Medical Management for Parkinson's Disease

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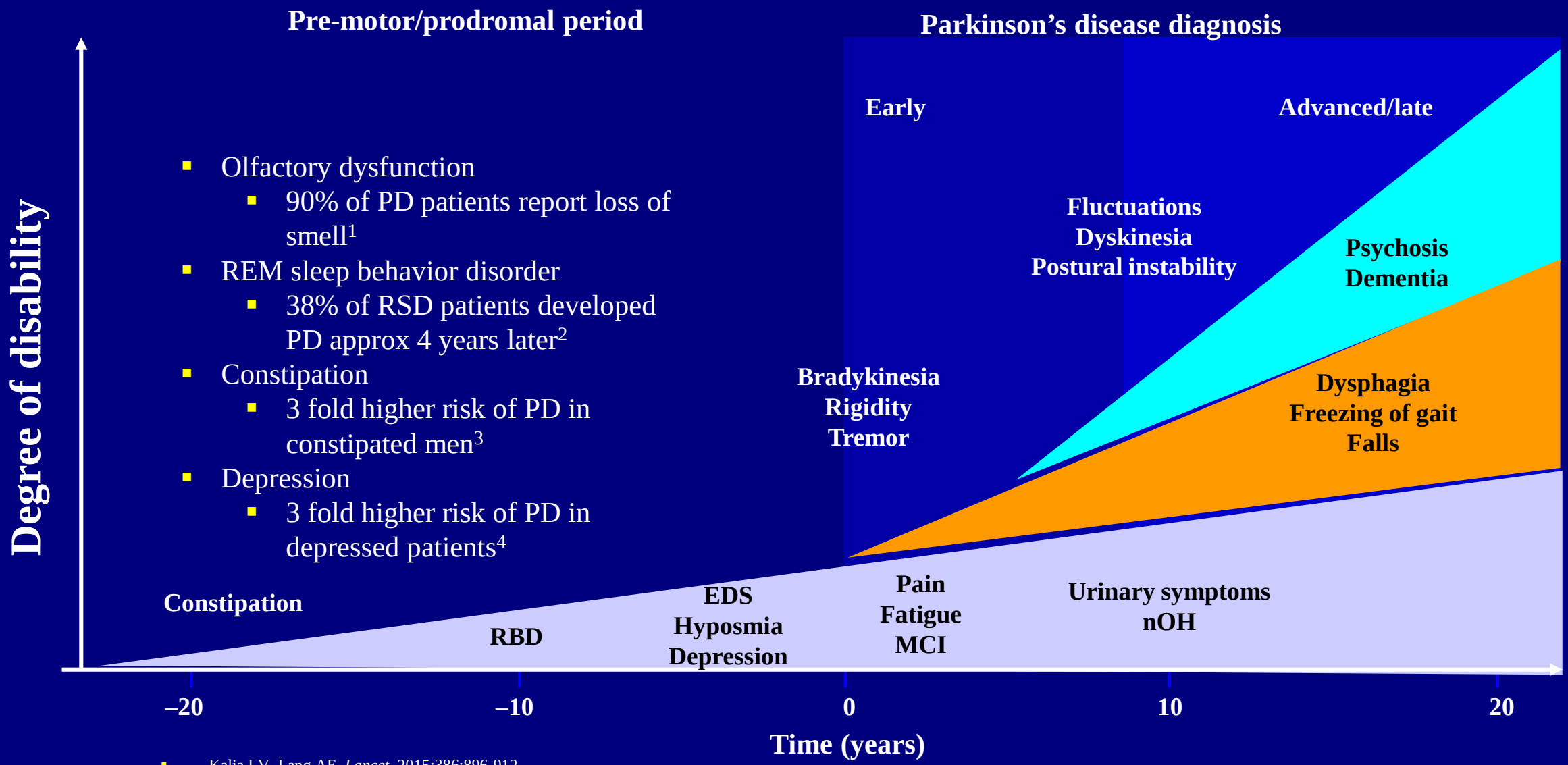
PD: Overview

- PD is a progressive disorder involving the degeneration of dopaminergic neurons
  - Degeneration of other neurons is widespread
- Characteristic motor symptoms are directly related to dopamine loss, and include bradykinesia, tremor, and rigidity; later, postural instability
  - Nonmotor symptoms also occur
- As degeneration progresses, continued loss of dopamine leads to emergence of motor symptoms
  - -50% loss at diagnosis
- As PD progresses, motor complications invariably disrupt symptom control
  - Dopaminergic nonresponsive symptoms also common

Cheng H-C et al. *Ann Neurol*. 2010;67:715-525: .Jankovic J. *Handbook of Parkinson's Disease*, 4th ed. 2007:49-76; Jankovic J. *J Neurol Neurosurg Psychiatry*. 2008;79:368-376; Langston JW. *Ann Neurol*. 2006;59:591-596; Morgan J et al. *Handbook of Parkinson's Disease*, 4th ed. 2007:29-47; Schapira AH. *Arch Neurol*. 2007; 64:1083-1088.

When Does Synuclein Degeneration Begin?

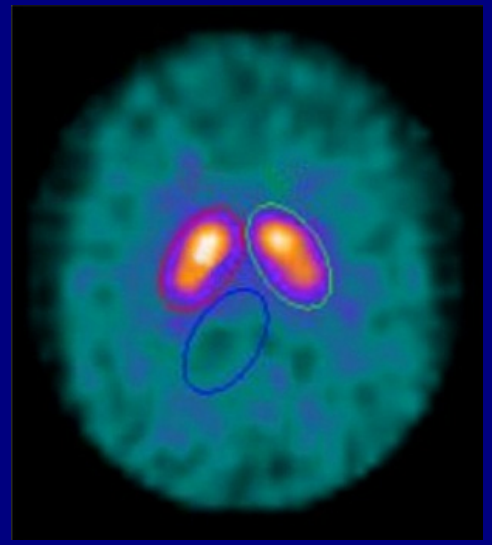


- Kalia LV, Lang AE. *Lancet.* 2015;386:896-912.

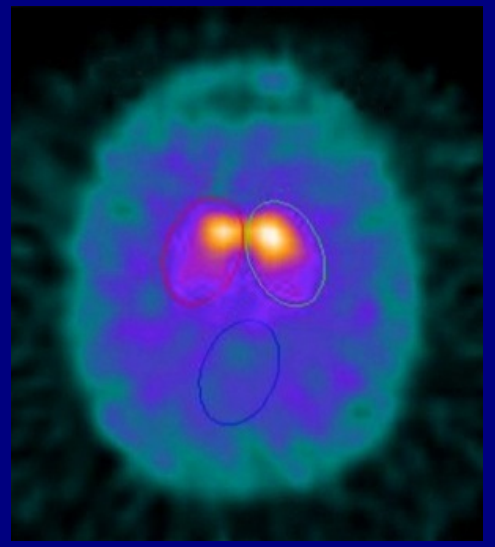
Clinical Diagnosis of PD

- PD is diagnosed based on:
  - Clinical examination
  - Exclusion of other causes of parkinsonism
- No definitive diagnostic or imaging test is currently available for the diagnosis of PD
  - DaTscan™ is a biomarker of nigrostriatal dopaminergic degeneration

Normal Uptake,
No Dopaminergic Deficit



Patient With Abnormal Uptake,
Dopaminergic Deficit



DaTscan images provided courtesy of Richard B. Dewey, Jr, MD; Dallas, TX.

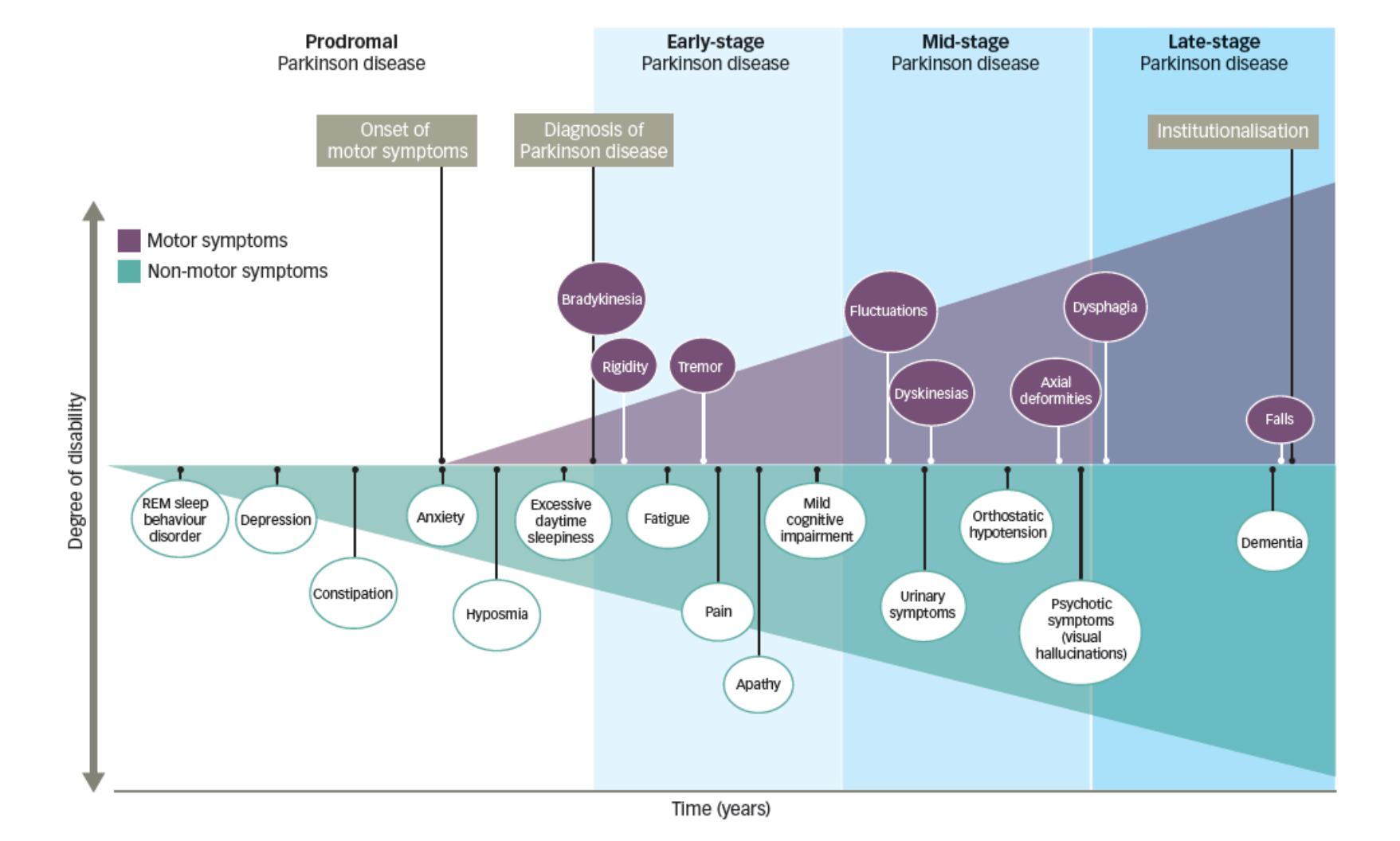
Adler CH. *Med Clin North Am*. 1999;83:349-367; Catafau AM, et al. *Mov Disord*. 2004;19:1175-1181; Hughes AJ et al. *J Neurol Neurosurg Psychiatry*. 1992;55:181-184; Hughes AJ et al. *Brain*. 2002;125;861-870; Newman EJ et al. *Mov Disord*. 2009;24:2379-2385; DaTscan [package insert]. Arlington Heights, IL: GE Healthcare; April 2011; de la Fuente-Fernández R. *Neurology*. 2012;78:696-701; Hauser RA et al. *J Neuroimaging*. 2012;22:225-230.

