MedStar Georgetown University Hospital

Parkinson's Foundation

200 Years of Parkinson's Disease:
Diagnosis And Treatments

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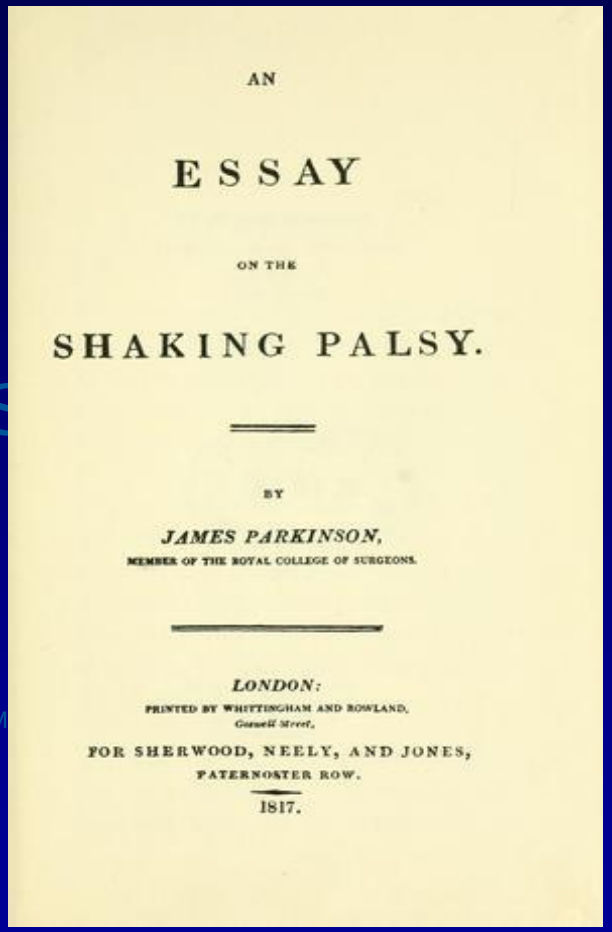
Translational Neurotherapeutics Penter

The First Account of PD

- "Shaking palsy" first described by James Parkinson in 1817
  - Involuntary tremor
  - Lessened muscular power
  - Tendency to bend forward
  - Tendency to pass from walking to running pace
  - Senses and intellect uninjured



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

Cursell Street,

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.

Parkinson J. An essay on the shaking palsy. 1817. *J Neuropsychiatry Clin Neurosci* 2002;14:223-236.

Goldman JG et al. *Parkinson's Disease*. 2005:1-10.

Cardinal Features and Clinical Manifestations: Traditional Definition

Motor Signs

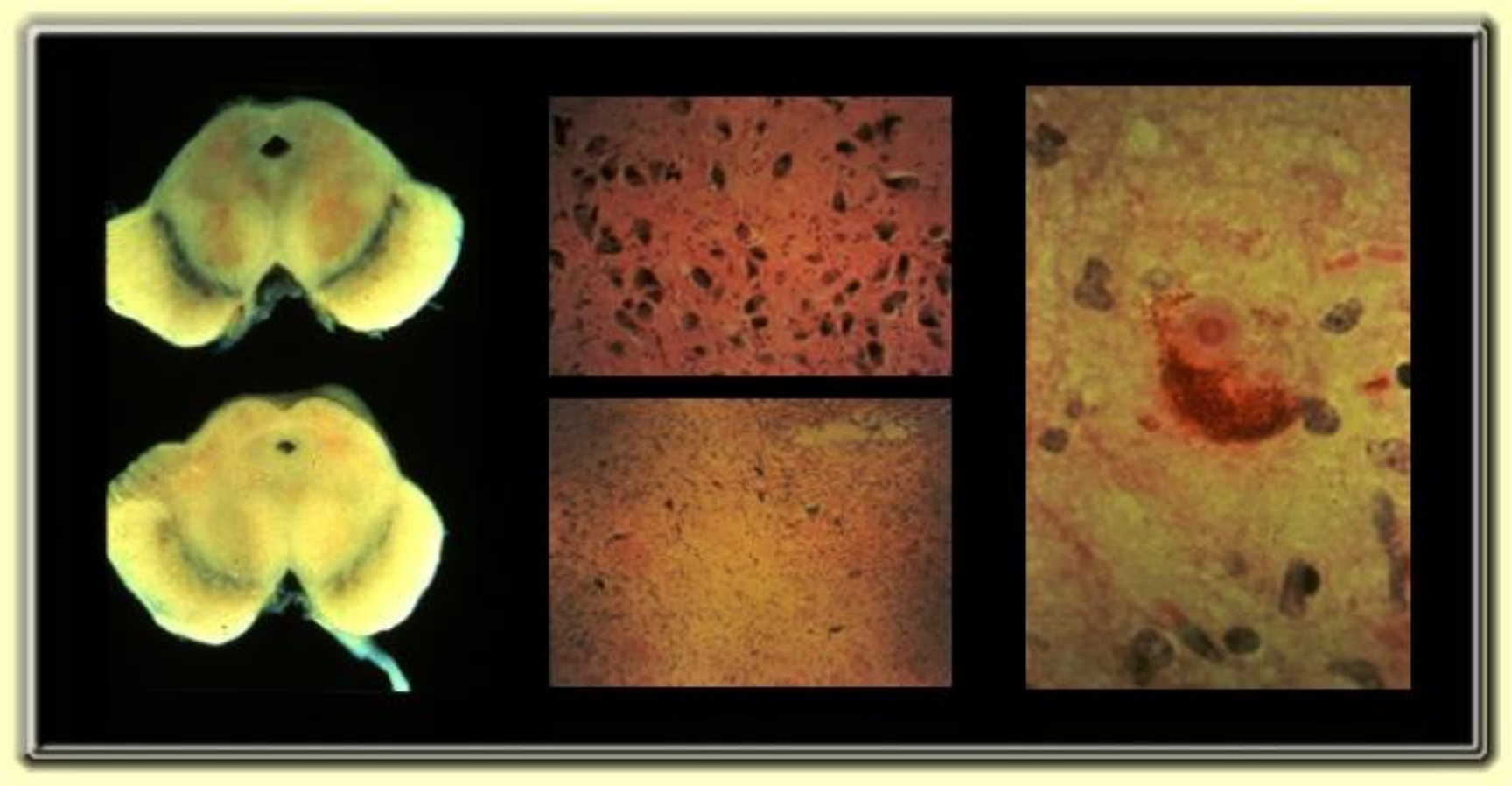
- Bradykinesia
- Tremor at rest
- Rigidity
- Postural instability

Clinical Manifestations

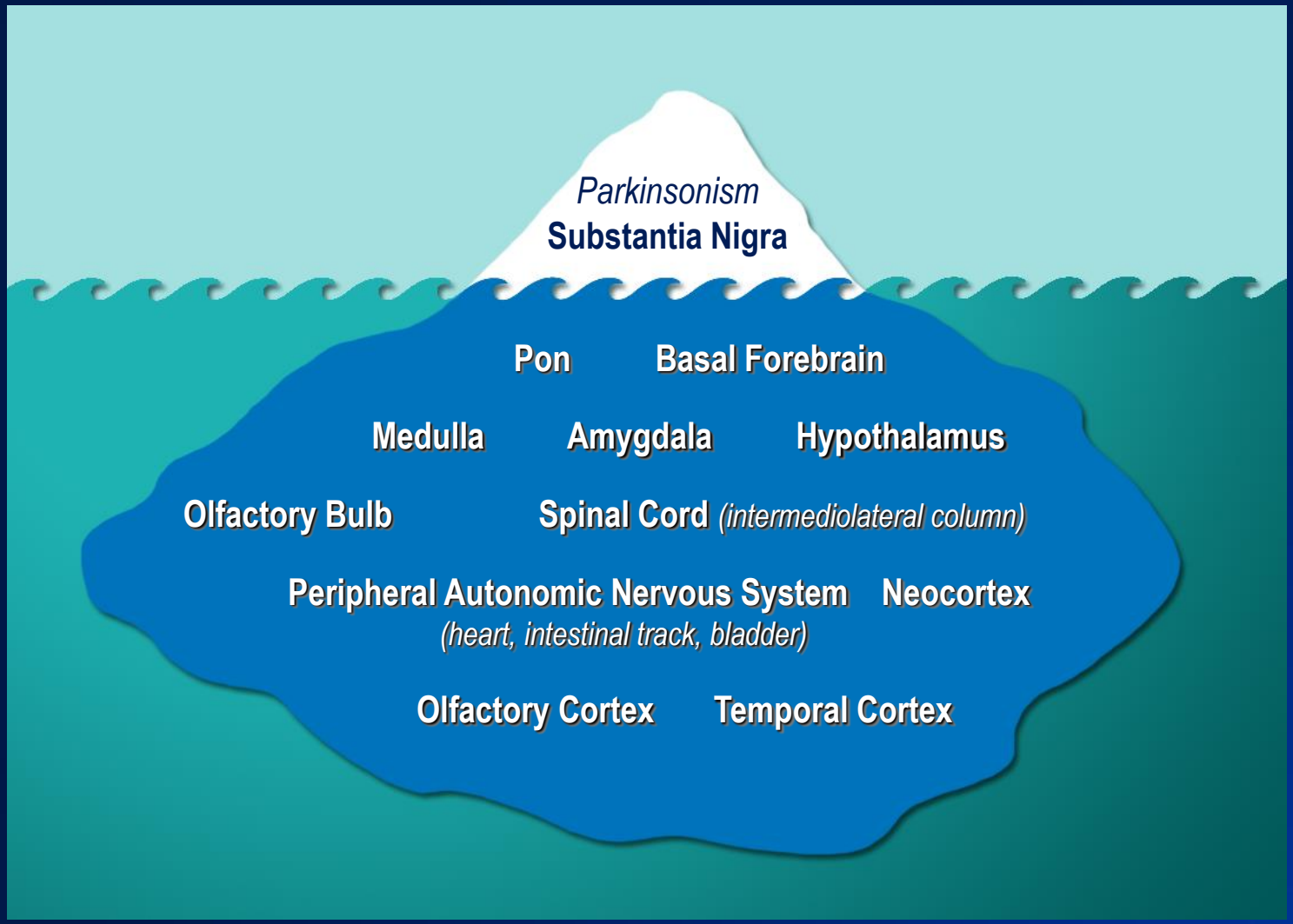
- Decreased arm swing
- Hypomimia
- Hypophonia
- Micrographia

Hughes AJ et al. *J Neurol Neurosurg Psychiatry*. 1992;55:181-184.
Jankovic J. *Handbook of Parkinson's Disease, 4th ed*. 2007:49-76.
Jankovic J. *J Neurol Neurosurg Psychiatry*. 2008;79:368-376.
Morgan J et al. *Handbook of Parkinson's Disease 4th ed*, 2007:29-47.

Pathology of Parkinson's Disease



The Parkinson's Complex

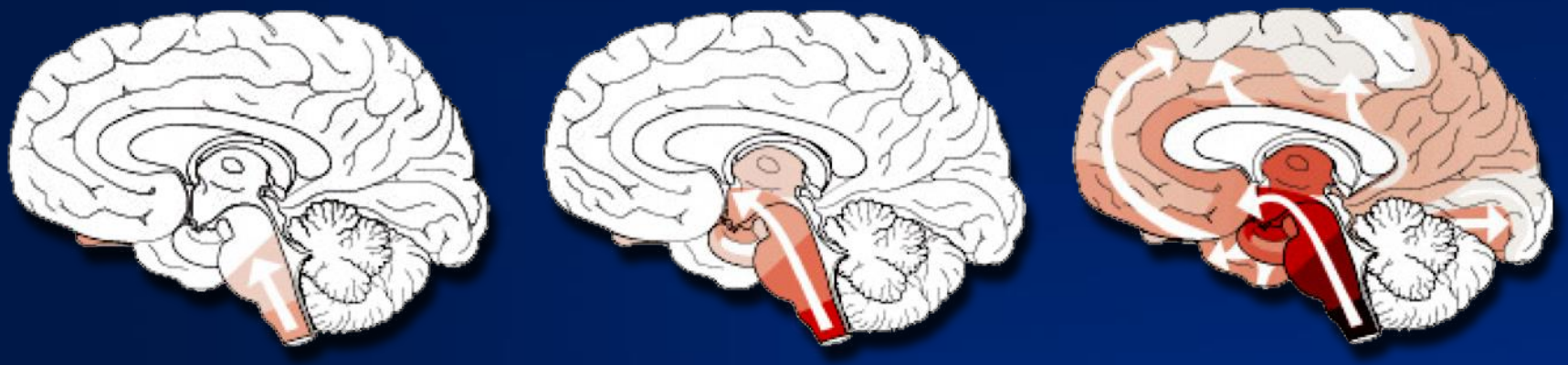


Reproduced from Langston JW. *Ann Neurol*. 2006;59:591-596.

