

Update on Parkinson's disease and other Movement Disorders

October 2018

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Disclosures:

Honoraria – UCB, Britannia, Allergan, AbbVie

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Dr. Evans' use of the Parkinson's Kinetigraph has been made possible by an unrestricted service development grant from Britannia pharmaceuticals and AbbVie

Overview and Objectives

- To provide an update on the current “state of the art” in the diagnosis and management of PD
- To look at the therapeutic landscape in PD – new therapies, novel therapies and future therapies
- To look at the natural history of the condition, the natural history and prognosis of PD in the era of effective therapy
- To provide a framework for understanding non-PD movement disorders
- To attempt to relate some of these insights to the practise of occupational medicine!

This is not designed to be comprehensive
Introduce terms you may find in e.g. correspondence from Neurologists,
and allow you to “talk-the-talk” of Movement Disorders

The “Update” in Neurology!



The “Update” in Neurology!

The True Take Home Slide for PD - 2018



Novel MAO-B inhibitor: Safinamide

Ongentys 50 mg
hard capsules/Hartkapseln
opicapone/Opicapone
oral use/Zum Einnehmen



30 hard capsules/Hartkapseln



Novel COMT inhibitor: Opicapone



Pr **Duodopa**[®]
LEVODOPA/CARBIDOPA INTESTINAL GEL

Epidemiology

Present in all populations and territories without any major ethno-geographic variations in Incidence

Incidence: 6-10/100,000 person years

Prevalence: 60-180/100,000 person years

Incidence increases with age – 1-2% prevalence in the over 70s (UK) and rising

Incidence is higher in Males – Approx 1.3:1, but differences in population structure mean greater numbers of female patients

Occupational
aspects! -

J Neurol (2015) 262:2171–2176
DOI 10.1007/s00415-015-7828-y

ORIGINAL COMMUNICATION

Artistic occupations are associated with a reduced risk of Parkinson's disease

Charlotte A. Haaxma^{1,2} · George F. Borm³ · Dimitri van der Linden⁴ ·
Arnoud C. Kappelle¹ · Bastiaan R. Bloem^{1,2}

Professional occupation and the risk of Parkinson's disease

S. K. L. Darweesh^{a,b,c,d} , M. K. Ikram^{a,e}, M. J. Faber^{c,d}, N. M. de Vries^{c,d}, C. A. Haaxma^{c,d},
A. Hofman^{a,b}, P. J. Koudstaal^e, B. R. Bloem^{c,d} and M. A. Ikram^a

*European Journal of
Neurology* 2018, **0**: 1–7

Epidemiology

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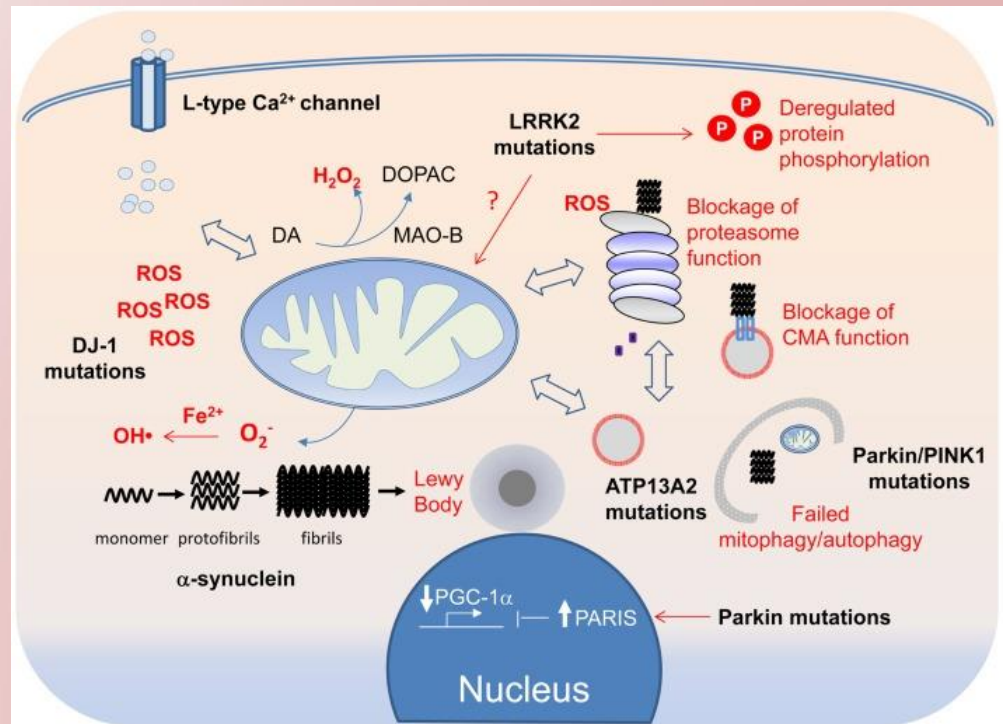
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- The aetiology of PD is unknown (Idiopathic)
- Rare monogenic forms of PD that have made a disproportionate contribution to our understanding of the pathogenesis of PD: An ***“alpha-synucleinopathy”***
- In sporadic PD, genetic factors account for some of the variation we see in phenotype and progression