Treatment of Parkinson's Disease

Treatment Options

Non-Pharmacologic Therapy	Pharmacologic Therapy
Education	Anticholinergics
Exercise	Amantadine
Nutrition	MAO-B Inhibitors
OT/PT/Speech	Dopamine Agonists
Psychological	Levodopa

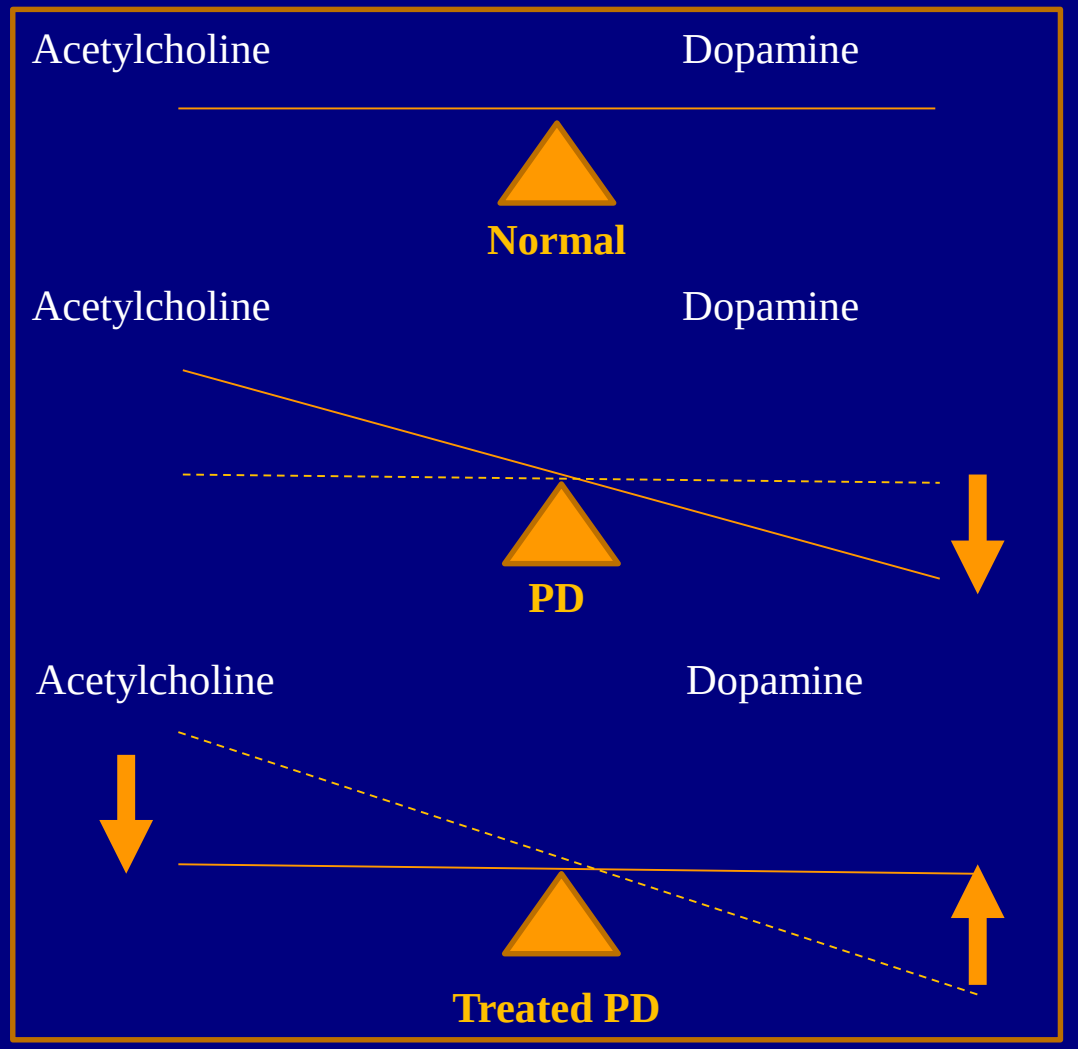
Parkinson's Disease Journey Over the Years



Eur Neurol Rev 2018;13(Suppl 2):3-13

Anticholinergics

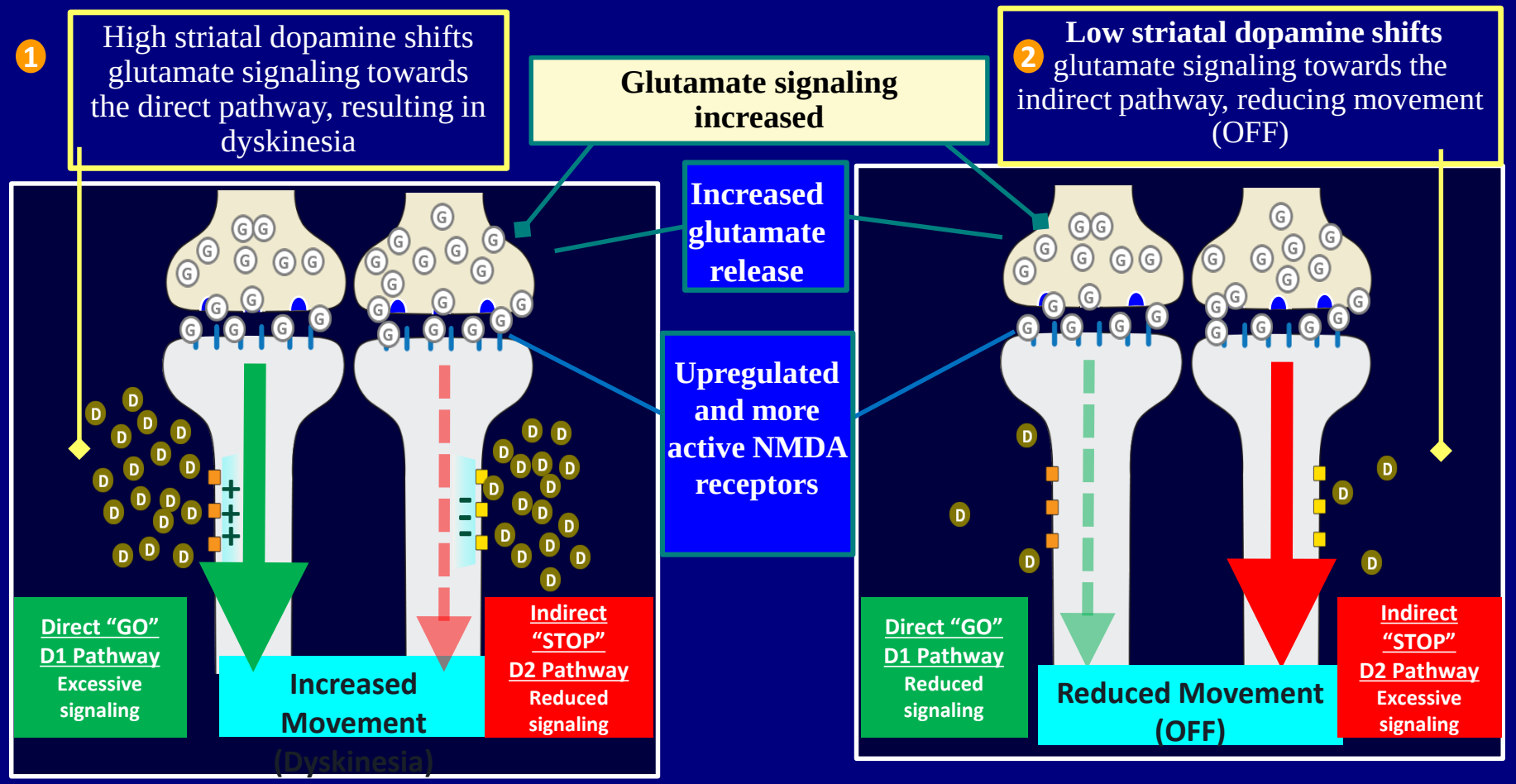
- Used only in young patients (< 55 years)
- Mainly effective for tremor
- AEs common and include confusion, hallucinations, constipation
- Commonly used for PD:
  - Trihexyphenidyl: 6 -10 mg/day
  - Benztropine: 1.5–6.0 mg/day