Evolution of Lewy Body Pathology

Pre-clinical PD

Clinical PD



Stage 1/2

Stage 3/4

Stage 5/6

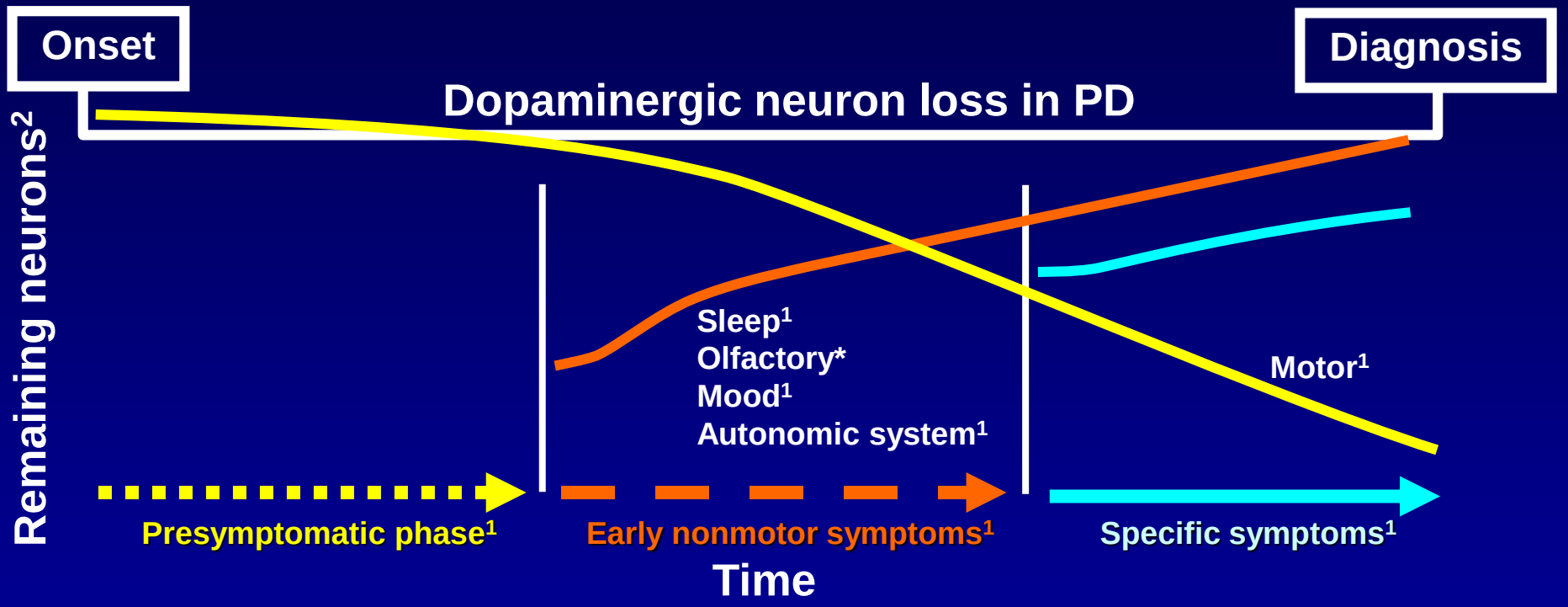
PD-related Lewy body pathology evolves in predictable stages. According to the staging system of Braak, Lewy bodies (LB) first form within in the olfactory bulb and dorsal motor nucleus of the vagal nerve (Stage 1). In Stages 2 and 3, LB pathology expands from these induction sites into additional brain stem nuclei (e.g. locus coeruleus and substantia nigra) and then into the amygdala. In Stages 5 to 6, the pathology extends into the cerebral cortex. Clinical symptoms arise during Stages 4 to 6, when the pathology involves significant regions of the substantia nigra and related brain areas.

Braak H et al. *Neurobiol Aging*. 2003; 24:197-211.

Non-motor Features of PD

- **Neuro-psychiatric and cognitive:**
  - Depression
  - Anxiety
  - Psychosis
  - ***Dementia***
  - Apathy
  - Fatigue
  - Sleep disturbance
- **Autonomic:**
  - Constipation
  - Hyperhidrosis
  - Urinary dysfunction
    Sexual dysfunction
  - Sialorrhea
- **Sensory**
  - Pain
  - Smell loss

Prodromal Phases of PD Reflect Neuronal Loss



*Olfactory dysfunction may predate clinical PD by at least 4 years[3]

[1]Halperin I, et al. *Neurotherapeutics*. 2009;6:128-140.
[2]Lang AE. *Neurology*. 2007;68:948-952.
[3]Ross GW, et al. *Ann Neurol*. 2008;63:167-173.

A New Definition of PD: A 3-Phase Disease

Phase 1	Preclinical PD	PD-specific pathology assumed to be present	• Asymptomatic, but will need to be supported by:
			  • Molecular markers (α-synuclein, DJ-1, LRRK2, parkin, PINK1 mutations)
			  • Imaging markers (transcranial sonography, PET, SPECT, MIBG SPECT, α-synuclein imaging)

Phase 2	Premotor PD	Presence of early nonmotor signs and symptoms due to extranigral PD pathology	• Premotor features commonly occur before the emergence of motor signs (olfaction abnormalities; constipation; cardiac involvement; neurobehavioral symptoms)
Phase 3	Motor PD	PD pathology involves substantia nigra leading to dopamine deficiency sufficient to cause classic motor manifestations followed by later nonmotor features	• Traditionally diagnosable symptoms (bradykinesia, tremor, rigidity) • May progress to include late PD features (dysautonomia, sensory symptoms, cognitive decline)

Stern MB et al. *Mov Disord*. 2012;27:54-60.

Classification of Parkinson's Syndromes

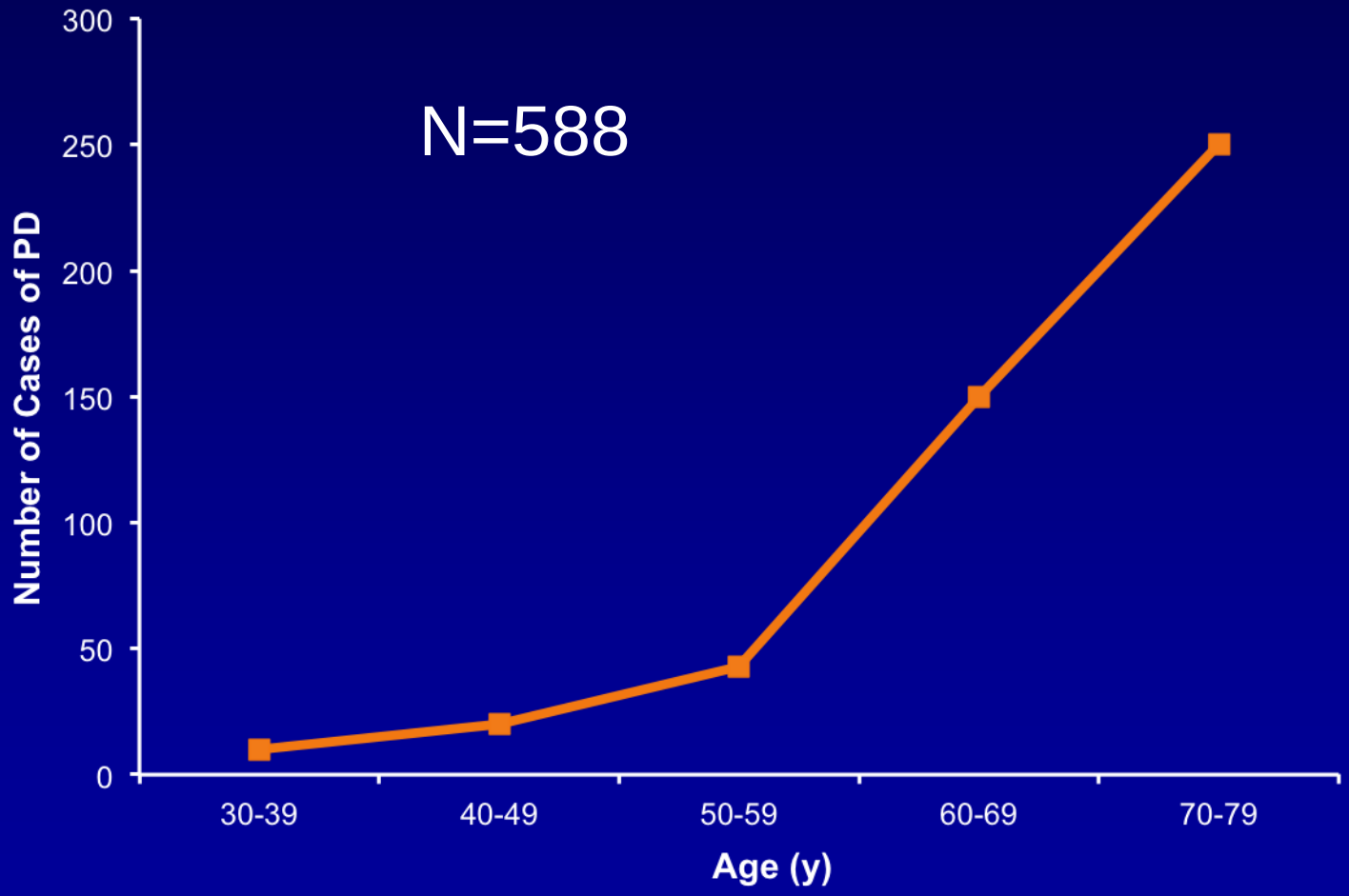
- Idiopathic PD ~ 85% of all PS
- Neuroleptic-induced parkinsonism (DIP) 7-9%
- MSA ~2.5%
- PSP ~ 1.5%
- Vascular Parkinsonism ~3%
- MPTP,CO,MN,recurrent head trauma is extremely rare
- No New cases of postencephalitic parkinsonism since 1960's

Epidemiology of PD

- PD is the second most common neurodegenerative disorder after Alzheimer's disease
- Affects 0.3% of worldwide population
  - 1%-2% of people aged >60 years
- Approximately 1 million people have PD in the US
- Prevalence predicted to almost double in US from 2005-2030 in individuals aged >50 yrs

Dorsey ER et al. *Neurology*. 2007;68:384-386.
de Lau LM and Breteler MMB. *Lancet Neurol.* 2006;5:525-535.
Nussbaum RL and Ellis CC. *N Engl J Med.* 2003;348:1356-1364.
Olanow CW et al. *Neurology*. 2009;72(21 suppl 4):S1-S136.

