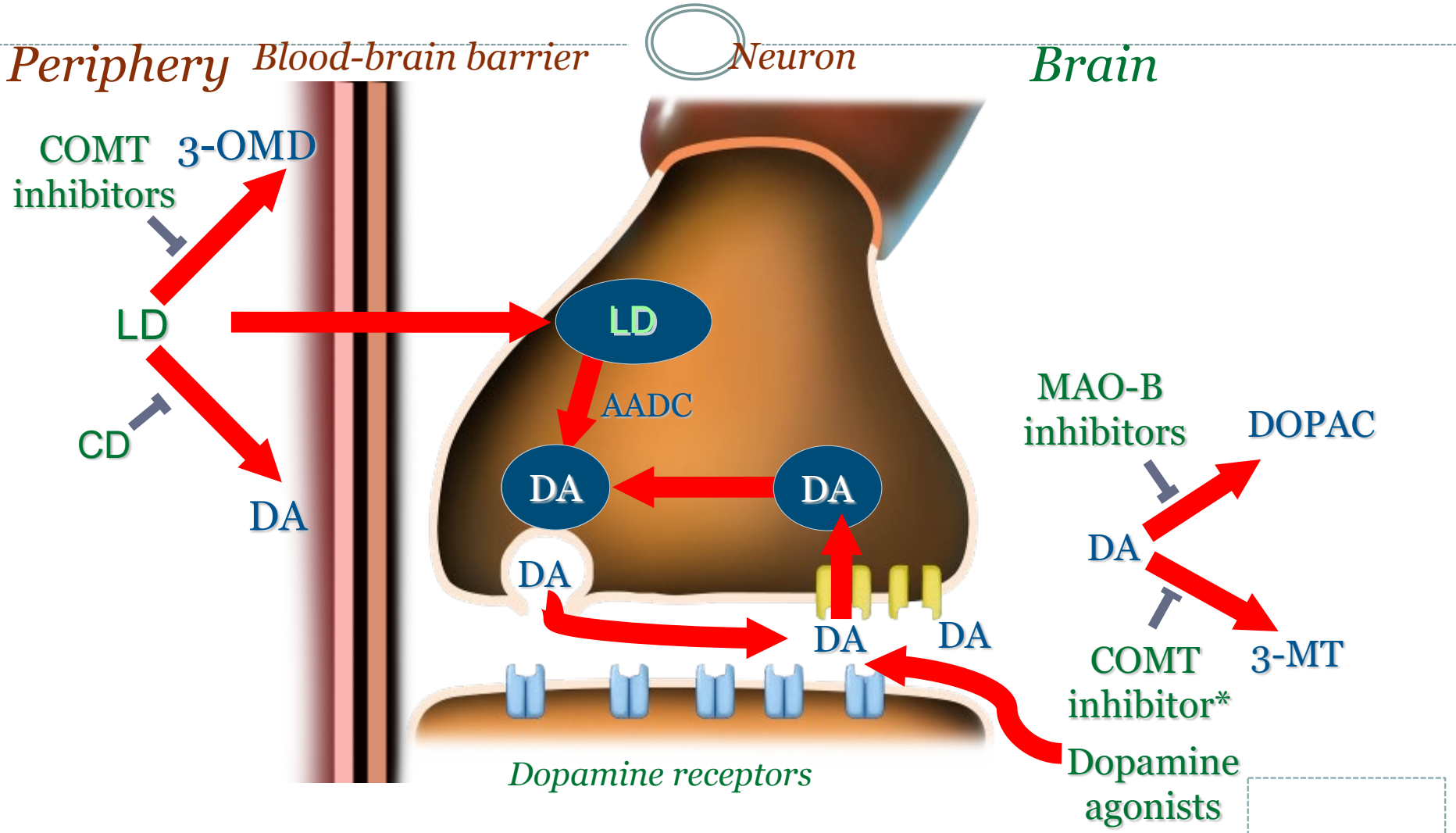
MAO Inhibitors

- 3 MAO Inhibitors on market:
  - selegiline
    - Eldepryl (1997) is regular tablet
    - Zelapar (2009) is dissolvable tablet
  - Azilect (rasagiline) 2006
  - Xadago (safinamide) 2017

COMT Inhibitors

- COMT is an enzyme in the brain that breaks down dopamine
- COMT Inhibitors block the enzyme, so there is less breakdown of dopamine, hence more dopamine
- 2 COMT Inhibitors on market:
  - Comtan (entacapone)
    - Also combined with C/L (Stalevo)
  - Tasmar (tolcapone) –rarely used due to liver failure
  - Ongentys (opicapone)

Sites of Action of PD Drugs



*Only tolcapone inhibits COMT in brain.
COMT indicates catechol-O-methyltransferase; CD, carbidopa; LD, levodopa; 3-OMD, 3-O-methyldopa; DA, dopamine; AADC, aromatic acid decarboxylase; MAO-B, monoamine oxidase type B; DOPAC, dihydroxyphenylacetic acid; 3-MT, 3-methoxytyramine.