Amantadine

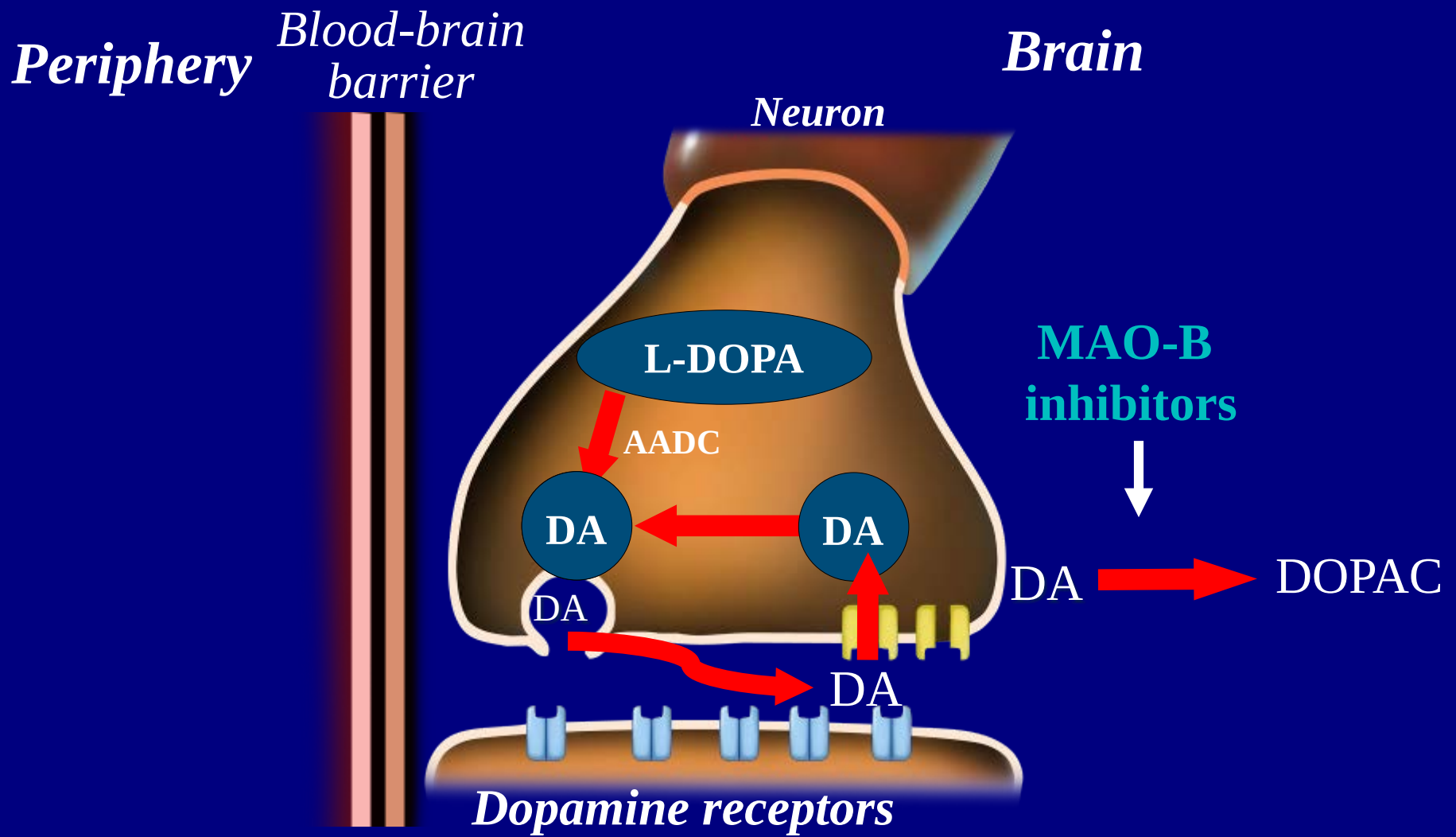
- Mechanism of action
  - Enhances release of stored catecholamines
  - Inhibits catecholamine reuptake at the presynaptic terminal
  - Agonism at dopamine receptors
  - NMDA antagonist
- Dosage
  - Immediate release amantadine (Symmetrel): 200-400 mg/day in multiple doses
- Common Side Effects
  - Anticholinergic-like side effects
  - Pedal edema/livedo reticularis

Increased Glutamatergic Signaling and Varying Plasma Dopamine Levels Lead to Motor Complications



Calabresi P, et al. *Nat Neurosci*. 2014;17(8):1022-1030. Bravo SA, et al. In: Rana AQ, ed. *A Synopsis of Parkinson's Disease*. London, UK: InTech; March 26, 2014.. Finlay C, Duty S. *J Neural Transm (Vienna)*. 2014;121(8):861-880.

Site of Action of MAO-B Inhibitors



L-DOPA = levodopa
3-OMD = 3-*O*-methyldopa
DA = dopamine

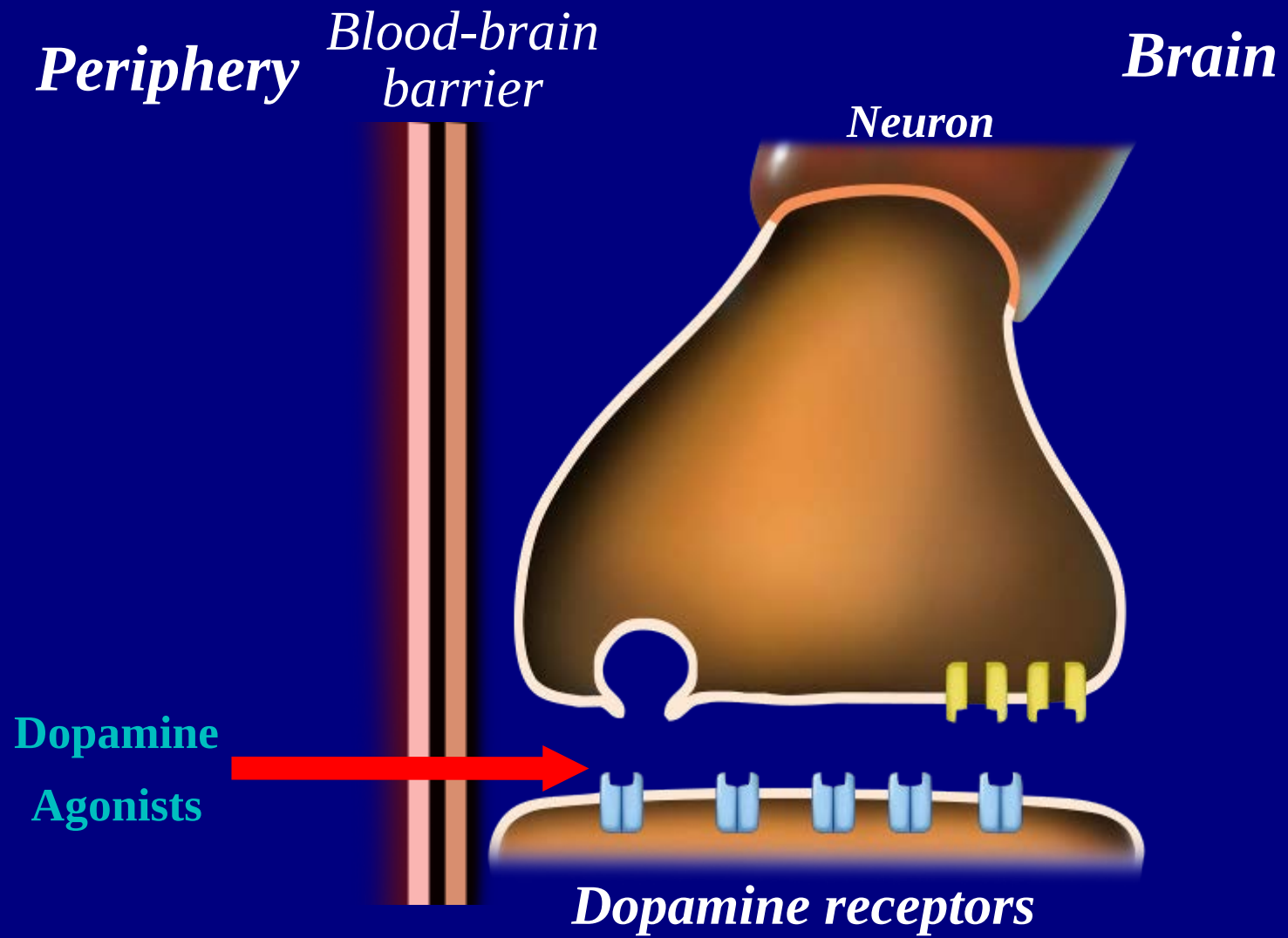
AADC = aromatic acid decarboxylase
DOPAC = dihydroxyphenylacetic acid
3-MT = 3-methoxytyramine

MAO-B Inhibitors

- Rasagiline
  - Once per day dosing
  - Dose 1 mg daily
- Selegiline *
  - Twice daily dosing – morning and noon
  - Amphetamine metabolites can cause insomnia or confusion
  - Dose 5mg once or twice daily
- Zydis selegiline and safinamide are for motor fluctuation
- Contraindications
  - Meperidine, tramadol, methadone or propoxyphene; dextromethorphan, St John's wort, cyclobenzaprine, other MAO inhibitors

Package inserts

Site of Action of Dopamine Agonists



L-DOPA = levodopa
DA = dopamine
AADC = aromatic acid decarboxylase

Dopamine Agonists

- Stimulate postsynaptic dopamine receptors directly
- Do not require metabolic conversion
- No competition with dietary amino acids
- Half-life longer than that of levodopa
- Indicated for initial monotherapy or as an adjunct to levodopa
- Reduced risk of dyskinesia compared to levodopa
- Adverse effects: nausea, vomiting, sedation, insomnia, orthostatic hypotension, hallucinations, leg edema, impulse control disorders, dyskinesia in advanced disease

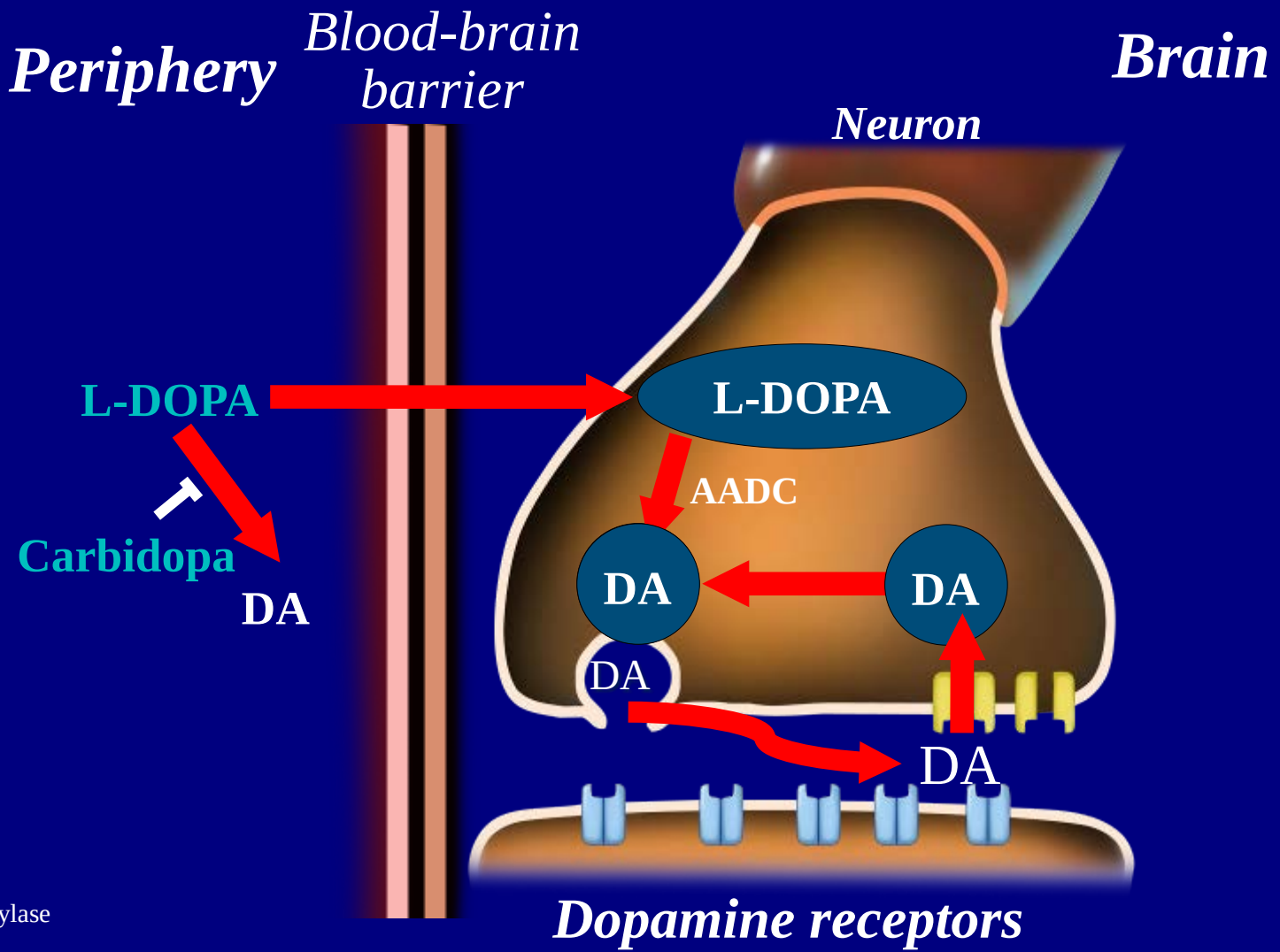
Lyons and Pahwa. Int J Neurosci 2011;121(suppl 2):27-36.