The Incidence of PD Increases With Aging



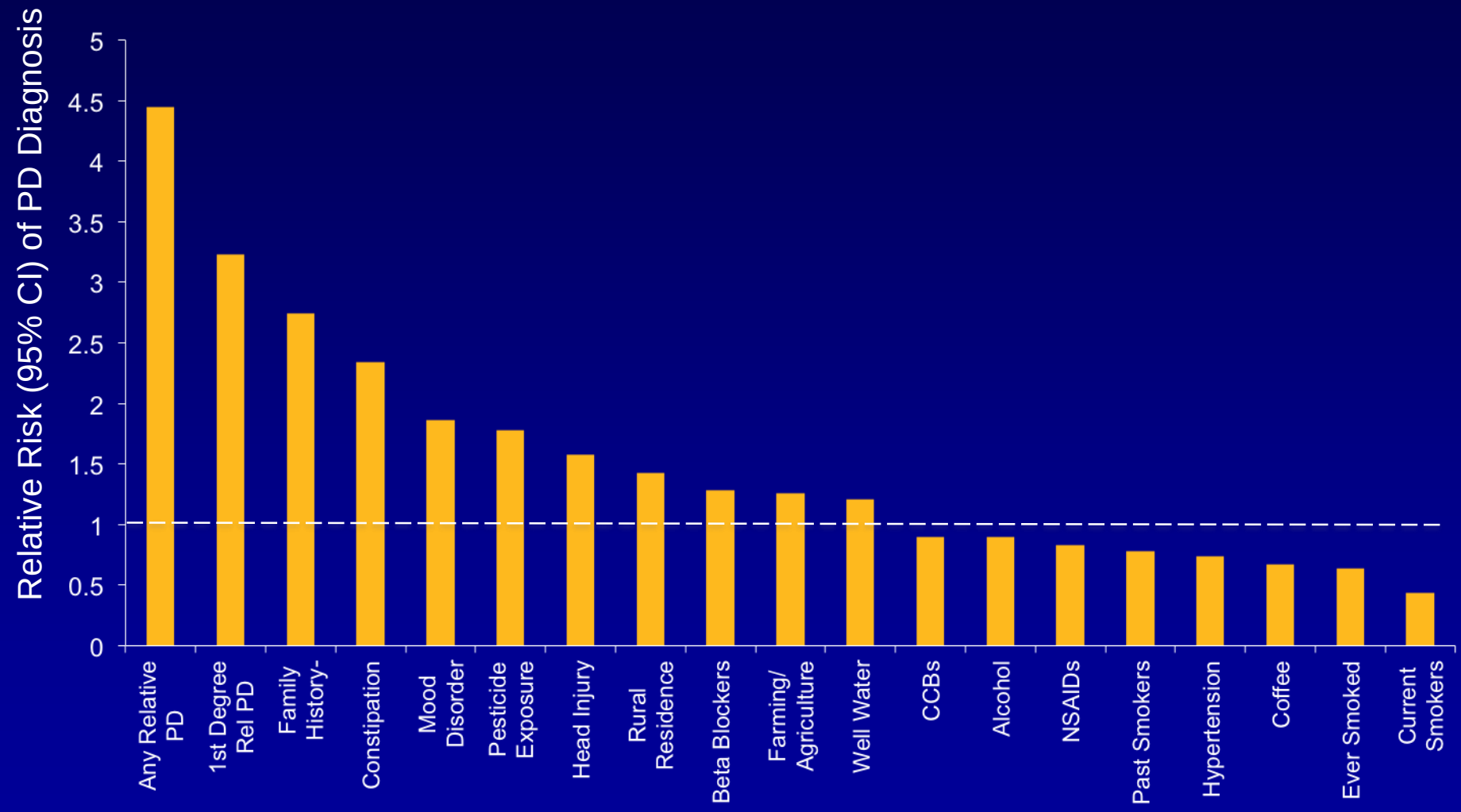
Van Den Eeden SK et al. *Am J Epidemiol.* 2003;157:1015–1022.

Causes of PD

- PD is heterogeneous
  - Unlikely there is a single etiology
- Contributing factors may include:
  - Environment
  - Genetics
  - Combination of both
- Abnormal aggregation of α-synuclein may play a role in the development of PD

de Lau LM and Breteler MMB. *Lancet Neurol.* 2006;5:525-535.
Olanow CW et al. *Neurology.* 2009;72:S1-S136.

Risk Factors for PD



CCB indicates calcium channel blocker; NSAID, nonsteroidal anti-inflammatory drug.

Noyce AJ et al. *Ann Neurol.* 2012. [Accepted]. doi: 10.1002/ana.23687.

Genetics and PD

- PD is primarily a sporadic or idiopathic disorder
- The Human Genome Project has helped to better define the gene association
  - Up to 20% of patients with PD have the familial variety
  - Causal and susceptibility genes discovered for PD
  - Monogenic forms account for only a very small portion of patients with PD

Coppede F. *The Scientific World Journa*l, 2012, Article ID 489830, 12 pages. doi:10.1100/2012/489830.
de Lau LM and Breteler MMB. *Lancet Neurol.* 2006; 5: 525–535.
Nussbaum RL and Ellis CC. *N Engl J Med.* 2003;348:1356-1364.

Genes Identified for Familial PD

Name	AD/AR	Prevalence	Lewy Bodies
Causal Genes and Loci			
SNCA (PARK1, PARK4)	AD	Very rare	LB
LRRK2 (PARK8)	AD	5% familial Caucasian; 1%-2% of sporadic cases	LB
PRKN (PARK2)	AR	Most prevalent in early-onset (<45 years) but relatively uncommon	Nigral degeneration; rare LB
PINK1 (PARK6)	AR	Rare cause of recessively inherited, early-onset Parkinsonism	Unavailable
DJ-1 (PARK7)	AR	<1% of early-onset PD	Unavailable

AD indicates autosomal dominant; AR, autosomal recessive.

Coppede F. *The Scientific World Journa*l, vol 2012, Article ID 489830, 12 pages. doi:10.1100/2012/489830.
HUGO (Human Genome Organization). HUGO Genome Nomenclature Committee. genenames.org/genefamilies/PARK .
Wider C et al. *Mov Dis.* 2010. Vol. 25, Suppl. 1, 2010, pp. S15–S20.

Additional Genes Associated With PD

- UCH-L1
- POLG
- GBA
- UNKNOWN (PARK3, 10, 12)
- NR4A2/NURR1
- Synphilin-1
- OMI/HTRA2
- ATP13A2
- PLA2G6
- FBXO7
- GIGYF2

DaTScan: Evolving Imaging That May Aid in Diagnosis of PD

DaTScan™ (Ioflupane I 123 Injection), is a radiopharmaceutical agent recently 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.

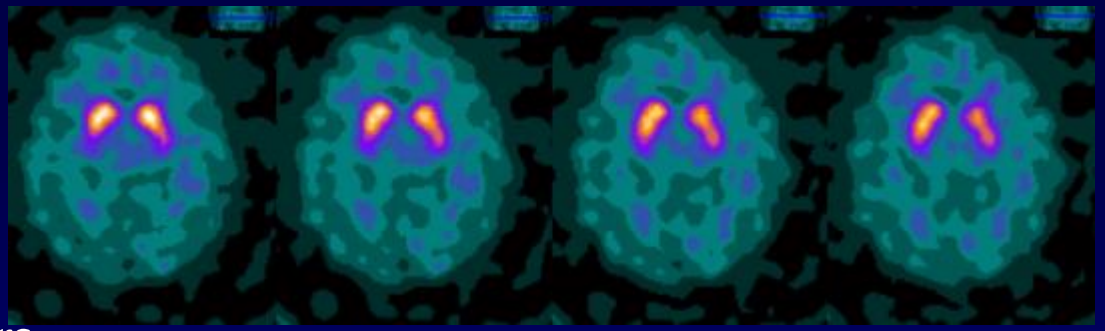
DaTScan is a potential adjunct in the diagnosis of Parkinsonian symptoms.

DaTScan does not differentiate Parkinsonian Syndromes

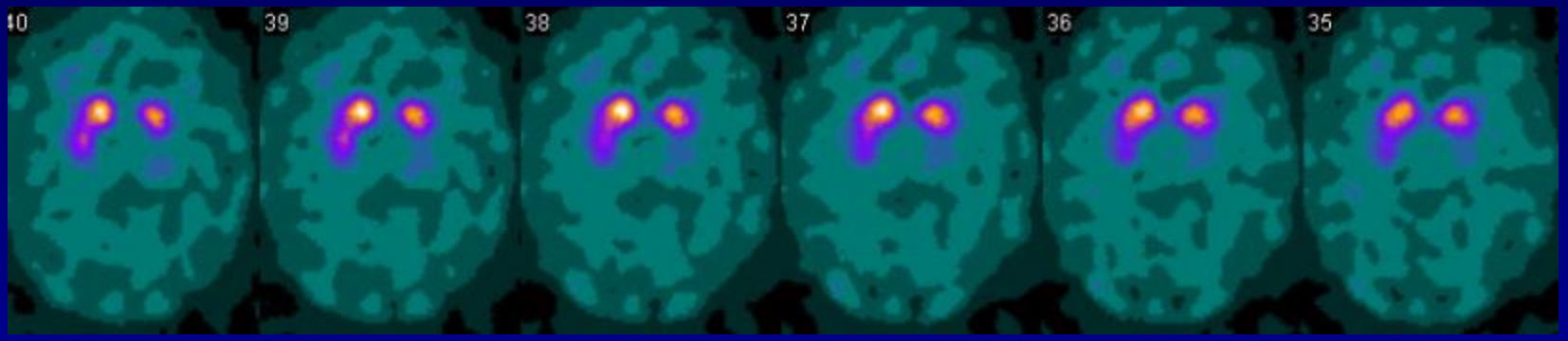
FDA indicates United States Food and Drug Administration.
DaTscan [package insert]. Arlington Heights, IL: GE Healthcare; January 2011.
Hauser RA et al. J Neuroimaging. 2011; DOI: 10.111/j.1552-6569.2011.00583.x