Amantadine

- Unique kind of PD medication (no other medication like it)
- Affects many different kinds of receptors
  - Dopamine
  - Acetylcholine
  - Glutamate
  - Adrenergic

Amantadine

- First used to treat influenza (1966)
- Users found it helped their Parkinson's Disease
- Also used to treat fatigue in Multiple Sclerosis

Amantadine

- In PD patients, mainly used to treat dyskinesias
- Can also treat other motor symptoms, like tremor

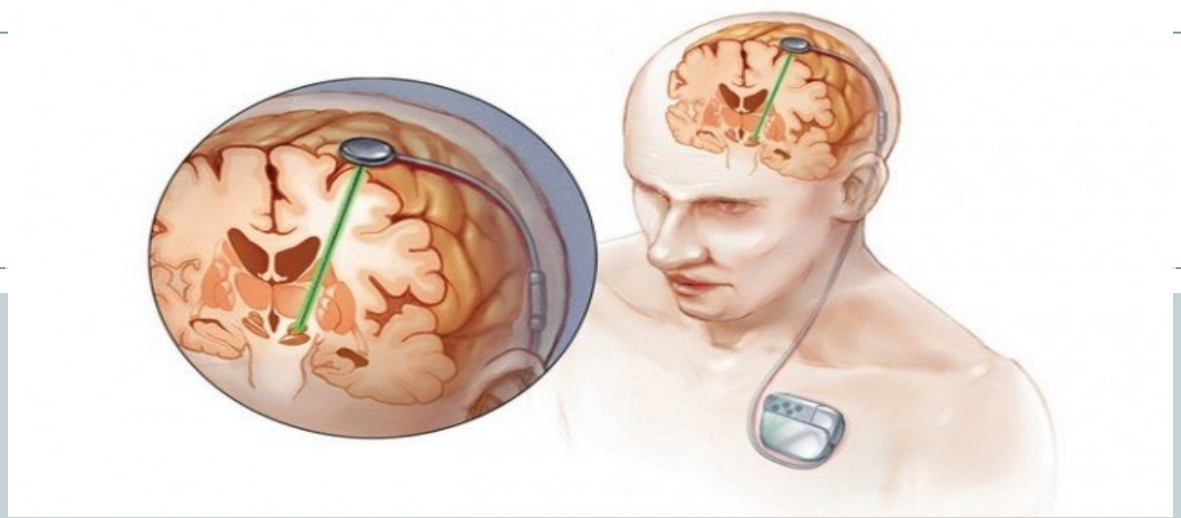
Anticholinergics

- There are several drugs in this class
- Main one used in PD is Trihexyphenidyl
  - Brand name Artane
- Blocks Acetylcholine receptors in brain
- Good medicine for tremor
- Not so good for other symptoms
- Lots of side effects (dryness, sedation, confusion, hallucinations, urinary retention)

Non-Pharmacologic Therapies

- Exercise!!
  - the ONLY treatment proven to slow down progression of disease
- Physical Therapy
- Occupational Therapy
- Speech Therapy
- Nutrition
- Education

Surgical Therapies



- Deep Brain Stimulation (DBS)
  - FDA approved 1997 for Essential Tremor
  - FDA approved 2002 for PD
  - Expanded approval in 2015 for PD
  - Reduces OFF time in PD patients
  - Reduces Dyskinesias in PD patients

DBS Indications

- Actual PD, not atypical parkinsonian syndrome
  - MUST have robust levodopa response
  - This is non-negotiable!!
- Troublesome ON/OFF fluctuations
- Troublesome dyskinesias
- High amplitude tremor
- Severe levodopa side effects
  - Caution: may not be as confident in PD diagnosis!!!!