Dopamine Agonists Dose

	Half Life (hr)	Initial Target Dose	Maximum Dose
Bromocriptine (Parlodel)	3-6	2.5 mg tid	15 mg/day
Pramipexole (Mirapex)	9-12	0.5 mg tid	4.5 mg/day
Pramipexole extended release (Mirapex ER)	9-12	1.5 mg qd	4.5 mg/day
Ropinirole (Requip)	6	3 mg tid	24 mg/day
Ropinirole extended release (Requip XL)	6	8 mg qd	24 mg/day
Rotigotine transdermal system (Neupro)	5-7	6 mg qd	max of 6 mg /24 hours for early disease and 8 mg/24 for advanced disease

Package inserts

Sites of Action of Levodopa



L-DOPA = levodopa
DA = dopamine
AADC = aromatic acid decarboxylase

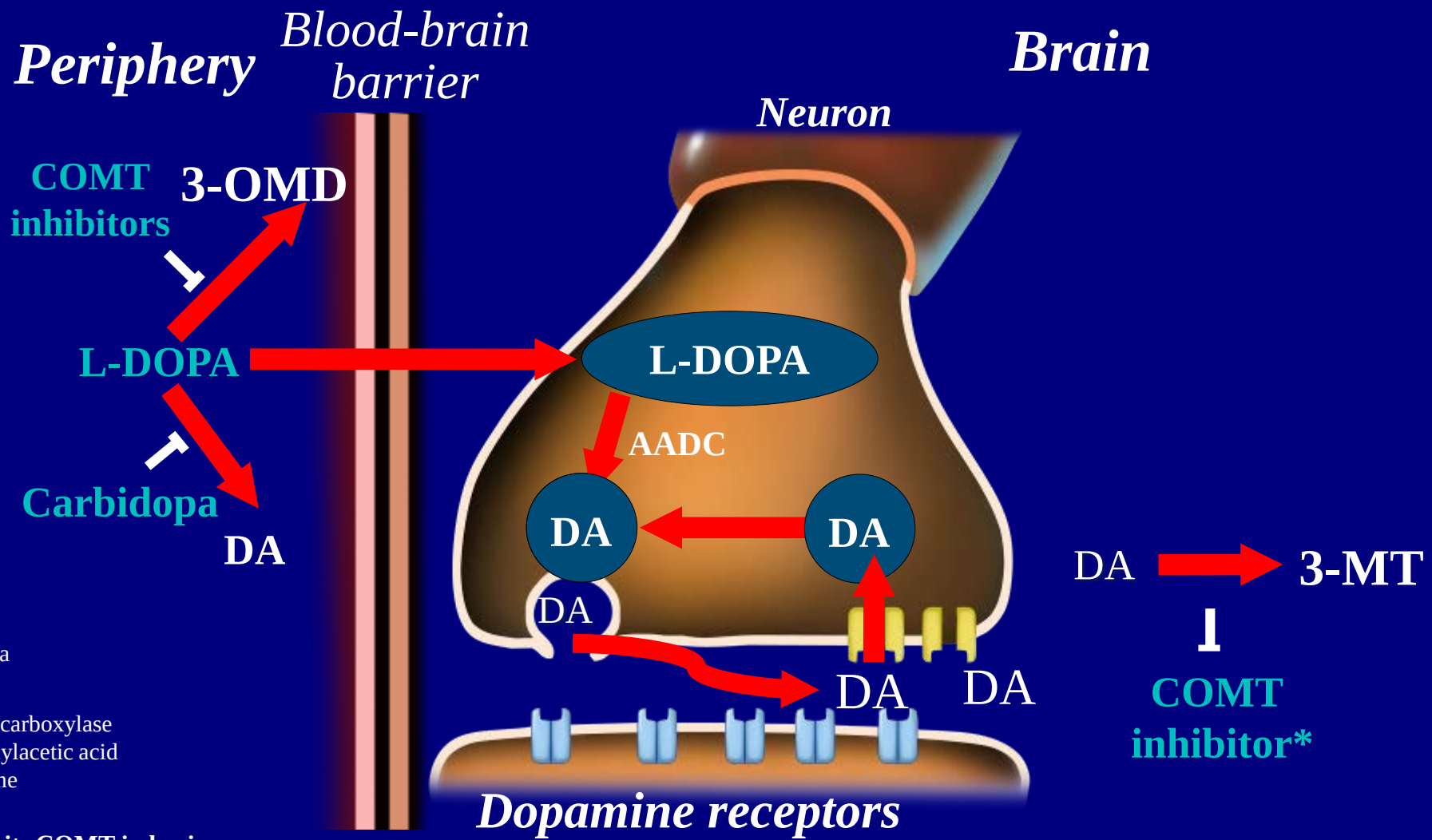
Levodopa

- Most effective agent for the treatment of PD
- Virtually all patients with PD have significant benefit with levodopa
- Almost all patients with PD require levodopa at some point
- Half life of levodopa with carbidopa is 90 minutes
- Long term use causing motor fluctuations (OFF time) and dyskinesia
- Levodopa is efficacious even in late stage of disease
- Not all symptoms are responsive to levodopa such as falls, freezing of gait, dementia, speech, swallowing

Levodopa

- Immediate release: 10/100, 25/100, 25/250
- Orally disintegrating tablets (Parcopa): 10/100, 25/100, 25/250
- Sustained release: 25/100, 50/200 (increase dose by 20-30% when switching from immediate release)
- Extended release capsules: 23.75/95; 36.25/145; 48.75/195; 61.25/245 (increase dose by 100% when switching from immediate release)

Sites of Action of COMT Inhibitors



L-DOPA = levodopa
3-OMD = 3-*O*-methyldopa
DA = dopamine

AADC = aromatic acid decarboxylase
DOPAC = dihydroxyphenylacetic acid
3-MT = 3-methoxytyramine

***Only tolcapone inhibits COMT in brain.**

COMT Inhibitors
Reductions in Off Time
Adjusted Treatment Effect ~ 1.0 hr/day

Treatment	Titration/Dose Ranges	Daily "Off" time reduction*
Entacapone (Comtan)	200 mg with each dose of levodopa up to 8 times/d not to exceed 1600 mg/d of entacapone	12-22% 0.7-1.2 hr
Carbidopa/levodopa/ entacapone (Stalevo)	Replace each levodopa dose up to 1600 mg/d entacapone or 1200 mg/d levodopa	Same as entacapone
Opicapone (Ongentys)	50mg once daily at bedtime one hour before or at least one hour after food, no titration	0.9-1.0 hr
Tolcapone (Tasmar)	Start with 100 mg tid and increase to 200 mg tid as necessary	12-28% 0.9-1.8 hr