DaTScan

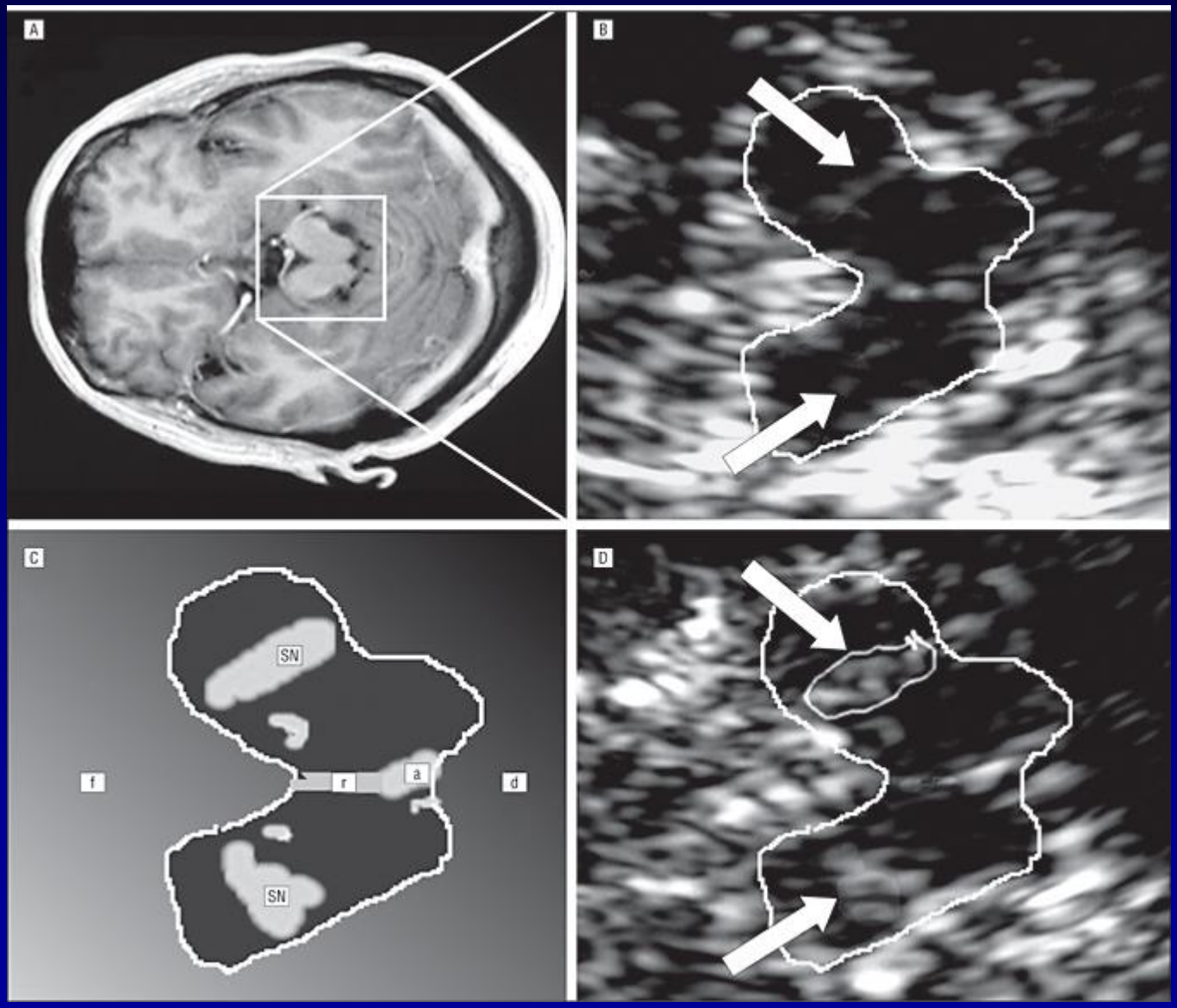
Normal or Essential Tremor



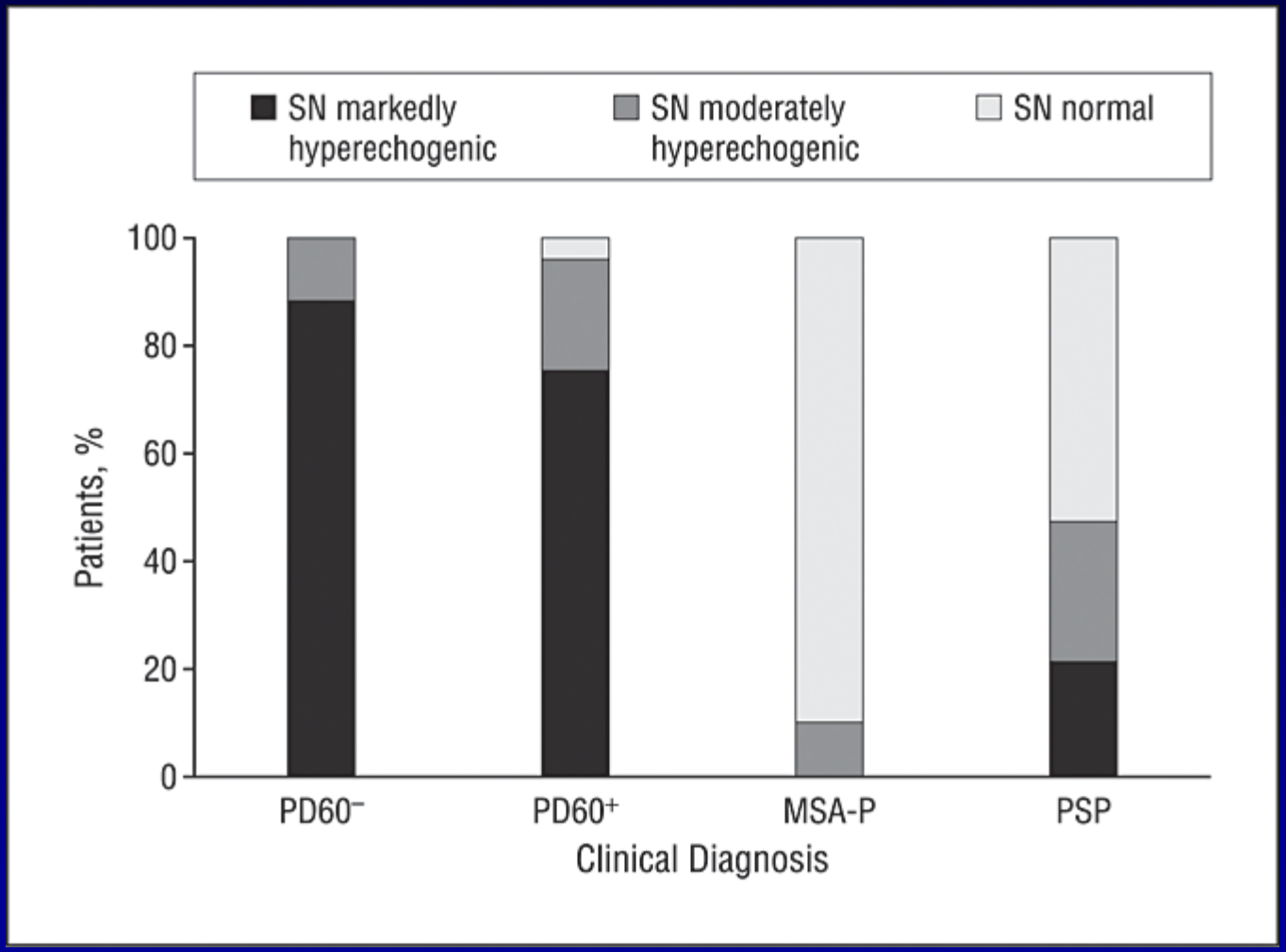
PD or PD related disorders



Newer Imaging Techniques: TCD for Parkinsonian Syndromes



Arch Neurol. 2007;64(11):1635-1640



Transcranial Brain Sonography Findings in Discriminating Between Parkinsonism and Idiopathic Parkinson Disease Uwe Walter, MD; Dirk Dressler, MD; Thomas Probst, MD; Alexander Wolters, MD; Mazen Abu-Mugheisib, MD; Matthias Wittstock, MD; Reiner Benecke, MD

Arch Neurol. 2007;64(11):1635-1640

DO MEDICINES CHANGE THE COURSE OF PARKINSON'S DISEASE?

Survival Prior to L-dopa

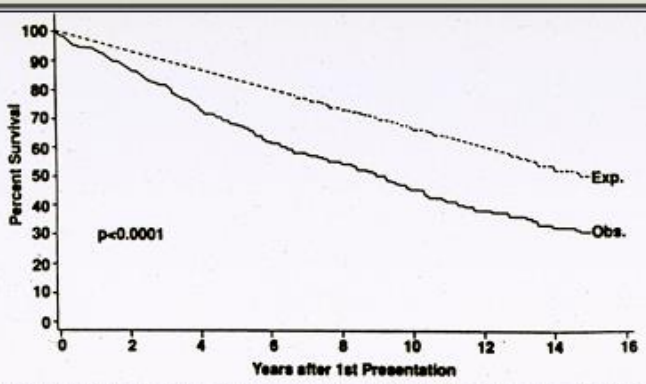


FIGURE 1. Obs = Observed survival in patients. Exp = Expected survival in general population. Observed survival in 215 parkinsonian patients who had onset and were first evaluated at Movement Disorder Clinic before 1-1-74 (Group IA) compared to expected survival in the general population matched for age, sex and the year of birth.

TIMELY LEVODOPA PROLONGS SURVIVAL IN PARKINSON'S DISEASE

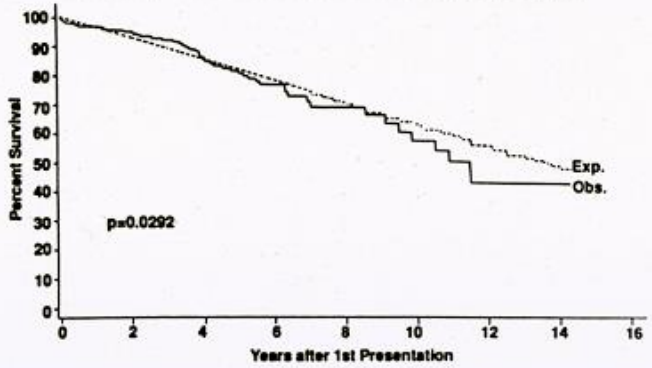
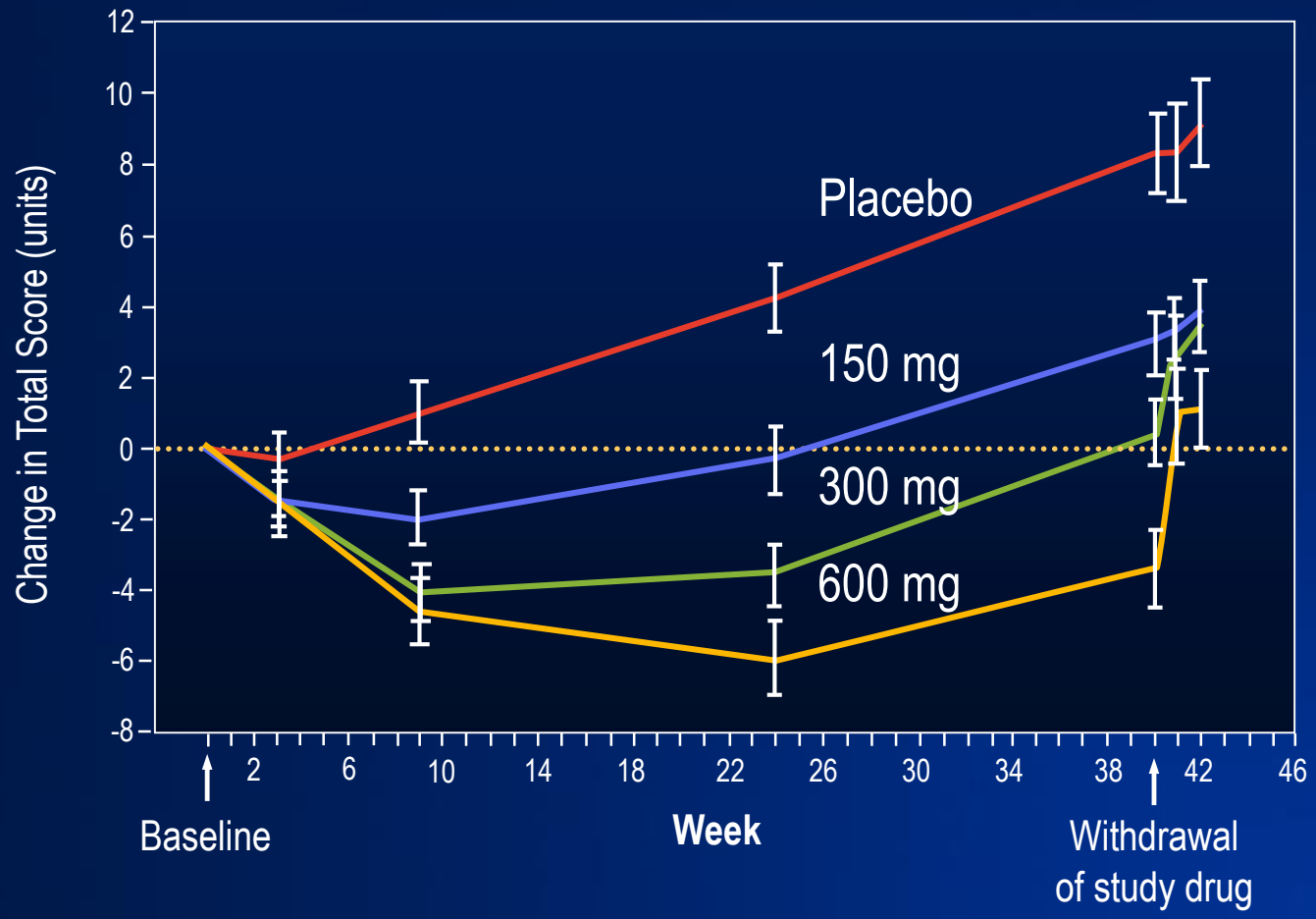