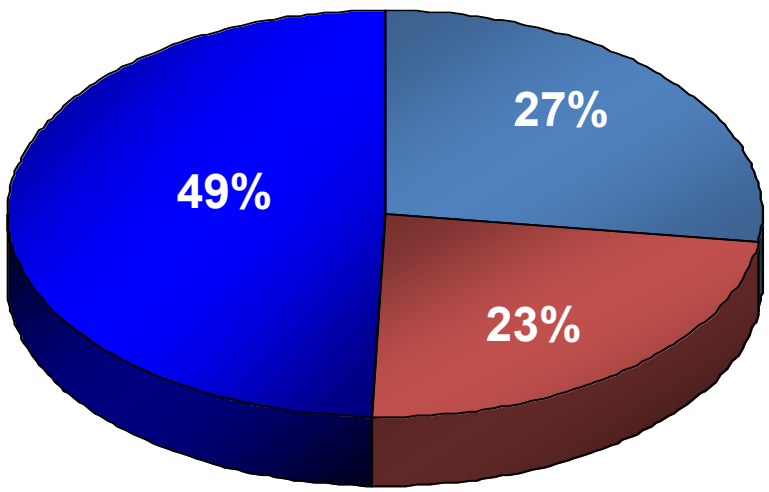
DBS Contraindications

- Atypical PD syndrome (MSA, PSP, vascular parkinsonism, CBD, FTD w/ parkinsonism, LBD)
- Poor response to levodopa
- Dementia
- Severe mood disorder

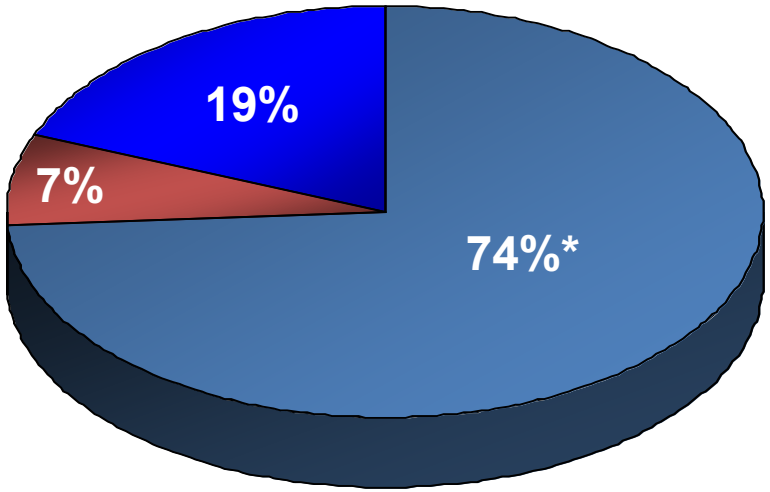
DBS manufacturers

- Medtronic
- Abbott
- Boston Scientific
- All are MRI compatible, but only under these conditions:
- MRI w/ head/receive coil
- MRI power reduced considerably
- DBS system must be OFF or in MRI mode (depends on manufacturer)
- Neurologist or company rep must interrogate system just before MRI to ensure no open/closed circuits

“ON” Time Without Dyskinesias Improves from 27% to 74% of a Patient’s Waking Day*



Before Surgery
(n=96)