Pahwa et al, Neurology 2006; package inserts

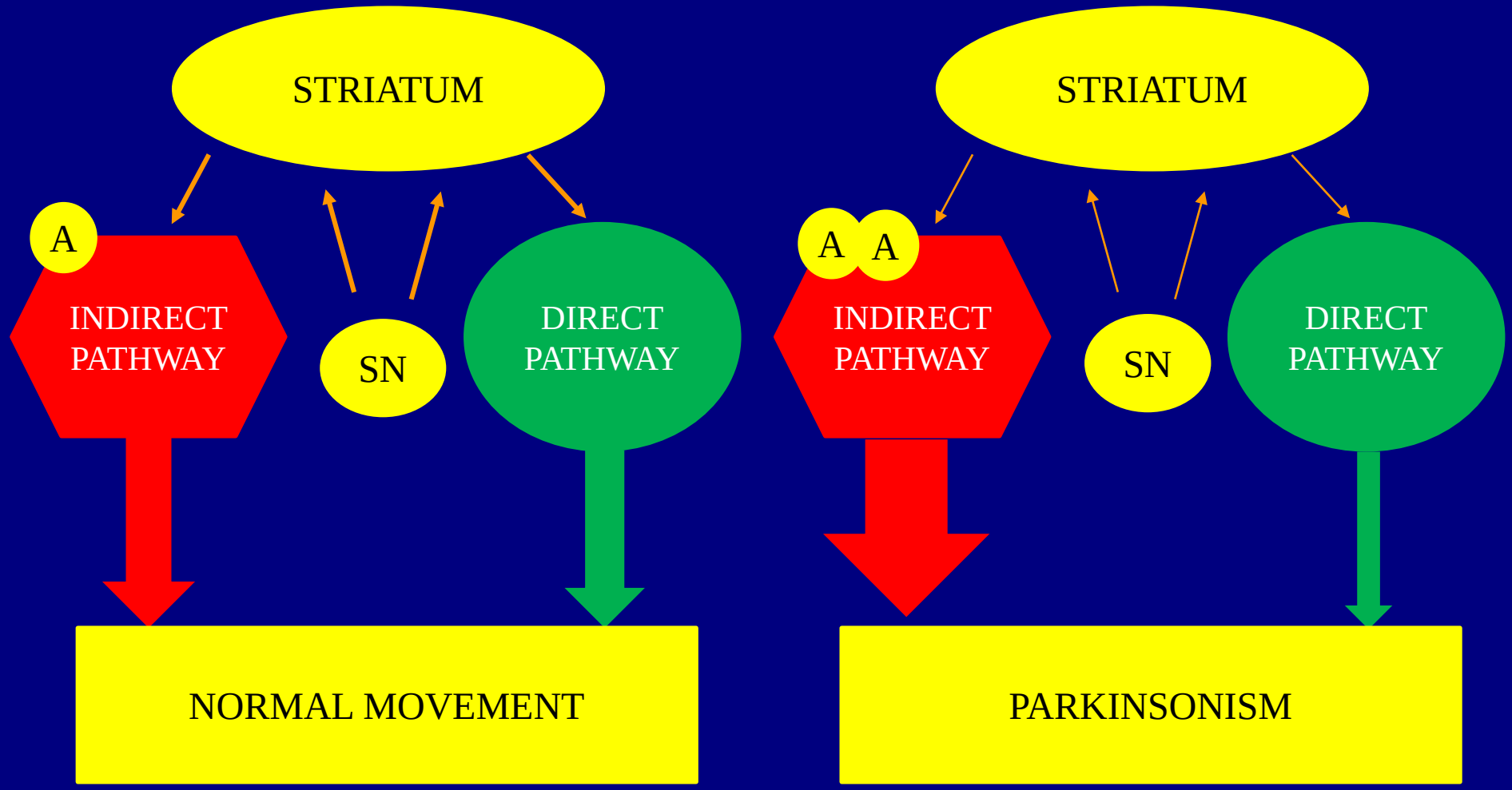
* Adjusted treatment effect

Adenosine A_{2A} Antagonist

- Adenosine regulates neuronal activity
- Adenosine A_{2a} receptors
  - Enriched in the basal ganglia[1,2]
  - Regulate the indirect pathways[3]
  - Activation reduces motor activity[4]
    - In contrast, dopamine increases motor activity[4]

1. Kalia LV, et al. *Mov Disord*. 2013;28(2):131-144. 2. Mishina M, et al. *PLoS One*. 2011;6(2):e17338. 3.Saki M, et al. Naunuyn-Schmiedeberg's Arch Pharmacol.2013;(386):963-972. 4. Varani K, et al. *FASEB J*. 2010;24(2):587-598.

Adenosine A2A Antagonist



Medication Choices: Initial Target Dose

- Anticholinergics
- Amantadine: 100 mg BID
- MAO-B Inhibitors
  - Rasagiline 1 mg daily
  - Selegiline: 5 mg with breakfast/lunch
- Dopamine Agonists
  - Pramipexole: 0.5 mg TID
  - Pramipexole ER: 1.5 mg daily
  - Ropinirole: 3mg TID
  - Ropinirole ER: 8 mg daily
  - Rotigotine: 6 mg daily
- Carbidopa/Levodopa
  - Immediate release: 25/100 TID
  - Sustained release: 50/200 BID
  - Extended release capsules: 23.75/95 TID

Differential Profiles of Drug Classes for Early Parkinson's Disease

	Levodopa	Dopamine Agonists	MAOB Inhibitors
Symptomatic Efficacy	+++	++	+
Acute dopaminergic side effects	++	+++	+
Prevention of motor complications		++	+
Convenience	+	++	+++
Risk Profile			
Somnolence	+	++	-
Hallucinations	+	++	+/-
Impulse disorders	+/-	++	-
Pedal edema	-	+	-

Adapted from Poewe and Mahlkne in Movement Disorders. Watts, Standaert, Obeso (eds) 2012;271-305

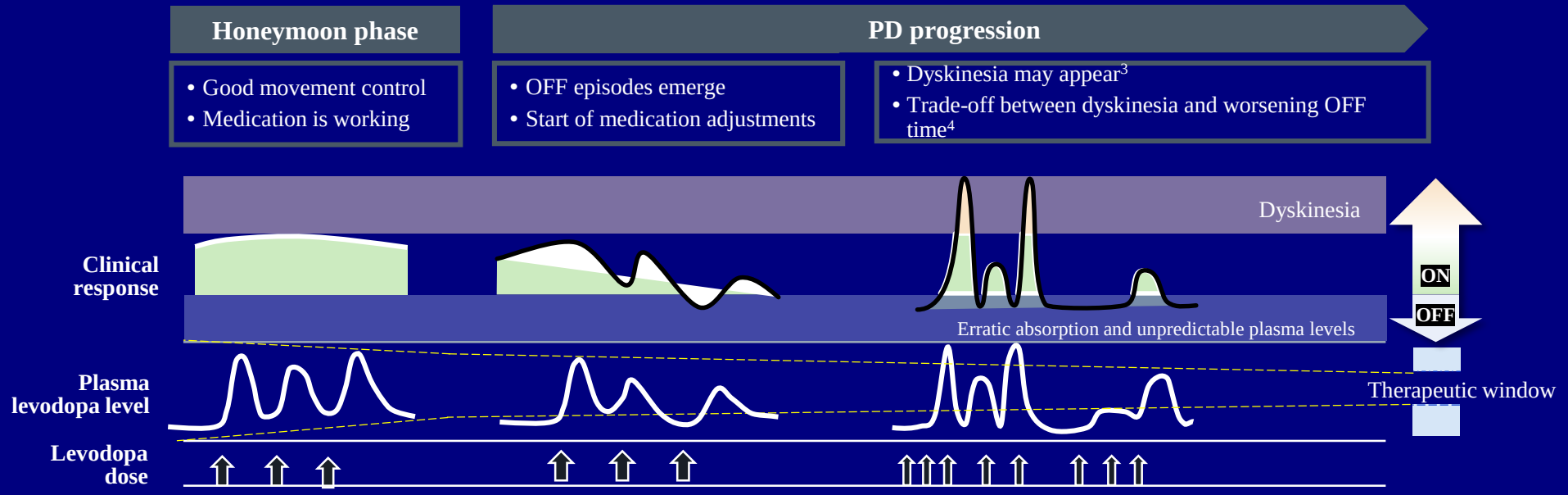
+ mild, ++ moderate,
+++ marked +/- uncertain

Common Adverse Events in Early PD

	Dizziness	Hallucinations	Nausea	Orthostatic Hypotension	Pedal Edema	Somnolence	Confusion
MAO-B inhibitors	1 - 14%	1 -6%	4 -20%	3%	1%	1%	2%
Dopamine Agonists	6-40%	5-9%	19-60%	1-6%	2-7%	11-40%	4-17%
Carbidopa/ levodopa	6-19%	6-8%	13-49%	1-12%	6%	19-21%	NR

Data from package inserts; PI does not list frequency of AEs; taken from ELLDOPA, CALM-PD and 056