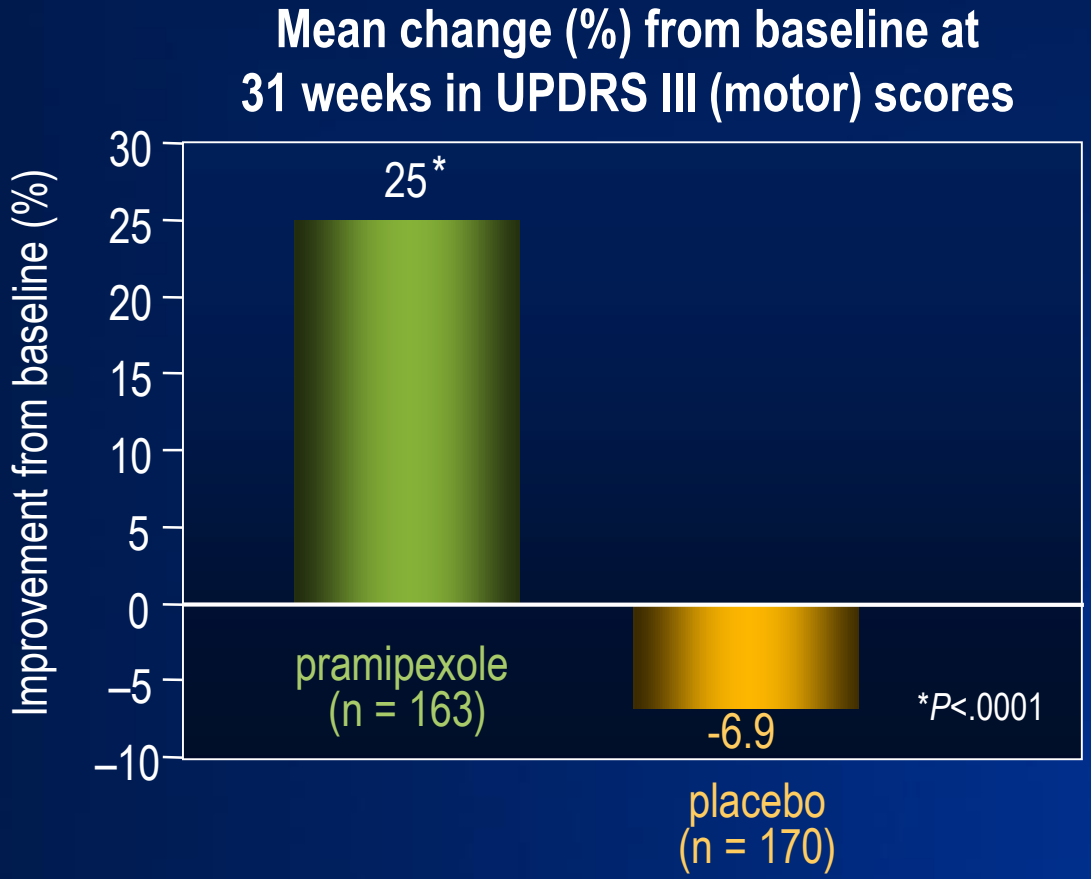
FIGURE 2. Obs = Observed survival in patients. Exp = Expected survival in general population. Observed survival in 565 parkinsonian patients who had symptomatic onset after December 31, 1973 (Group IIB) compared to the expected survival in general population matched for age, sex and the year of birth.

Effects of Levodopa on Motor Function in Early PD



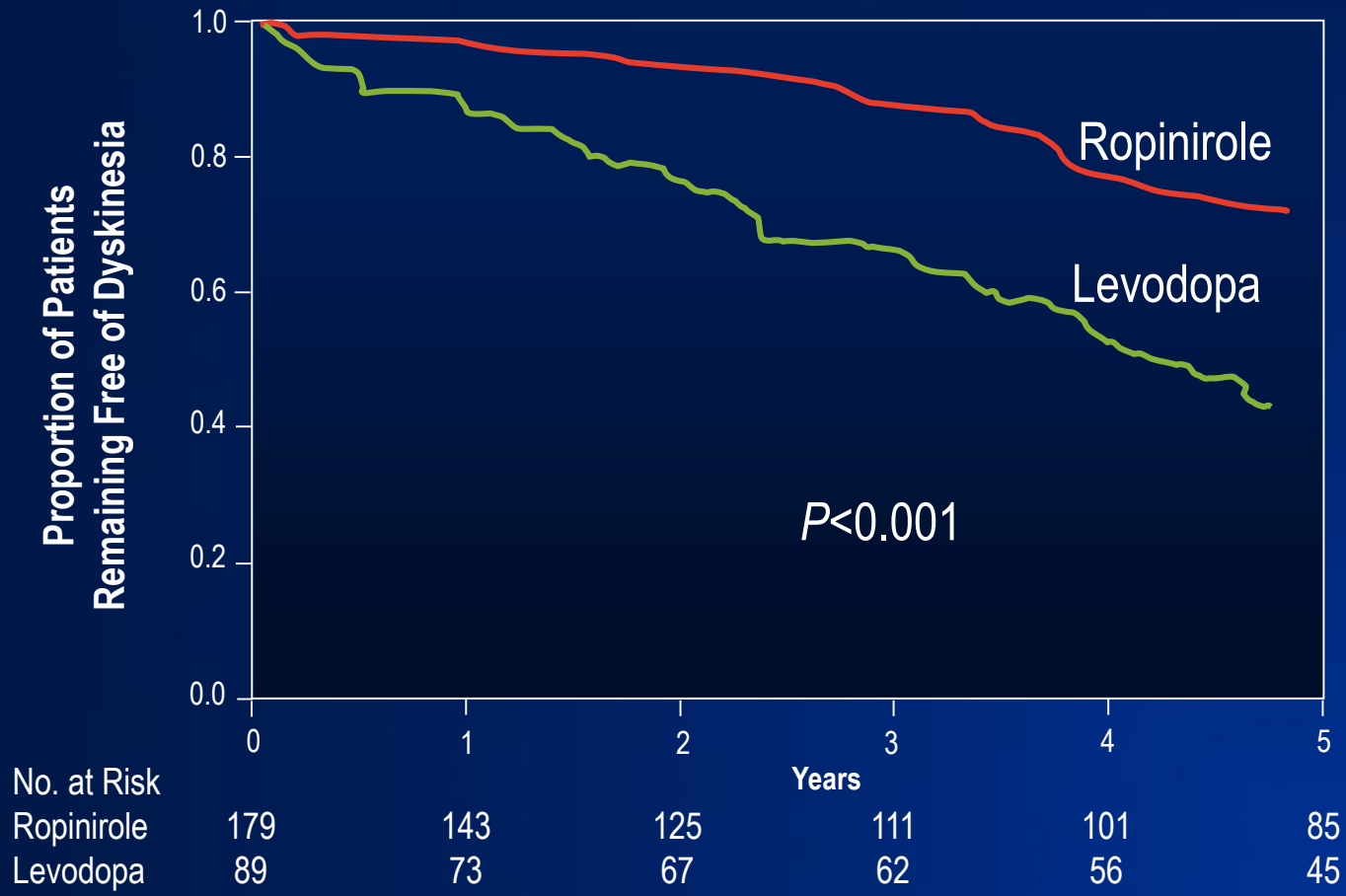
The Parkinson Study Group. *N Engl J Med.* 2004;351:2498-2508.

Pramipexole Improves Motor Function in Early PD



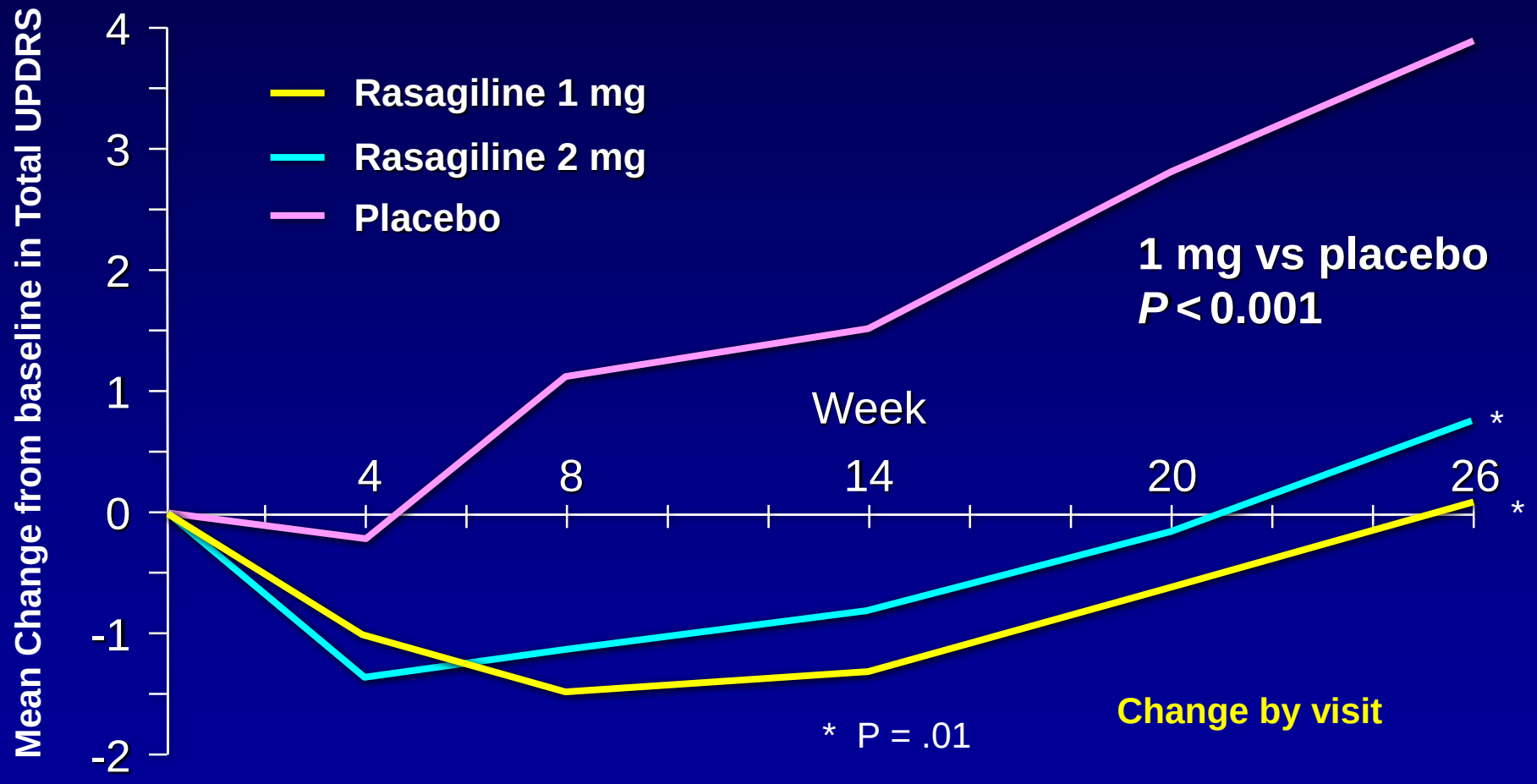
Shannon KM et al. The Pramipexole Study Group. *Neurology.* 1997;49:724-728.

Risk of Dyskinesia Depending on Initial Treatment



Rascol O et al. *N Engl J Med*. 2000;342:1484-1491.

TEMPO: Maintenance of Effect on Total UPDRS over 6 month period



Parkinson Study Group. *Arch Neurol.* 2002; 59:1937-43.