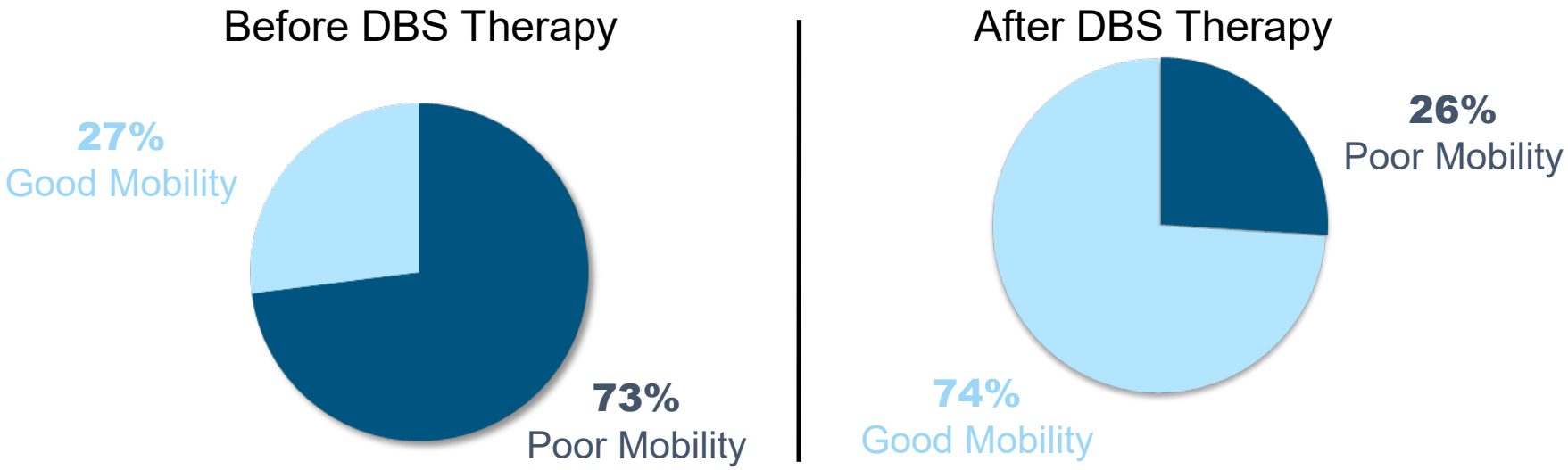


6 Months After Surgery
Bilateral STN Activa® Implant
(n=91)

‘ON’ with Dyskinesia **‘ON’ without Dyskinesia** **‘OFF’**

* The Deep-Brain Stimulation for Parkinson’s Disease Study Group. Deep-brain stimulation of the subthalamic nucleus for the pars interna of the globus pallidus in Parkinson’s disease. *N Eng J Med.* 2001;345:956-63.

Medtronic DBS Therapy for PD Increases "On" Time Without Dyskinesia[1]



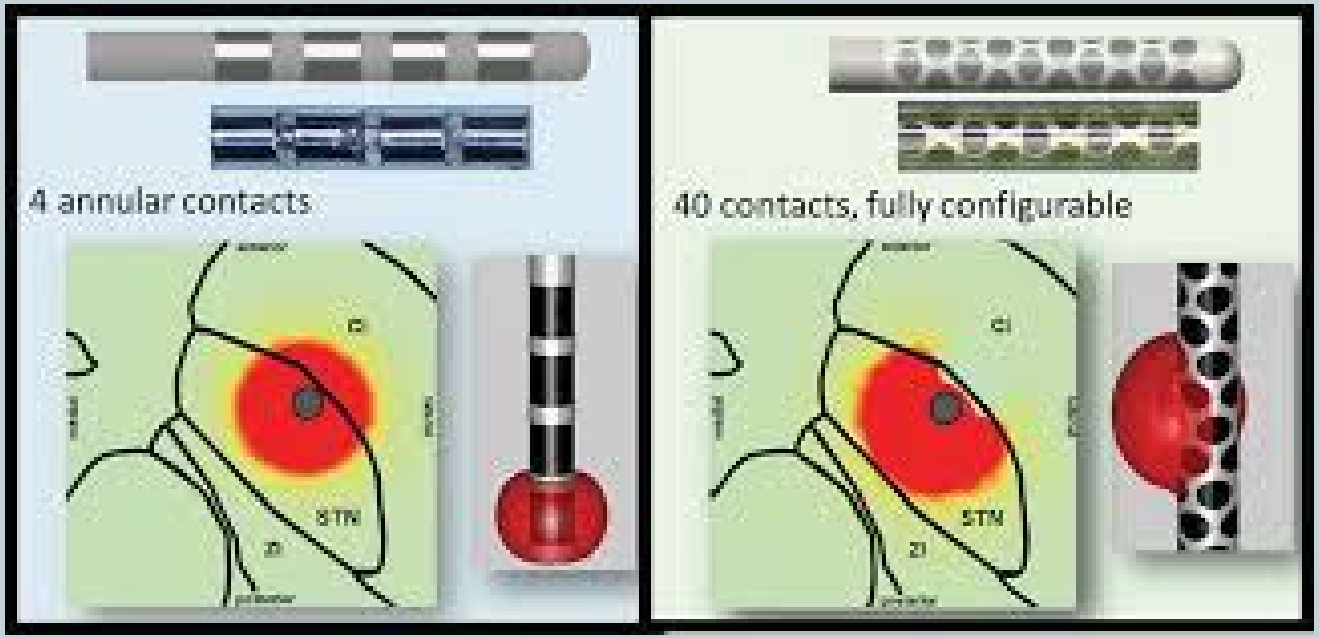
Good mobility: "On" time without dyskinesia

Poor mobility: "Off " time and "on" time with dyskinesia

1. The Deep-Brain Stimulation for Parkinson's Disease Study Group. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. *N Engl J Med.* 2001;345:956-963.