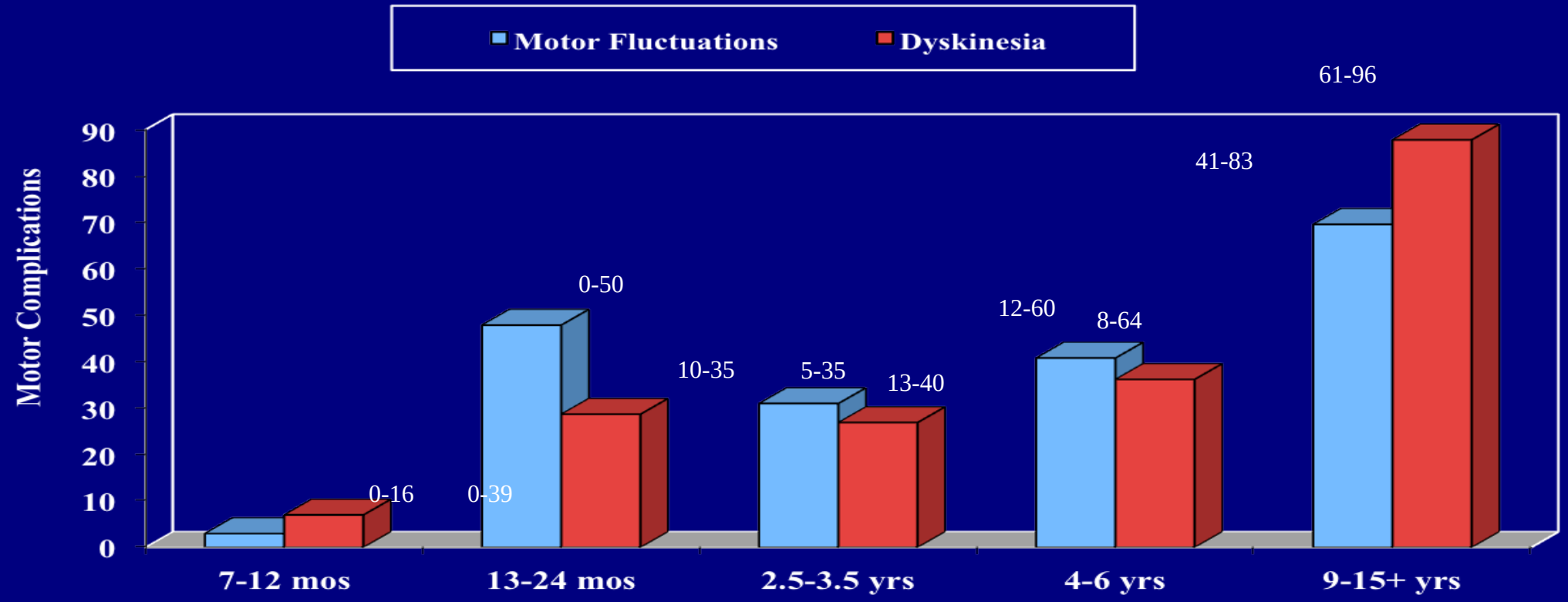
Levodopa Treatment Response Over Time



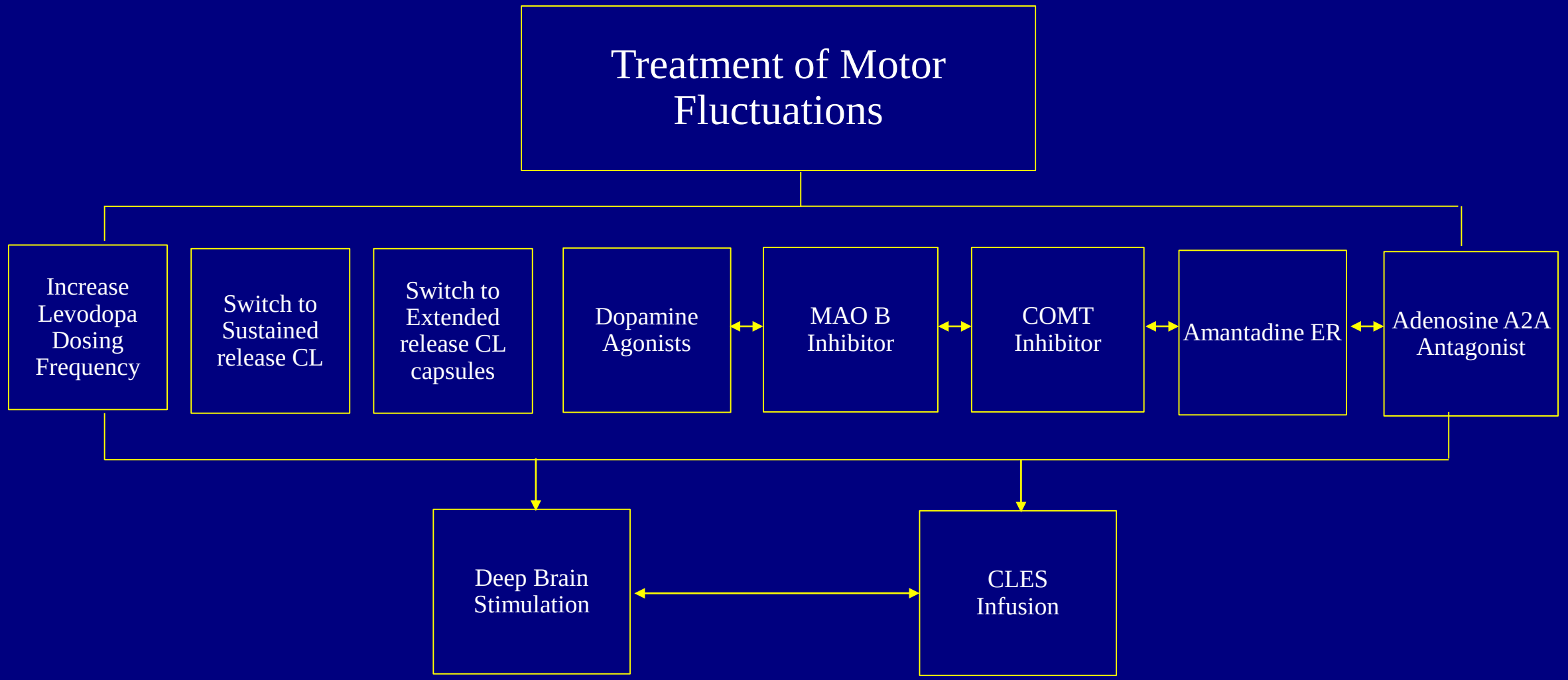
As the disease progresses, the response to each dose of levodopa is shortened
Patients also develop peak-dose dyskinesia, leading to an **unpredictable "on-off" response** and narrowing of the therapeutic window

Jankovic J. *Mov Disord*. 2005;20(SUPPL. 11); Obeso JA, Rodriguez-Oroz MC, Chana P, Lera G, Rodriguez M, Olanow CW. *Neurology*. 2000;55(11 Suppl 4):S13-20; discussion S21-3; Goubault E, Nguyen HP, Bogard S, et al. *J Parkinsons Dis*. 2018;8(2):323-331; Olanow CW, Stern MB, Sethi K. *Neurology*. 2009;72(21 Suppl 4):S1-136; Brooks DJ. *Neuropsychiatr Dis Treat*. 2008;4(1):39-47.

Incidence of Levodopa Induced Motor Complications



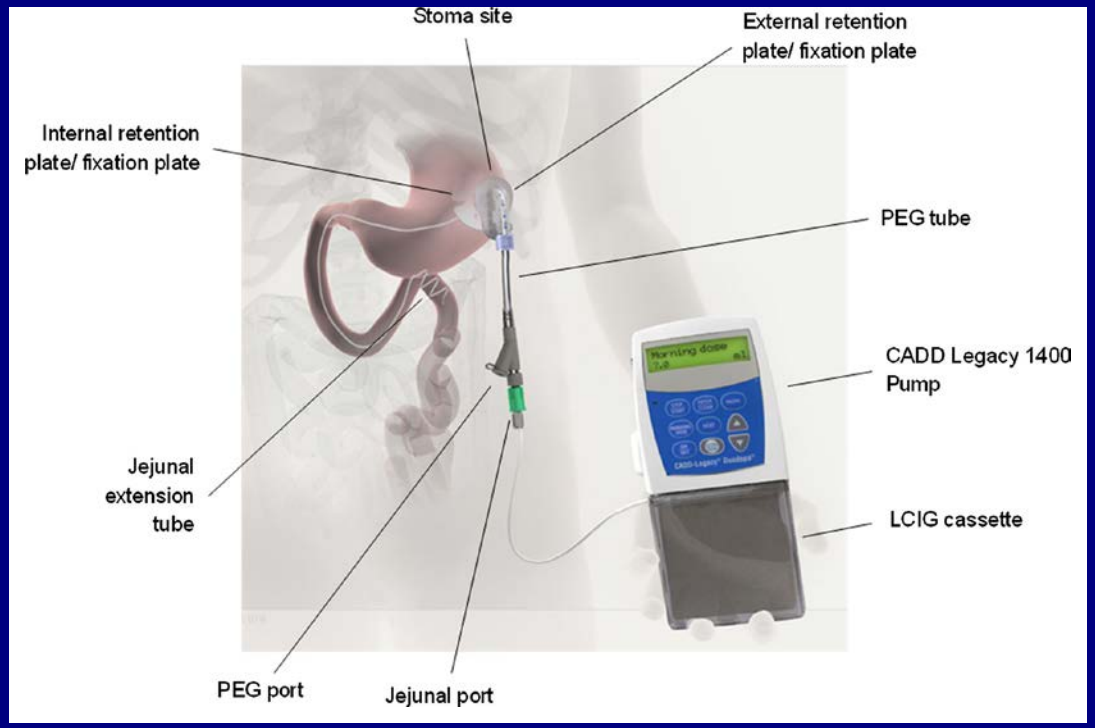
Ahlskog et al. Mov Disord 2001;16:448-458


Treatment of Motor Fluctuations
Increase Levodopa Dosing Frequency
Switch to Sustained release CL
Switch to Extended release CL capsules
Dopamine Agonists
MAO B Inhibitor
COMT Inhibitor
Amantadine ER
Adenosine A2A Antagonist
Deep Brain Stimulation
CLES Infusion

On Demand/Rescue/
As Needed/When Needed Therapies

Carbidopa Levodopa Enteral Suspension (Duopa)

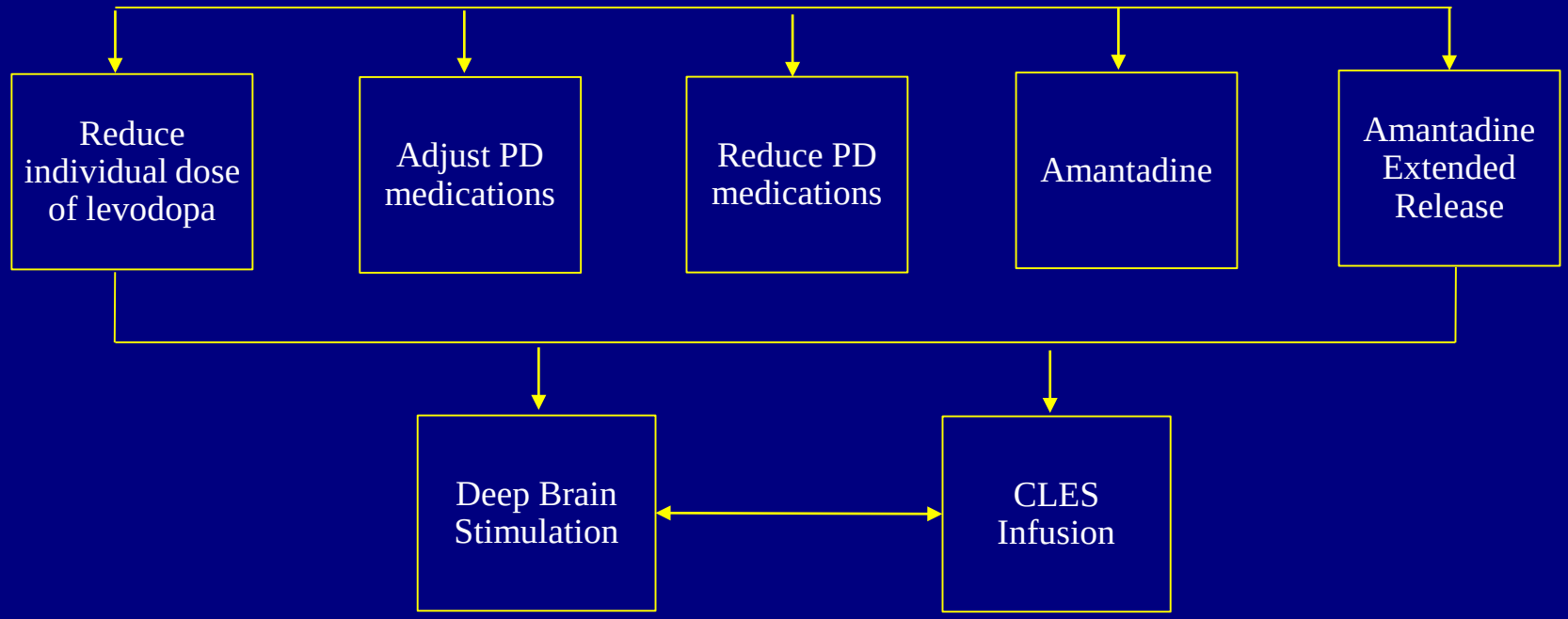
Carbidopa Levodopa Enteral suspension is infused via a intrajejunal tube in the abdomen and an external pump



Dyskinesia

- Dyskinesia are involuntary movements that occur during awake hours in PD patients
- Non-rhythmic, purposeless, unpredictable
- Chorea, dystonia, myoclonus, ballism, stereotypy
- Usually due to levodopa
- Resolves when levodopa levels are reduced
- Often leads to suboptimal levodopa management