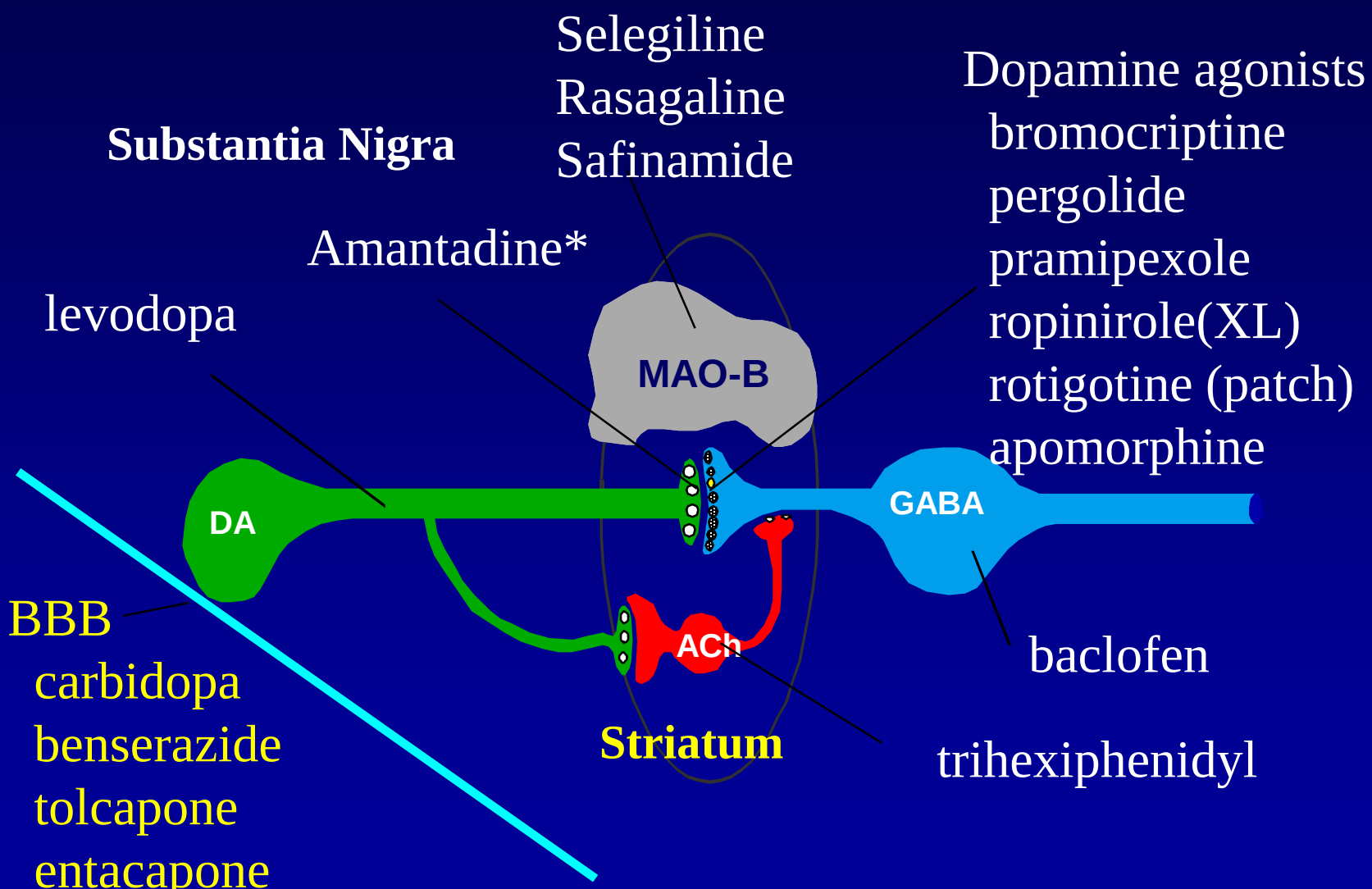
Treatment Options

- Preventive treatment
  - No definitive treatment available
- Symptomatic treatment
  - Pharmacological
  - Surgical
- Non-motor management
- Restorative—experimental only
  - Transplantation
  - Neurotrophic factors

Drug Classes in PD

- Dopaminergic agents
  - Levodopa
  - Dopamine agonists
- COMT inhibitors
- MAO-B inhibitors
- Anticholinergics
- Amantadine

Sites of Action of PD Drugs



Anticholinergics

- Dopaminergic depletion→cholinergic overactivity
- Initially used in the 1950s
- Effective mainly for tremor and rigidity
- Common agents (Start low, go slow):
  - Trihexyphenidyl: 2-15 mg/day
  - Benztropine: 1-8 mg/day
  - Ethopropazine: 10-200 mg/day
- Side effects:
  - Dry mouth, sedation, delirium, confusion, hallucinations, constipation, urinary retention

Amantadine

- Antiviral agent; PD benefit found accidentally
- Tremor, bradykinesia, rigidity & dyskinesias
- Exact mechanism unknown; possibly:
  - enhancing release of stored dopamine
  - inhibiting presynaptic reuptake of catecholamines
  - dopamine receptor agonism
  - NMDA receptor blockade
- Side effects —autonomic, psychiatric
- 200-300 mg/day
- NOW a Long Acting Formulation: Gocovri

Carbidopa/Levodopa (Sinemet)

- Most effective drug for parkinsonian symptoms
- First developed in the late 1960s; rapidly became the drug of choice for PD
- Large neutral amino acid; requires active transport across the gut-blood and blood-brain barriers
- Rapid peripheral decarboxylation to dopamine without a decarboxylase inhibitor (DCIs: carbidopa, benserazide)
- Side effects: nausea, postural hypotension, dyskinesias, motor fluctuations

Levodopa/Carbidopa Formulations

	Onset	Duration
Immediate Release 10/100, 25/100, 25/250, Parcopa 10/100,25/100	20-40 min	2-4 hr
Controlled Release 25/100, 50/200	30-60 min	3-6 hr
“Liquid levodopa” (dissolved tablets)	10-20 min	0.5-1 hr

Carbidopa/Levodopa

- IPX066 (Rytary)- True long acting

- Cabidopa/Levodopa Enteral Suspension
  - (CLES or DUOPA)

Selegiline

- Irreversible MAO-B inhibitor
- Clinically active by inhibiting dopamine metabolism in brain
- Dosage: 5 mg at breakfast and lunch
- Side effects: insomnia, hallucinations, nausea (rarely), orthostatic hypotension
- Potential interactions with tricyclics and SSRI antidepressants (cheese reaction)

Rasagaline

- 1mg daily more potent?
- Safer?
- Increases on time up to 2hrs daily?
- Delay need for Levodopa?
- Neuronal Protection :TEMPO, ADAGIO TRIALS

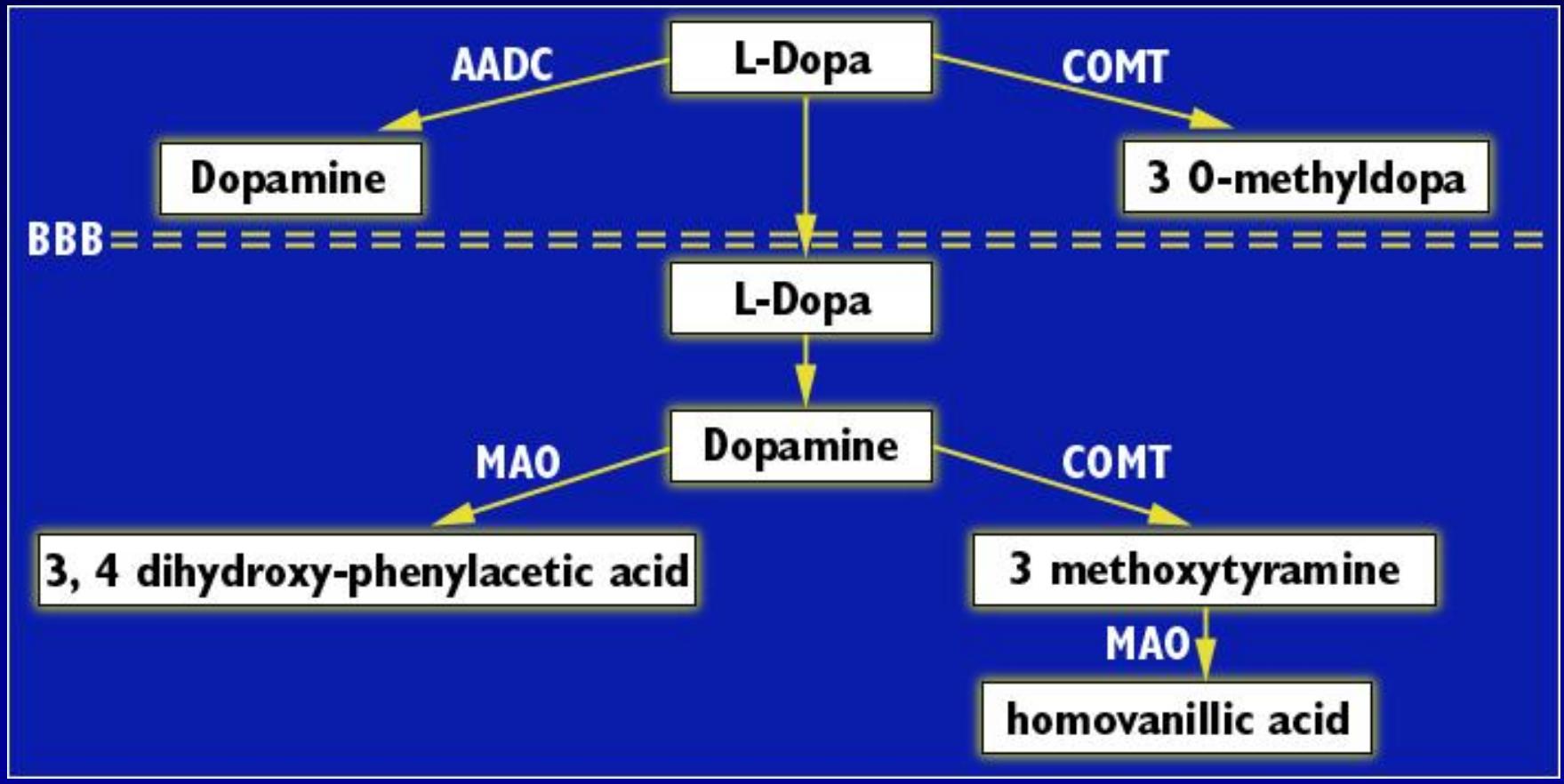
Safinamide

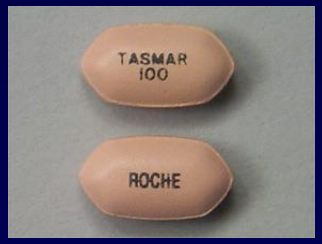
- Reversible MAO-B inhibitor
- NMDA Blockade for Dyskenesias??
- Once Daily

COMT Inhibitors

- Newest class of antiparkinsonian drugs: tolcapone, entacapone
- MOA similar to dopa decarboxylase inhibitors
- Potentiate LD: prevent peripheral degradation by inhibiting catechol O-methyl transferase
- Reduces LD dose necessary for a given clinical effect
- Helpful for both early and fluctuating Parkinson's disease
- May be particularly useful for patients with "brittle" PD, who fluctuate between off and on states frequently throughout the day

Diagram of LD Metabolism





Tolcapone (Tasmar®)

- First COMT inhibitor licensed in the U.S.
- 100 mg TID or 200 mg TID
- Reduced LD dosage by 12%, improved motor fluctuations by 14% in non-fluctuating pts
- Reduced LD dosage by 30%, and on time increased from 1.7 to 2.9 hrs/day in fluctuating pts
- Side effects: Diarrhea, OH, dyskinesias, confusion
- Acute culminant hepatic necrosis
  - 3/60,000+
  - FDA warning prevents use unless alternative therapy unsuccessful
  - liver monitoring every 2 weeks for a year and less frequently thereafter

Entacapone (Comtan®)

- Dosage: 200 mg w/each levodopa dose
- Parkinson's Study Group 1997: Increased on time by 5%, more in pts w/least on time
- Rinne et al., 1998: Increased on time by ~10%; decreased levodopa
- Diarrhea, dopaminergic SEs

Levodopa/carbidopa/entacapone (Stalevo™)

- Dosage: 50/12.5/200, 100/25/200, 150/50/200
- Dosing is similar to taking traditional levodopa/carbidopa and entacapone
- Do not give more than one tablet of triple combination (TC) therapy at one time
- Side effect profile similar to these agents alone
- Appropriate for de novo and advancing PD patients
- less dyskinesias later on?

Dopamine Agonists: Distinguishing Features

- Directly stimulate dopamine receptors
- No metabolic conversion; bypasses nigrostriatal neurons
- No absorption delay from competition with dietary amino acids
- Longer half-life than levodopa
- Monotherapy or adjunct therapy
- May delay or reduce motor fluctuations & dyskinesias associated with levodopa
- May be neuroprotective

DAs: Receptor Effects

	D1	D2	D3	D4	D5
Ergot					
Bromocriptine	-	++	++	+	+
Cabergoline	**0**	+++	**?**	**?**	**?**
Lisuride	+	++	**?**	**?**	**?**
Pergolide(Permax)	+	+++	++++	+	+
Non-Ergot					
Pramipexole(Mirapex)	**0**	++	++++	++	**?**
Ropinirole **(Requip)**	**0**	++	++++	+	**0**
Apomorphine	++	++			

Neurology 1998; 50(suppl 3)

DA Pharmacokinetics and Dosage

	T½	Dosage
(monotherapy)		
Bromocriptine (Parlodel)	6 hr	7.5-30 mg/day
Cabergoline	65+ hr	2-5 mg/day
Lisuride	2-4 hr	1-5 mg/day
Pergolide (Permax)	12-27 hr	1.5-12 mg/day
Pramipexole (Mirapex)	8 hr	1-4.5 mg/day
Ropinirole (Requip)	4 hr	3-24 mg/day
Apomorphine injectable	40 m	1-10 mg/day
Rotigotine (Neupro)	24 hr patch	4-8 mg/day

DAs: Common Adverse Effects

- Nausea, vomiting
- Dizziness, postural hypotension
- Headache
- Dizziness
- Drowsiness & somnolence
- Dyskinesias
- Confusion, hallucinations, paranoia
- Erythromelalgia; pulmonary & retroperitoneal fibrosis; pleural effusion & pleural thickening; Raynaud's phenomena. May be more common with ergotoline DA's

Apomorphine (APOKYN)

- D1/D2 agonist
- Parenteral delivery- Subcutaneous injection only in US (s.c., i.v., sublingual, intranasal, rectal)
- Rapid “off” period rescue (10-20 minutes)
  - 2-10 mg s.c.; pen injection systems
- Treatment of unpredictable, frequent motor fluctuations
  - continuous s.c. infusion via mini-pump
- SE: nausea, vomiting, hypotension
  - trimethobenzamide 300 mg t.i.d.
  - domperidone 20 mg t.i.d.; not available in U.S.