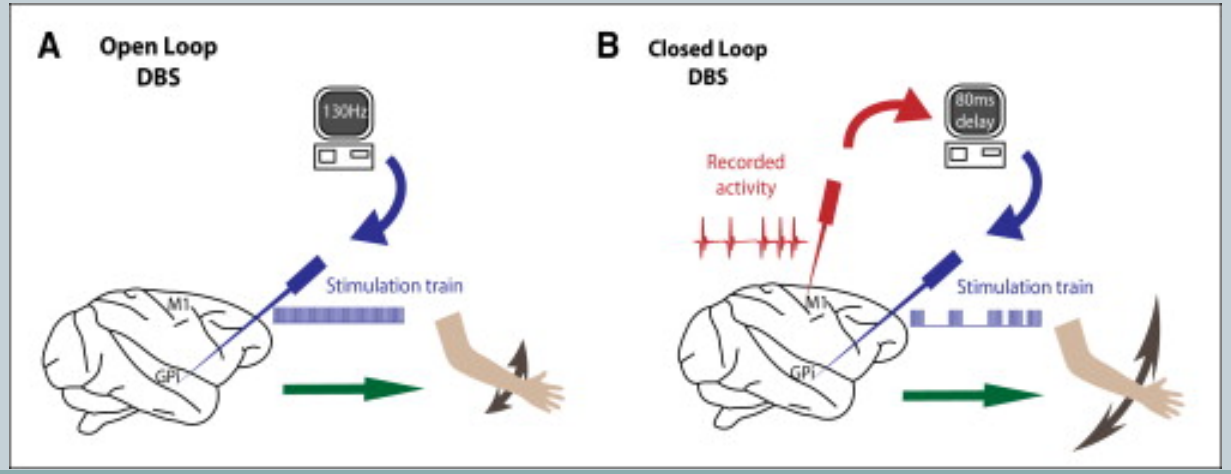
DBS new feature

- Current steering



DBS future directions

- Adaptive DBS
  - DBS can "listen" to brainwaves and adjust stimulation accordingly
  - Also known as "closed loop system"

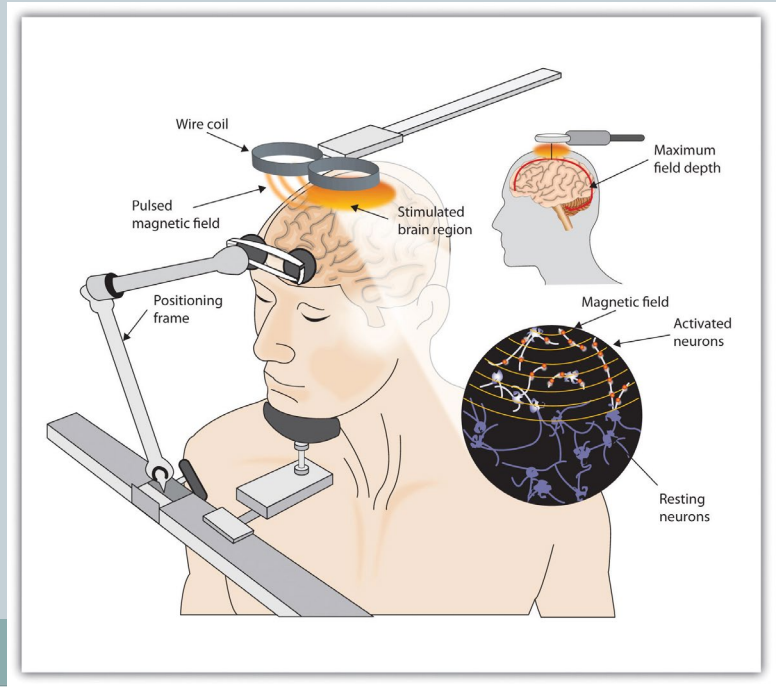


Other surgical therapies

- Lesioning
  - This means destroying small area of brain tissue to treat PD symptoms
  - Pre-cursor to DBS
  - Can be done with focused ionizing radiation or by “burning” tissue with a wire
  - Lately, focused ultrasound waves used

Other future PD therapies

- TMS (transcranial magnetic stimulation)
  - So far, only small temporary beneficial effects