Treatment of Dyskinesia



Common Dopaminergic Adverse Events in Advanced PD

	Dizziness	Hallucinations	Nausea	Orthostatic Hypotension	Somnolence	Dyskinesia
Carbidopa/ levodopa[1]	2 -3%	3 -5%	4 -6%	1%	NR	13 -16%
MAO-B inhibitors	2 -14%	<3 - 6%	6 -20%	2 -9%	2 -6%	18 -21%
Dopamine Agonists	2 -26%	7 -17%	11-30%	1 -53%	7 -32%	13 -47%
Apomorphine	20%	10%	30%	20%	35%	35%
Entacapone	8%	4%	14%	4%	2%	25%
Istradefylline	6%	6%	6%	<2%	<2%	17%
Amantadine ER	16%	21%	8%	13%	NR	NR

Data from package inserts; PI does not list frequency of AEs; taken from ELLDOPA, CALM-PD and 056

[2] PI lists AEs in moderate to advanced disease compared to carbidopa/levodopa

Impulse Control Disorders

- Approx 20% of DA treated patients
  - Pathological gambling
  - Hypersexuality
  - Obsessional shopping
  - Internet “addiction”
- Often caregiver input needed to diagnose

Pezzella et al. Mov Disord 2005;20:77-80
Voon. Move Disord 2006;19:367-70
Bastiaens et al, Mov Disord 2013

Daytime Sleepiness in PD

Razmy, Arch Neurol 2004

- Approximately 20% of PD patients with pathologic daytime sleepiness
- No difference in previous amount of nighttime sleep in those with excessive daytime sleepiness (EDS) compared to those without
- Any dopaminergic drug can cause EDS
- The higher the combined dopaminergic effect of levodopa and agonist, the greater the risk of EDS

Neuroleptic Malignant Syndrome (NMS)

- Symptoms begin after initiating or increasing DBA dose or abruptly discontinuing or reducing dopaminergic therapy
- Incidence of 0.1 to 1.8% of patients exposed to DBA
- Consider in any patient with acute onset parkinsonism and fever
- Young and middle aged men at higher risk
- Symptoms begin 3-9 days following DBA administration
- Symptoms increase in severity for 48-72 hours and last for 7-14 days
- High mortality rate (5-20%)

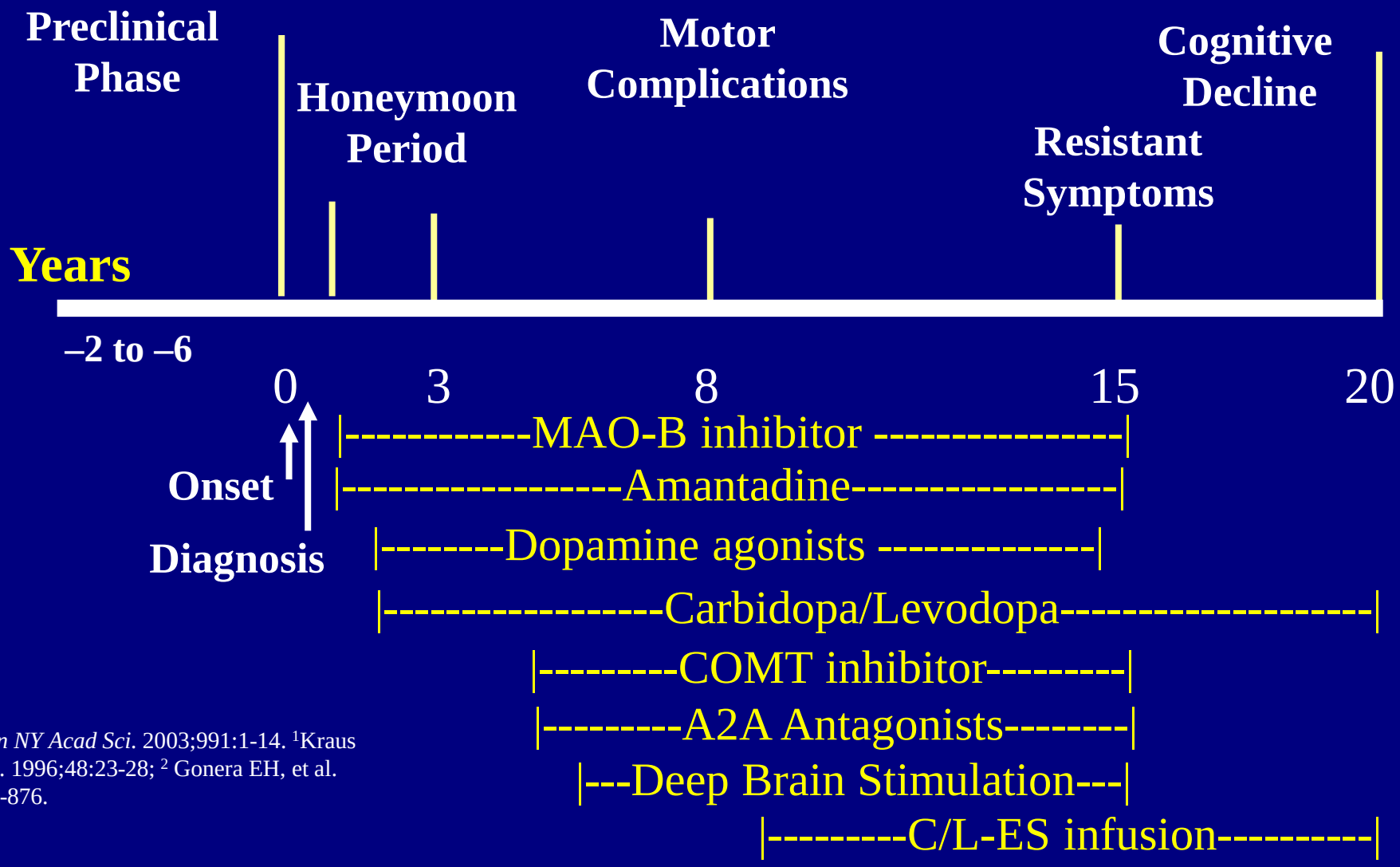
Watts RL, Koller WC. Movement Disorders: Neurologic Principles and Practice, McGraw Hill, 2004;
Jankovic J, Tolosa E. Parkinson's Disease and Movement Disorders. Lippincott Williams & Wilkins, 2007

Serotonin Syndrome

- Caused by medications that enhance serotonin transmission
  - MAOI, SSRI, SNRI, TCA antidepressants, buspirone, opiates (except morphine), lithium, triptans, amphetamine, etc
- Withdrawal of causative agent
- Supportive Care
- Treatment with serotonin antagonist
  - Cyproheptadine up to 32 mg/day

Watts RL,Standaert D, Obeso JA. Movement Disorders 3rd Edition, McGraw Hill, 2011;
Jankovic J, Tolosa E. Parkinson's Disease and Movement Disorders. Lippincott Williams & Wilkins, 2007

Typical Clinical Course of PD



Adapted from Fahn S. *Ann NY Acad Sci.* 2003;991:1-14. [1]Kraus P. *J Neural Transm Suppl.* 1996;48:23-28; [2] Gonera EH, et al. *Mov Disord.* 1997;12:871-876.

Non-motor Symptoms of PD

Autonomic

- Orthostatic hypotension
- Sialorrhea
- Urinary problems
- Sexual problems
- Sweating and thermoregulation
- Seborrheic dermatitis

GI

- Esophogeal dysmotility
- Gastroparesis
- Constipation
- Weight loss

Sensory

- Hyposmia
- Pain
- Paresthesia

Sleep disorders

- Insomnia
- Sleep fragmentation
- REM Behavior Disorder
- Vivid dreams
- Restless legs syndrome, PLMS
- Excessive daytime sleepiness
- Fatigue
- Non-REM sleep movements

Psychiatric

- Dementia, MCI
- Psychosis
- Apathy
- Compulsive disorders
- Mood depressed, anxiety

Some Nonmotor Symptoms May Be Non-Dopaminergic

- NOH – norepinephrine
- PDP – serotonin, glutamate
- Sialorrhea – acetylcholine
- Constipation – prostaglandins, ghrelin
- EDS – histamine
- RBD - gaba
- Depression – serotonin, norepinephrine
- Cognition – acetylcholine

Drug	Droxidopa	Midodrine	Fludrocortisone
MOA	▪ NE prodrug ▪ Conversion to NE induces vasoconstriction and increases BP	▪ α1-adrenoreceptor agonist prodrug ▪ Raises BP by increasing vascular resistance	▪ Raises BP by increasing intravascular volume via renal sodium reabsorption
Indication	▪ Treatment of symptomatic NOH	▪ Treatment of symptomatic OH	▪ No labelled indication for OH/nOH[a]
Dosage	▪ 100–600 mg TID	▪ 10 mg TID	▪ 0.1–0.2 mg/day; off-label use
PD/PK data	▪ Droxidopa $t_{1/2}$, 2.5 h ▪ Droxidopa t_{max}, 2 h ▪ Peak pressor effect 3.5 h after dosing	▪ Midodrine $t_{1/2}$, 3–4 h ▪ Midodrine t_{max}, 1–2 h ▪ Peak effects: 1 h after dosing	▪ Fludrocortisone plasma $t_{1/2}$: ≥3.5 h; biological half-life: 18–36 h ▪ Peak effects: days
Summary of positional BP effects	▪ Standing↑ ▪ Seated↑ ▪ Supine↑	▪ **Standing↑↑** ▪ **Seated↑↑** ▪ **Supine↑↑**	▪ Standing↑ ▪ Seated↑↑ ▪ Supine↑↑↑
Common AEs	▪ Headache ▪ Dizziness ▪ Nausea	▪ Supine and seated hypertension ▪ Paresthesia and pruritus (scalp) ▪ Piloerection	▪ Supine Hypertension ▪ Pedal Edema, Congestive heart failure ▪ Potassium loss

Package inserts

Treatment of PD Dementia & Non-Dementia Cognitive Impairment

TABLE 5. Interventions to treat dementia and nondementia cognitive impairment in PD

Intervention				
Drug class/intervention strategy	Drug/intervention	Efficacy	Safety	Practice implications
Dementia				
Acetylcholinesterase inhibitors	**Donepezil**	Insufficient evidence	Acceptable risk without specialized monitoring[a]	*Possibly useful*[b]
	Rivastigmine	Efficacious	Acceptable risk without specialized monitoring[a]	Clinically useful
	Galantamine	Insufficient evidence	Acceptable risk without specialized monitoring[a]	*Possibly useful*[c]
N-methyl-D-aspartate (NMDA) antagonists	Memantine	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
Nondementia cognitive impairment				
Acetylcholinesterase inhibitors	**Rivastigmine**	*Insufficient evidence*	*Acceptable risk without specialized monitoring*[d]	*Investigational*
Monoamine oxidase B (MAO-B) inhibitors	**Rasagiline**	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
Nonpharmacological Interventions	**Transcranial direct-current stimulation (T-DCS)**	*Insufficient evidence*	*Insufficient evidence*	*Investigational*
	Cognitive rehabilitation	*Insufficient evidence*	*Insufficient evidence*	*Investigational*

RCTs, randomized controlled trials.
[a]See Table 1.
[b]Refers to donepezil 10 mg; although RCTs to treat dementia in PD with donepezil report conflicting data for efficacy, the practice implication for donepezil is "possibly useful" because of the proven antidementive efficacy and license outside of PD.
[c]Although there is "insufficient evidence" for galantamine to be rated for the treatment of dementia in PD, the practice implication is "possibly useful" because of the proven antidementive efficacy and license outside of PD. Moreover, there were positive signals in favor for galantamine in the trial performed for PD dementia.
[d]See Table 3.