Dopamine Agonist Patch

- Neupro® (rotigotine transdermal patch), developed by SCHWARZ PHARMA
- Once a day patch (24hrs)
- Same side effect profile as DA?
- Available in UK
- Long acting DA (once a day under Developments)

NON-MOTOR Treatments

- Orthostatic Hypotension (nOH or Neurogenic Orhtostatic Hypotension)
  - Droxydopa (Northera)
- Hallucinations and Delusions
  - Pimavanserin (Nuplazid)
- Constipation
  - On going studies Enterin

Deep Brain Stimulation (DBS)

- High frequency, pulsatile, bipolar electrical stimulation
- Stereotactically placed into target nucleus
- Can be activated and deactivated with an external magnet
- Exact physiology unknown, but higher frequencies mimic cellular ablation, not stimulation

CONCLUSION

- We have multiple medications to help improve quality of life of individuals with PD.
- “Polypharmacy” is common but it may help with some of the motor complications and minimize extremes of more than one medication.
- Every patient is different, what works for one may not necessarily work for another.
- Team effort approach between patient and physician to optimize therapy and quality of life.
- Medications are only part of a multi-disciplinary approach necessary in order to treat Parkinson’s Disease.

Motor Fluctuations

- “Wearing off”: re-emergence of symptoms prior to the next scheduled levodopa (LD) dose
- “On/off” phenomenon: unpredictable fluctuations of periods of good mobility and function followed by periods of poor symptom control
- Delayed-“on” responses: dose takes longer to improve symptoms than previously
- Dose failure: dose does not provide usual improvement in symptoms

Common Signs of Early Wearing Off

Motor

- Tremor
- Bradykinesia
- Muscle cramping
- Difficulty getting out of a chair
- Reduced dexterity
- Stiffness
- Balance problems
- Weakness
- Slowness in early morning/during the night

Nonmotor

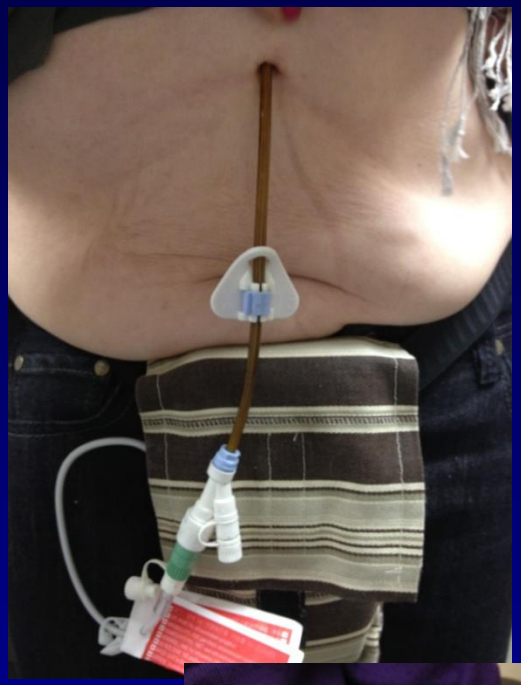
- Abdominal discomfort
- Akathisia (uncontrollable motor restlessness)
- Anxiety
- Cloudy mind, dullness of thinking
- Drenching sweats
- Drooling
- Dysphagia
- Dyspnea
- Facial flushing
- Fatigue
- Irritability
- Mood changes
- Numbness
- Pain
- Tightening sensations
- Tingling sensations

Stacy M et al. *Mov Disord*. 2005;20:726-733

FUTURE

- New Definition for PD
- Gene therapies
  - AV Viruses GAD, AADC, BDNF,GDNF
- Apomorphine pumps
- Protein Kinase Inhibitors
- New formulations of L-Dopa
  - IPX066 (Rytary), Xenoport

PUMPS

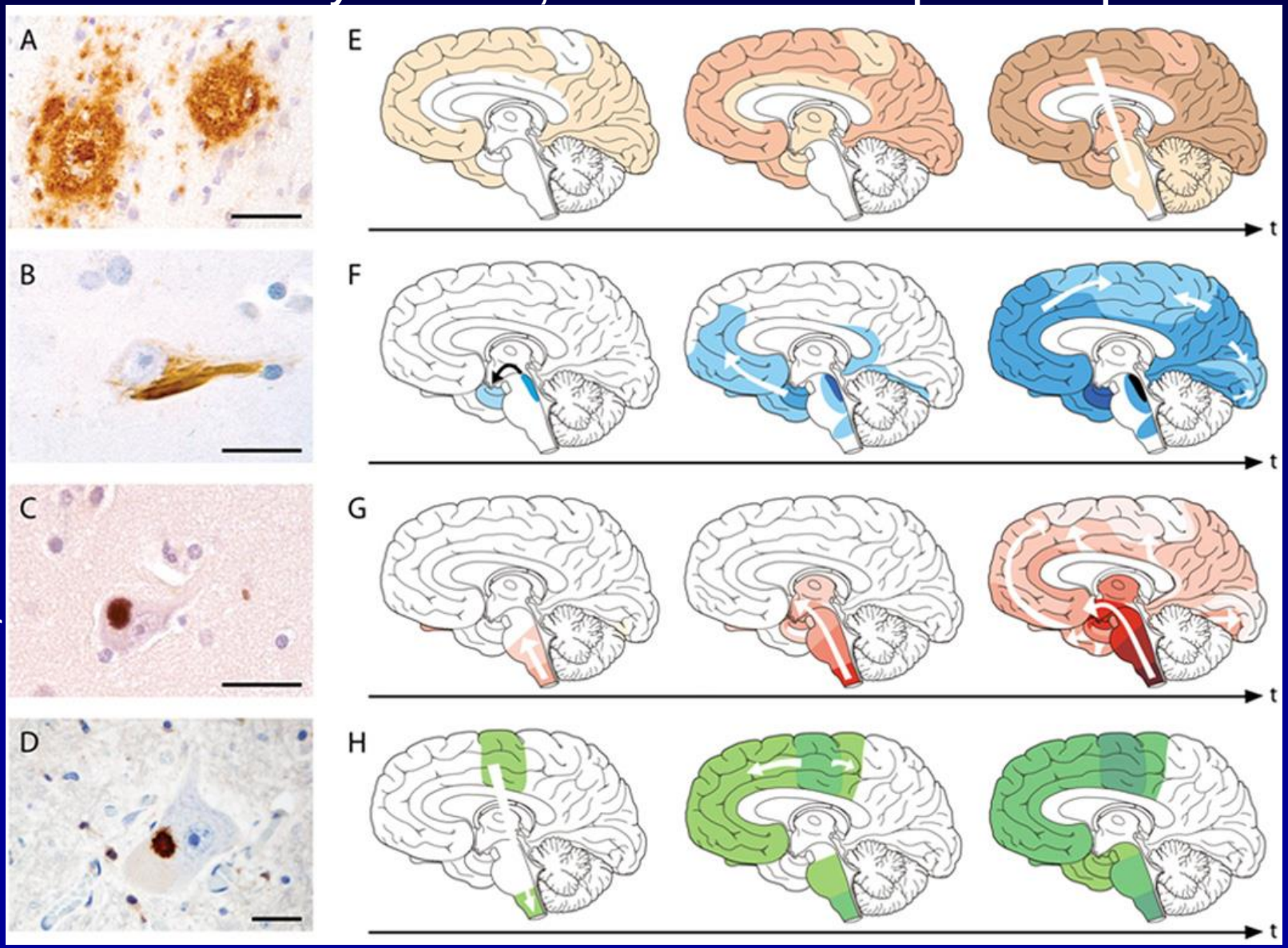


LCIG/CLES

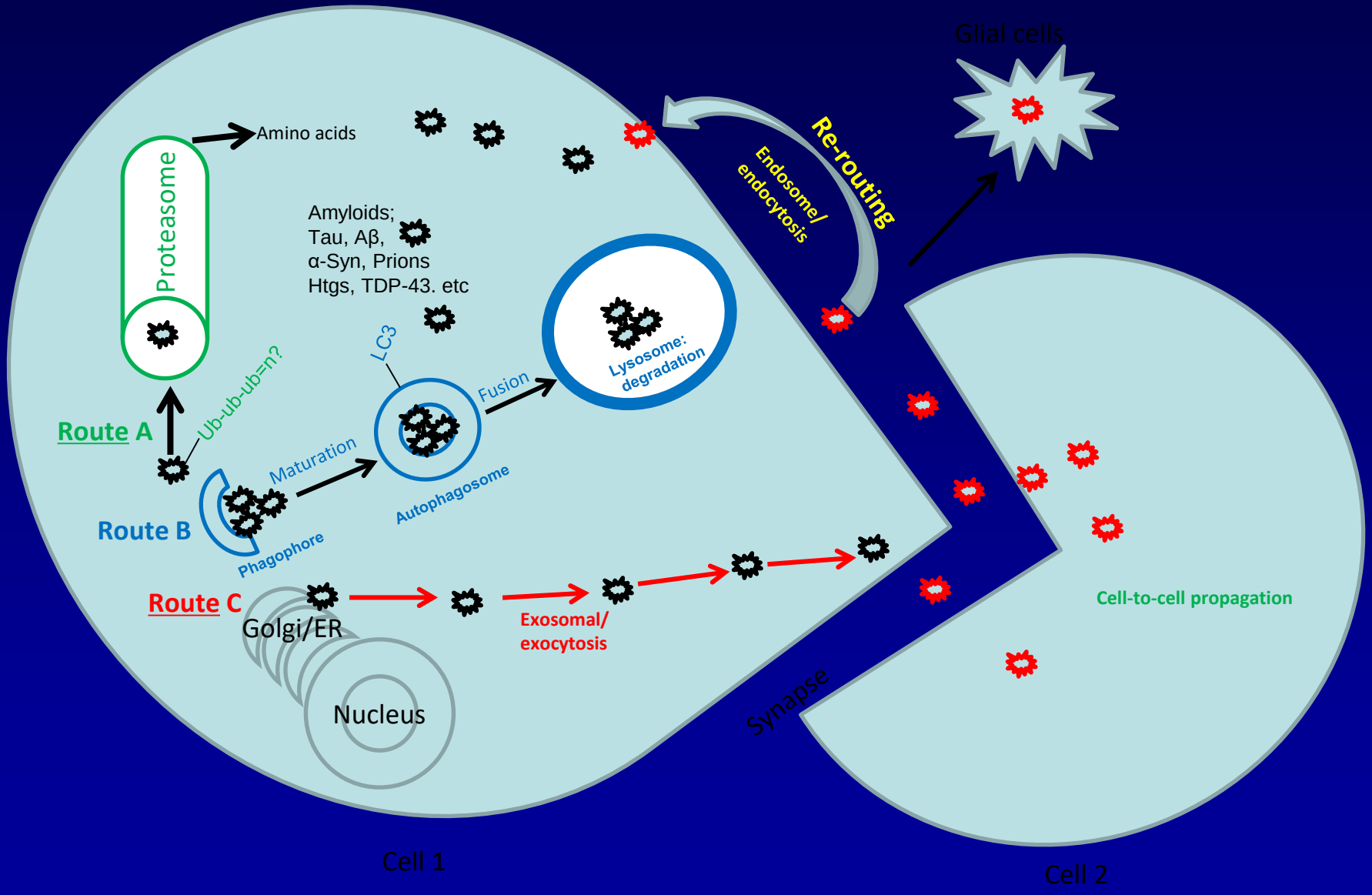
Apomorphine Pump

Self-propagation of pathogenic protein aggregates in neurodegenerative diseases.