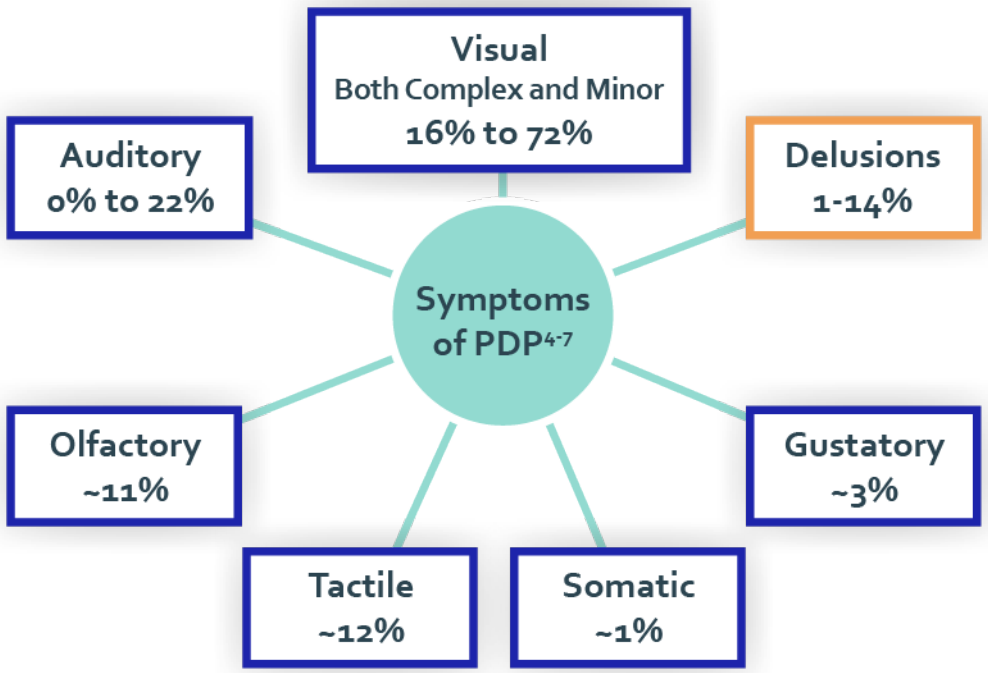
Other future PD therapies

- Stem Cells
- Vaccines
- Monoclonal Antibodies
- Gene Therapy

Identifying Parkinson's Disease Psychosis (PDP)

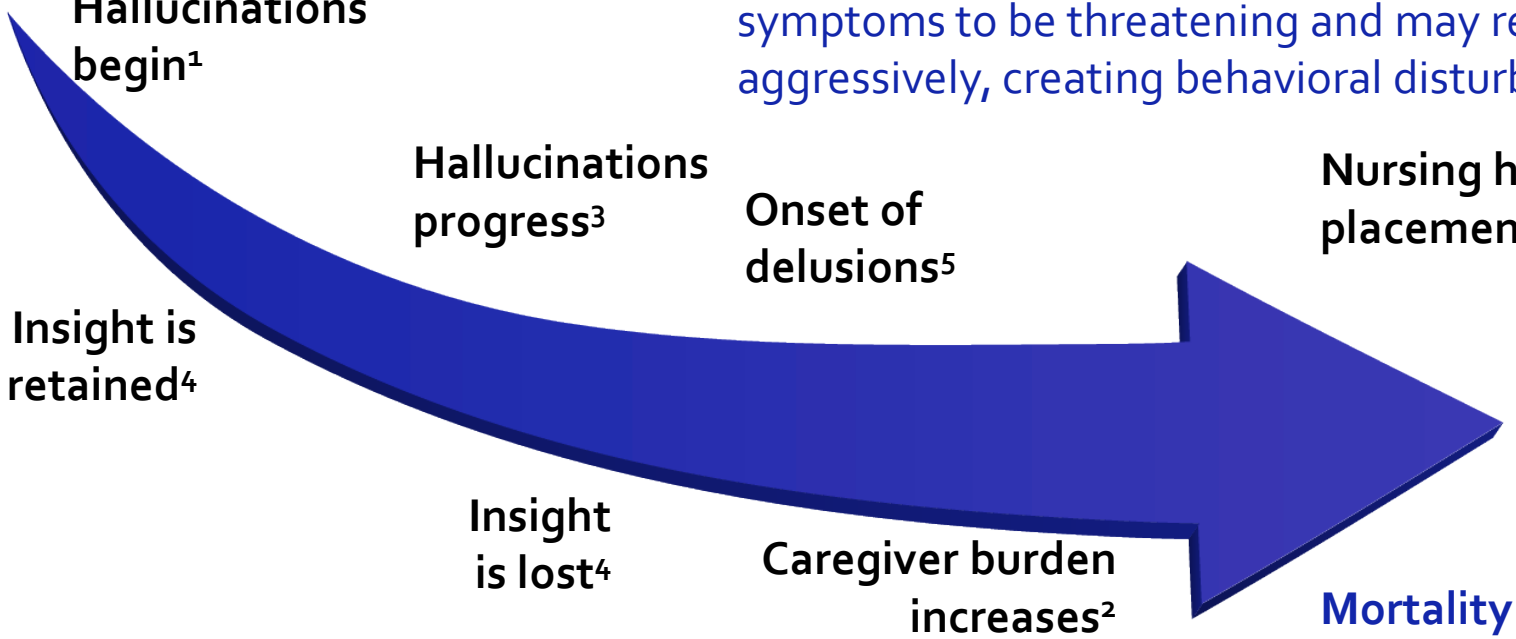
Approximately 1 million people in the US live with Parkinson's disease (PD); about 50% will develop PDP during the course of their disease[1,2]