Mov Disord 2019;34:180-198

Parkinson's Disease Psychosis - Treatment Options

Relative Receptor-Binding Affinities of Selected Atypical Antipsychotics		
Agent	**D2 Receptor**	**5-HT2A**
Pimavanserin	None	Very high affinity
Risperidone	Very high affinity	Very high affinity
Olanzapine	Moderate affinity	Very high affinity
Quetiapine	Low affinity	Low affinity
Clozapine	Low affinity	Very high affinity

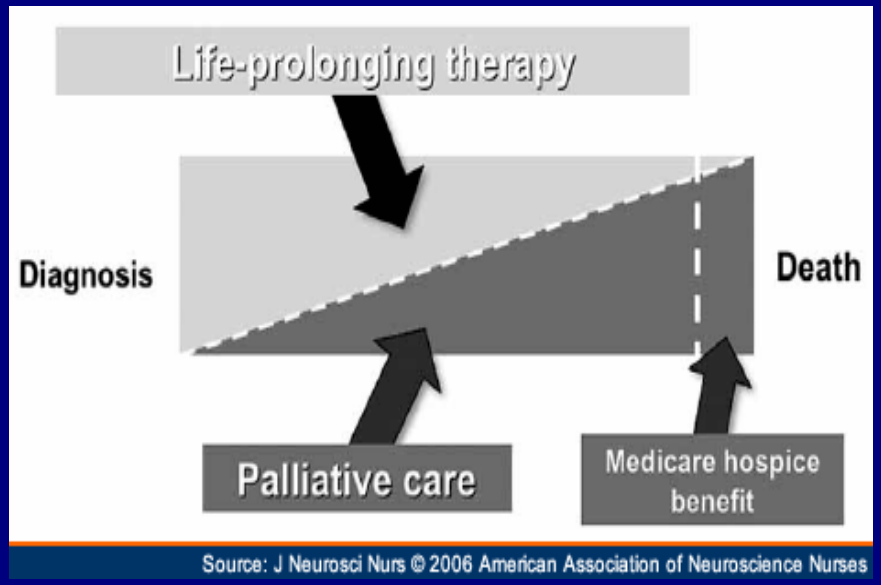
D2 = Dopamine; 5-HT2A = Serotonin

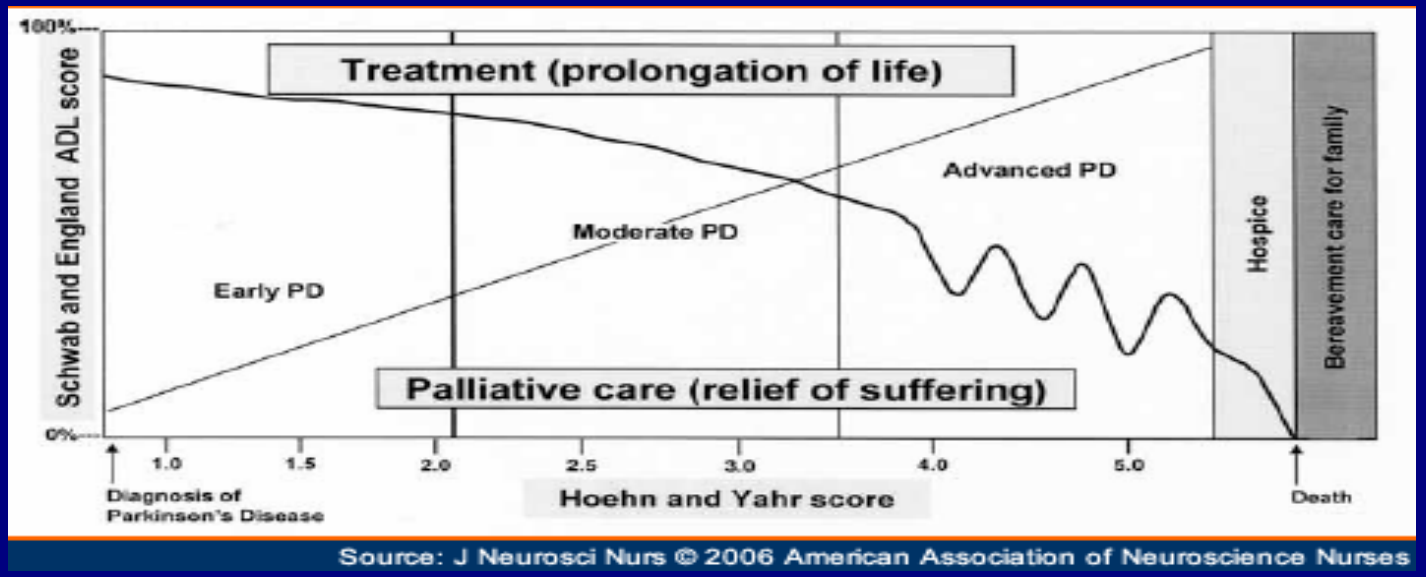
Interventions to Treat Psychosis in PD: MDS Recommendations			
Drug	Efficacy	Safety[a]	Practice Implications
Clozapine	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
Olanzapine	Not efficacious	Unacceptable risk	Not useful
Quetiapine	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful[b]
Pimavanserin	Efficacious	Acceptable risk without specialized monitoring[c]	Clinically useful

Should Not Be Used in Parkinson's Disease Psychosis	
All typical antipsychotics	Significant worsening of PD symptoms
Aripiprazole	Inconsistent efficacy and worsening of PD symptoms
Olanzapine	No efficacy and worsening of PD symptoms
Risperidone	Some efficacy but worsening of PD symptoms
Ziprasidone	Insufficient evidence for efficacy and tolerability, but has limited use due to cardiac side effects and should be avoided

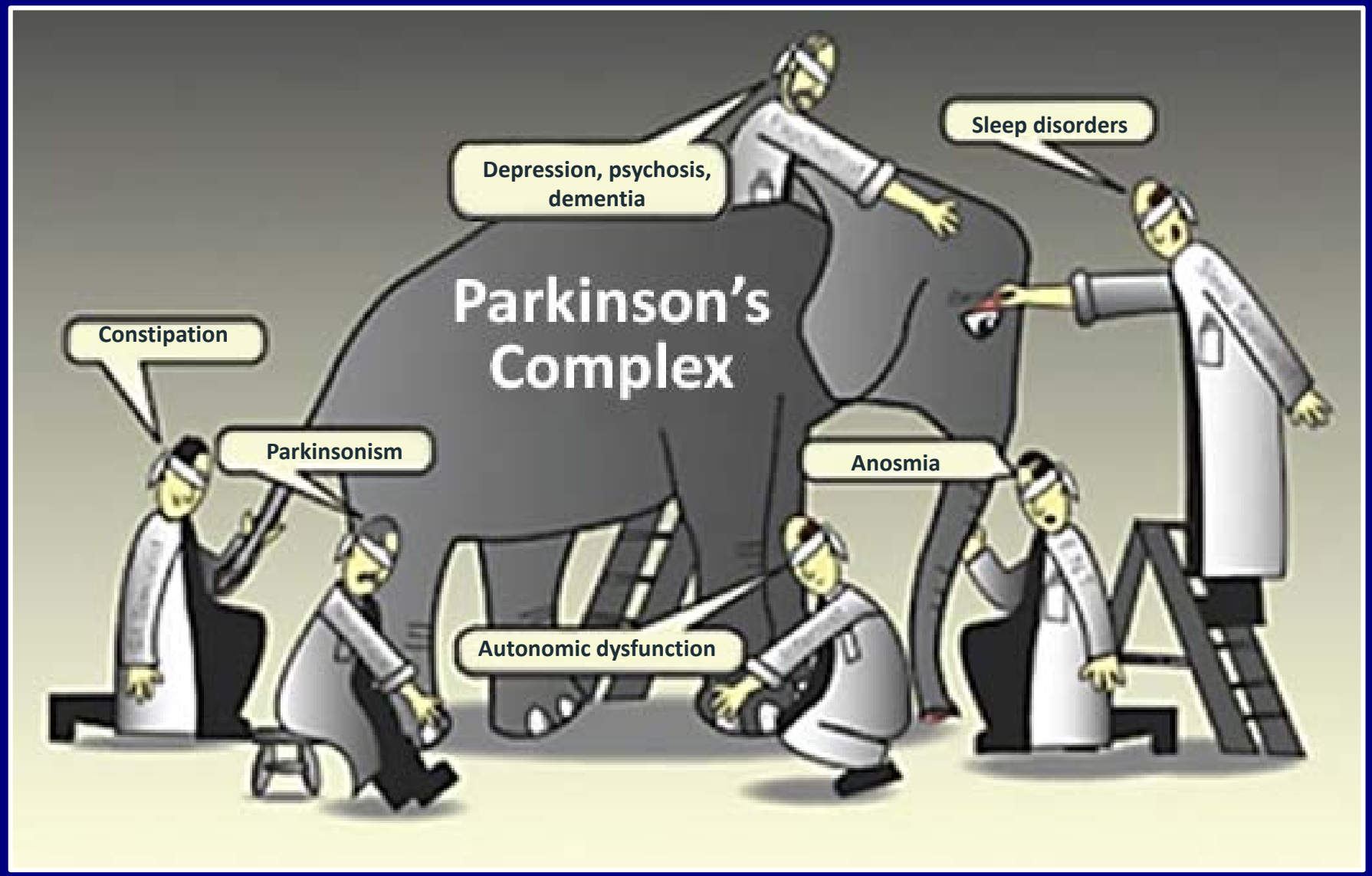
Casey DE, Zorn SH. J Clin Psychiatry 2001;62(suppl 7):4-10;
Pahwa R, Lyons KE, US Neurology, 2016;12(2):93-97;
Movement Disord 2019;34:180-198

Parkinson Disease: Palliative Care





Multidisciplinary Approach to PD



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