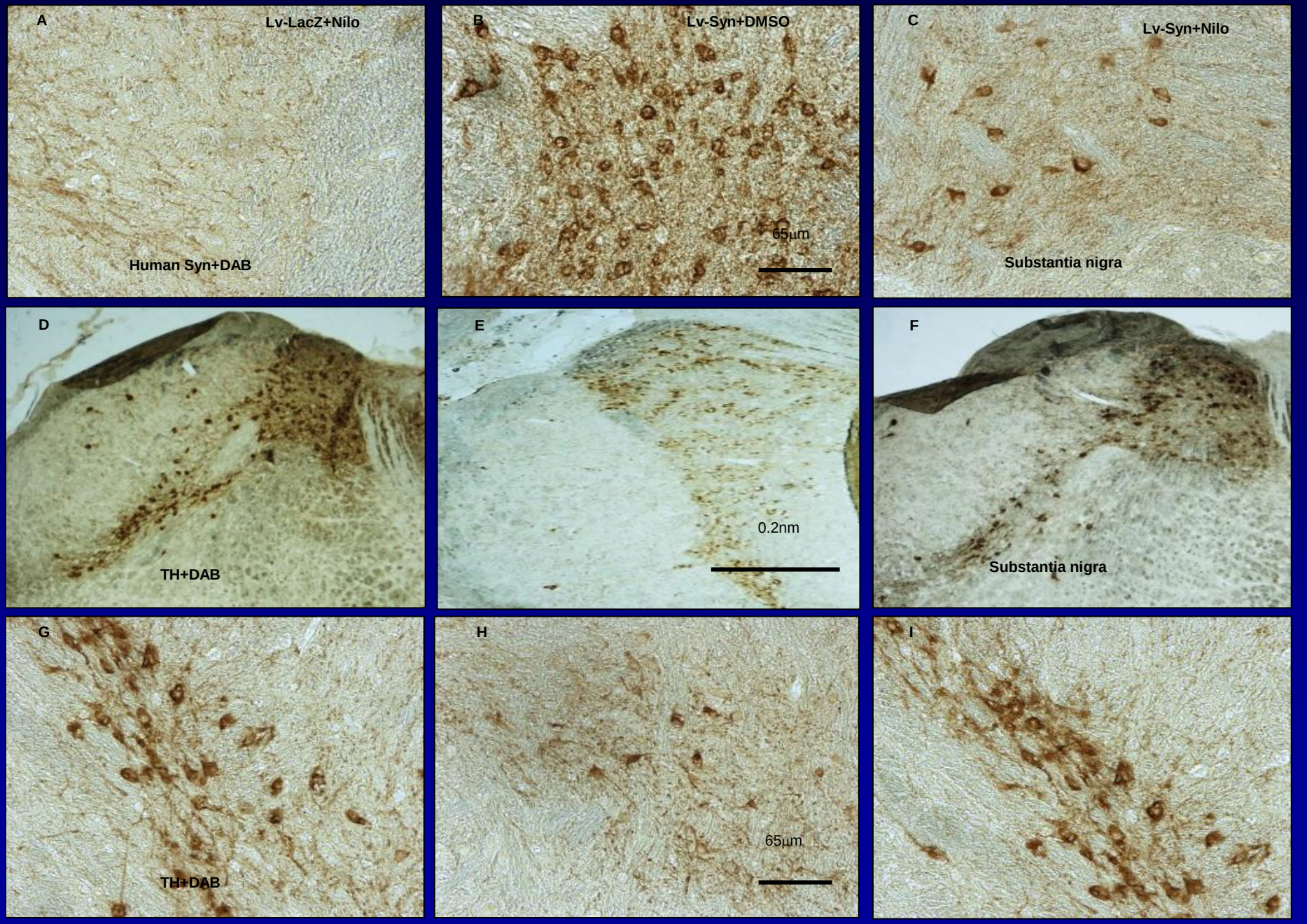
Mathias Jucker & Lary C. Walker, SEPTEMBER 2013 | VOL 501 | NATURE | 45



Can we halt neurodegenerative pathologies?
Possible quality control mechanisms for protein degradation or clearance.



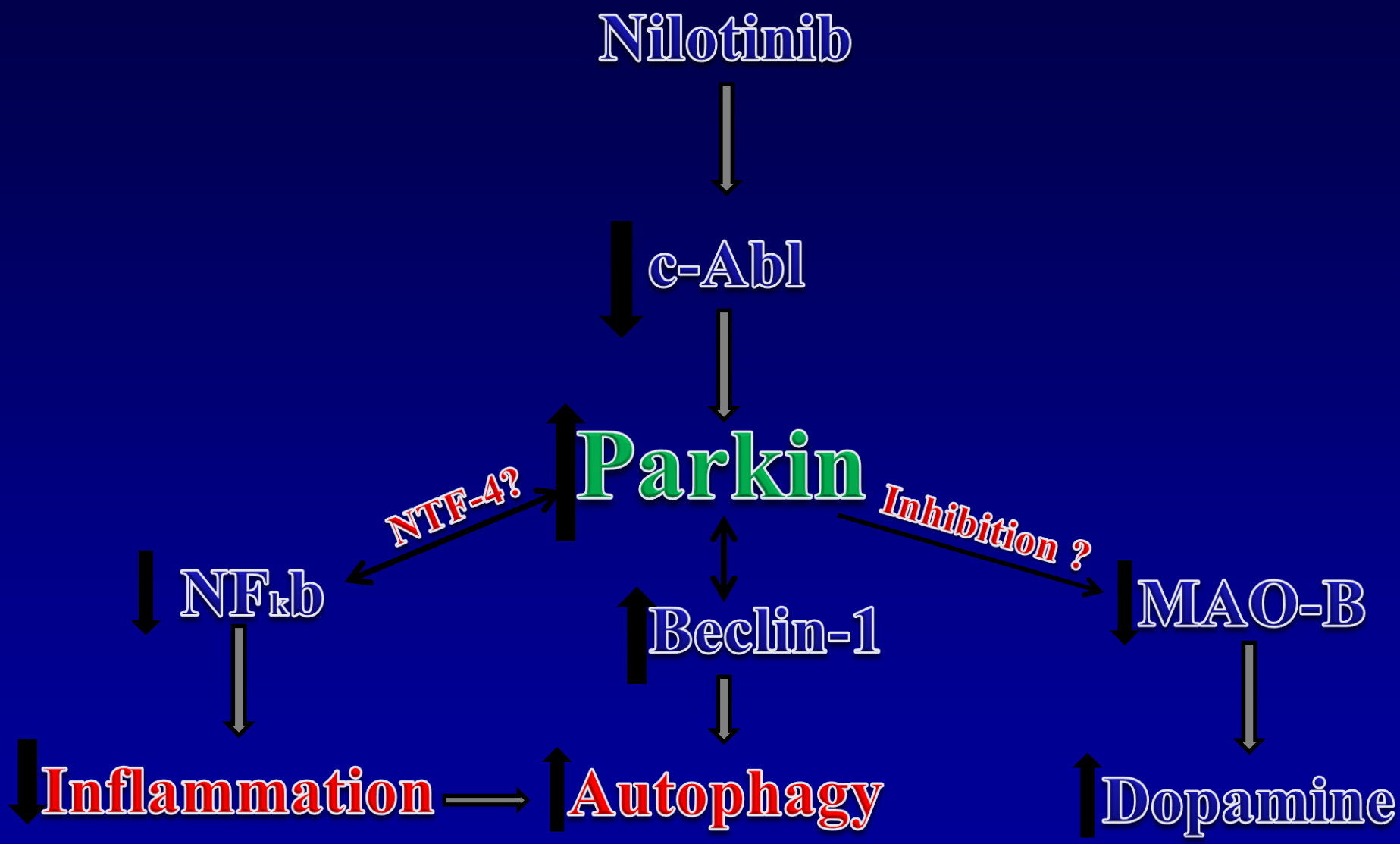
Nilotinib clears human α-Synuclein in PD mouse models



Parkinson's mouse model- baseline

Nilotinib (10mg/kg) every day for 3 weeks

Mechanistic effects of nilotinib: Abl inhibition activates Parkin



Future Directions / PD trials

Design: Placebo-controlled, double blind, randomized clinical trial

•Population/indication: Stage 2.5 to 3 PD

•Size: 3 groups, 25 patients/ group

•Duration: 6 months treatment and 3 months follow up
•Group -1- Placebo
•Group 2- 150 mg Nilotinib
•Group 3- 300 mg Nilotinib

•**Primary outcomes**. Determine the safety and tolerability of Nilotinib in PD patients, using strict safety guidelines through regular cardiovascular and clinical laboratory testing (Inclusions/exclusions: High QTc, drug contradiction, cardiovascular disease. Etc

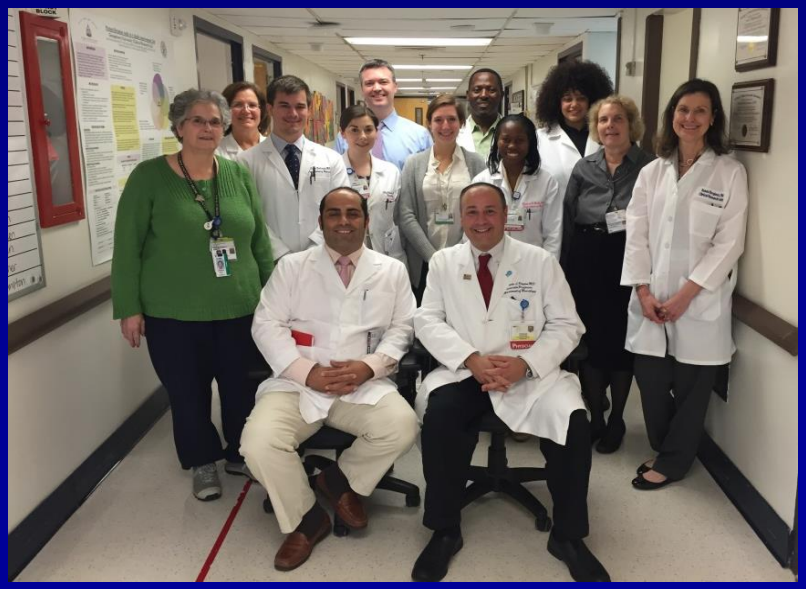
•Secondary Biomarkers: DAT Scan, CSF HVA, CSF and Plasma (Syn, Abeta and Tau), neuro-inflammatory/restorarive markers panel of 42 analytes at baseline and 12 months

•Tertiary: Clinical outcomes on UPDRS, SCOPA-Cog, MMSE, bowel movement, timed-up and go

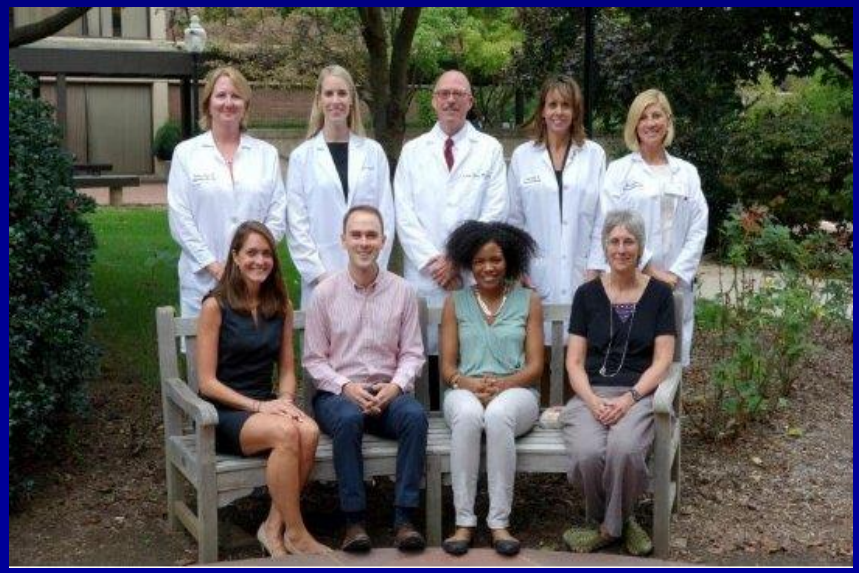
Translational Neurotherapeutics

Laboratory for Dementia and Parkinsonism

Movement Disorders Program
Clinical Research Unit



Memory Disorders Program



Thank You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