- PDP has a clinical profile that is distinct from other psychotic conditions[3]
- PDP symptoms increase in severity over time[3]



1. Parkinson's Disease Foundation. Statistics on Parkinson's. Available at: http://www.pdf.org/en/parkinson_statistics. Accessed Mar 4, 2015.
2. Forsaa EB, et al. *Arch Neurol.* 2010;67:996-1001.
3. Ravina B, et al. *Mov Disord.* 2007;22:1061-1068.
4. Fénelon G, et al. *Mov Disord.* 2010;25(6):755-759.
5. Goldman JG, et al. *Expert Opin Pharmacother.* 2011;12:2009-2024.
6. Voss T, et al. *Parkinsonism Relat Disord.* 2013;19:295-299.
7. Fénelon G and Alves G. *J Neurol Sci.* 2010;289:12-17.

The Course of Parkinson's Disease Psychosis (PDP)



As symptoms progress, patients may find these symptoms to be threatening and may respond/act aggressively, creating behavioral disturbances[9]

While insight is retained, patients are often able to cope with symptoms without behavioral disturbances[8]

Mortality at 3 years is approximately 40% for PD patients with psychosis[7]

1. Weintraub D, Hurtig HI. *Am J Psychiatry.* 2007;164:1491-1498.
2. Schrag A, et al. *Parkinsonism Relat Disord.* 2006;12:35-41.
3. Goetz CG, et al. *Arch Neurol.* 2006;63:713-716.
4. Jakel RJ, Stacy M. *J Parkinsonism Restless Legs Syndrome.* 2014;4:41-51.
5. Chaudhuri KR, et al. *Lancet Neurol.* 2006;5:235-245.
6. Goetz CG, Stebbins GT. *Neurology.* 1993;43:2
7. Forsaa EB, et al. *Neurology.* 2010;75:1270-1276.
8. Diederich NJ, et al. *Mov Disord.* 2003;18:831-832.
9. Weintraub D and Stern MB. *Am J Geriatr Psychiatry.* 2005;13:844-851.

Key Points in Management of Hallucinations

- Look for urinary tract and other infections
- Eliminate metabolic abnormalities
- Discontinue psychotropic medications if possible
- Eliminate antiparkinsonian drugs in order of their potential to produce delirium (anticholinergics, dopamine agonists, COMT-I, MAO-I)
- Use regular levodopa formulation at lowest possible dose
- If antipsychotic necessary, try to use quetiapine or pimavanserin. NOTE: pimavanserin is only FDA approved treatment for PD psychosis

NUPLAZID (pimavanserin) Is a Selective Serotonin Inverse Agonist (SSIA)

- It has high binding affinity to 5-HT_{2A} and lower binding affinity at 5-HT_{2C} receptors
- It has no appreciable affinity to dopaminergic (including D_2), muscarinic, histaminergic, or adrenergic receptors

Ki (nM) for NUPLAZID

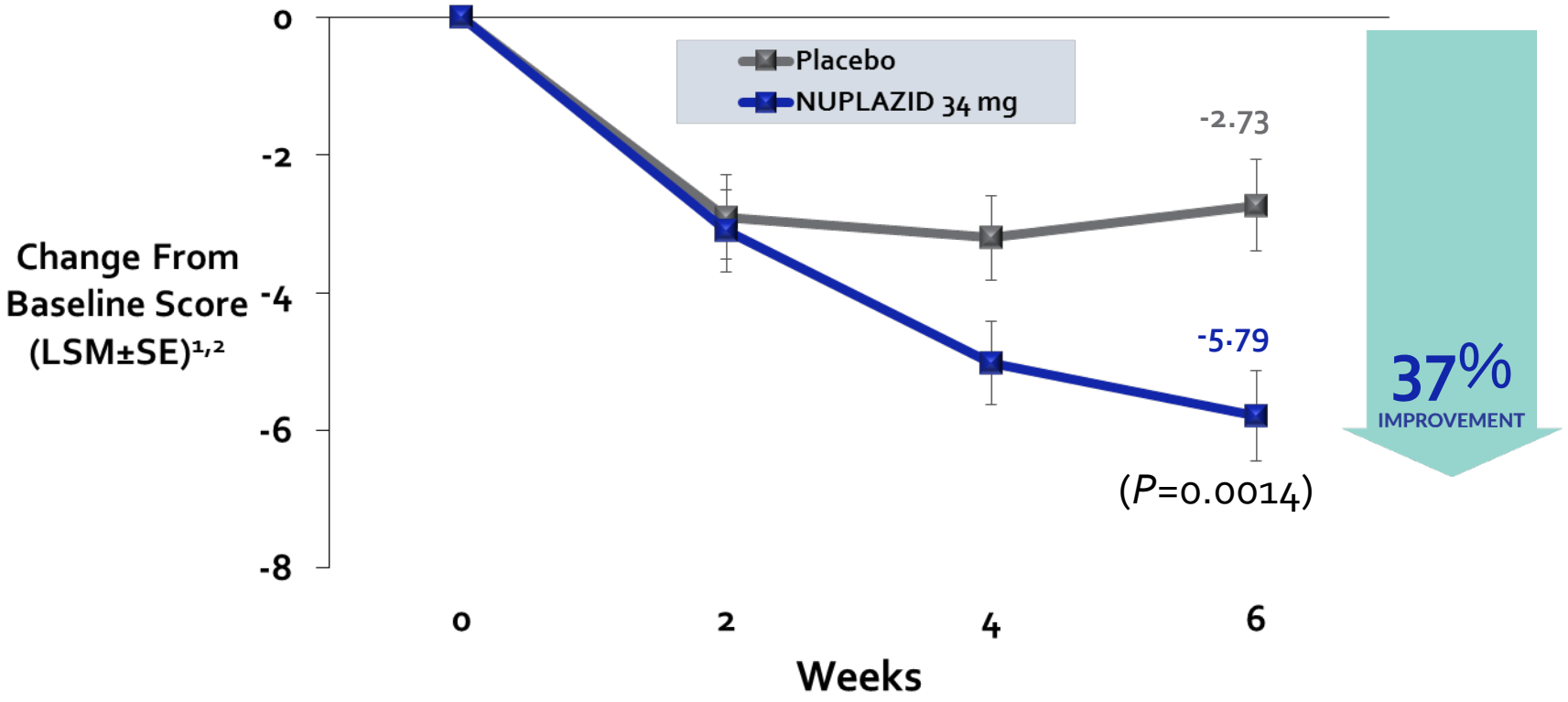
Lower Ki numbers indicate stronger binding

Receptor	Ki (nM)
5-HT_{2A}	**0.087**
5-HT_{2B}	–
5-HT_{2C}	**0.44**
D_1	–
D_2	–
D_3	–
Alpha 1A	–
Alpha 1B	–
Alpha 2A	–
Alpha 2B	–
H1	–
M1	–
M2	–
M3	–
M4	–
M5	–
Sigma 1	–

– = no response, Ki >100 nM

SAPS-PD Change From Baseline Through 6 Weeks

NUPLAZID 34 mg showed a 37% improvement in SAPS-PD from baseline at Week 6 versus 14% for placebo (*P*=0.006)[2]



The effect of NUPLAZID on SAPS-PD improved through the six-week trial period[1]

AAN: Recommended Quality Measures to Effectively Assess Care of PD Patients

1. Annual Parkinson disease diagnosis review
2. Psychiatric disorders or disturbances assessment
3. Cognitive impairment or dysfunction assessment
4. Querying about symptoms of autonomic dysfunction
5. Querying about sleep disturbances
6. Querying about falls
7. Parkinson disease rehabilitative therapy options
8. Parkinson disease-related safety issues counseling
9. Querying about Parkinson disease medication-related motor complications
10. Parkinson disease medical and surgical treatment options reviewed

AAN indicates American Academy of Neurology.
Cheng EM et al. *Neurology*. 2010:75:2021-2027.

Sydney Multicenter Study 15 years

- Motor fluctuations (on/off fluctuations) = 96%
- Dyskinesia = 94%
  - disabling dyskinesia = 46%
- Cognitive decline = 84%
  - dementia = 48%
- Falls = 81%
- Hallucinations = 50%
- Depression = 50%
- Choking = 50%
- Urinary incontinence = 41%
- Symptomatic orthostatic hypotension =35%

Hely et al. Movement Disorders 2005;20:190-199

Autonomic Dysfunction

- Orthostatic hypotension
  - Avoid diuretics; prob need to reduce/stop HTN meds over time
  - Treat with aggressive hydration, salt/electrolytes/magnesium
  - Then midodrine, fludrocortisone, droxidopa if needed
- Gastrointestinal
- Genitourinary
- Sweating

Sleep Disorders

- Insomnia and sleep fragmentation
- Nightmares, hallucinations
- REM behavior disorder
- Sleep apnea
- Excess daytime sleepiness and sleep attacks
- Frequent urination
- PD immobility