PARKINSON'S MEDICAL QUESTIONNAIRE

PK1 ONLINE
Rev Jul 17

1 Your condition

1.1 How long have you been diagnosed with Parkinson's?

- ☐ Less than one year ☐ 1 year to 3 years
☐ 3 years to 13 years ☐ More than 13 years

1.2 Do you experience episodes of slowing up (off periods or freezing)?

You should not drive when you are likely to experience off periods or freezing

- ☐ Yes ☐ No → Go to 1.4

1.3 If yes, are these periods sudden and unpredictable?

- ☐ Yes ☐ No

1.4 Due to your Parkinson's do you experience sleepiness that affects safe driving?

- ☐ Yes ☐ No

1.5 Have you been advised by a healthcare professional that you have memory loss problems, episodes of confusion or difficulty with concentrating that affects safe driving?

A healthcare professional could be your GP, consultant or nurse

- ☐ Yes ☐ No

1.6 Have you had an on-road driving assessment in the last 3 years?

If yes, and you have a copy, please enclose it with this form

- ☐ Yes ☐ No

2 Your Medication

2.1 Do you need to take medication for your Parkinson's?

- ☐ Yes ☐ No → Go to 3

2.2 If yes, does your medication make you drowsy or confused when driving?

You should not drive when you experience drowsiness or confusion as a result of taking your medication

- ☐ Yes ☐ No

NAME:	DOB:	REF:
DRIVER NUMBER:		

3 Healthcare Professional

3.1 Have you seen a healthcare professional about your Parkinson's in the last 9 months?

A healthcare professional could be your GP, consultant or specialist

- ☐ Yes ☐ No → Go to 4

3.2 If yes, who was the last healthcare professional you saw for your Parkinson's disease?

- ☐ GP ☐ Consultant / Nurse specialist at hospital clinic

4 Special Controls

4.1 As a result of your medical condition, do you have to drive a vehicle with automatic gears?

- ☐ Yes ☐ No

4.2 As a result of your medical condition, do you need to drive a vehicle with special controls?

- ☐ Yes ☐ No

4.3 Select any modifications that you need to drive a car

- ☐ Modified transmission (10) ☐ Modified clutch (15) ☐ Modified braking system (20)
☐ Modified accelerator system (25) ☐ Pedal adaptations and pedal safeguards (31) ☐ Combined service brake and accelerator systems (32)
☐ Combined service brake, accelerator and steering systems (33) ☐ Modified control layouts (35) ☐ Modified steering (40)
☐ Modified rear view mirror (42) ☐ Modified driver seat (43)

4.4 Select any modifications that you need to drive a motorcycle, moped or tricycle

- ☐ Single operated brake (44.01) ☐ Adapted front wheel brake (44.02) ☐ Adapted rear wheel brake (44.03)
☐ Adjusted accelerator (44.04) ☐ Adjusted manual transmission & clutch (44.05) ☐ Adjusted rear view mirror (44.06)
☐ Adjusted commands (light, indicators etc.) (44.07) ☐ Seat height (allows the driver to have two feet on the surface at once and balance the wheel when stopping/standing) (44.08)
☐ Adapted hand grip (44.12) ☐ Motorcycle with sidecar only (45)

NAME:	DOB:	REF:
DRIVER NUMBER:		

Diagnosis of PD:
Remains a clinical one

UK PDS Brain Bank Criteria:

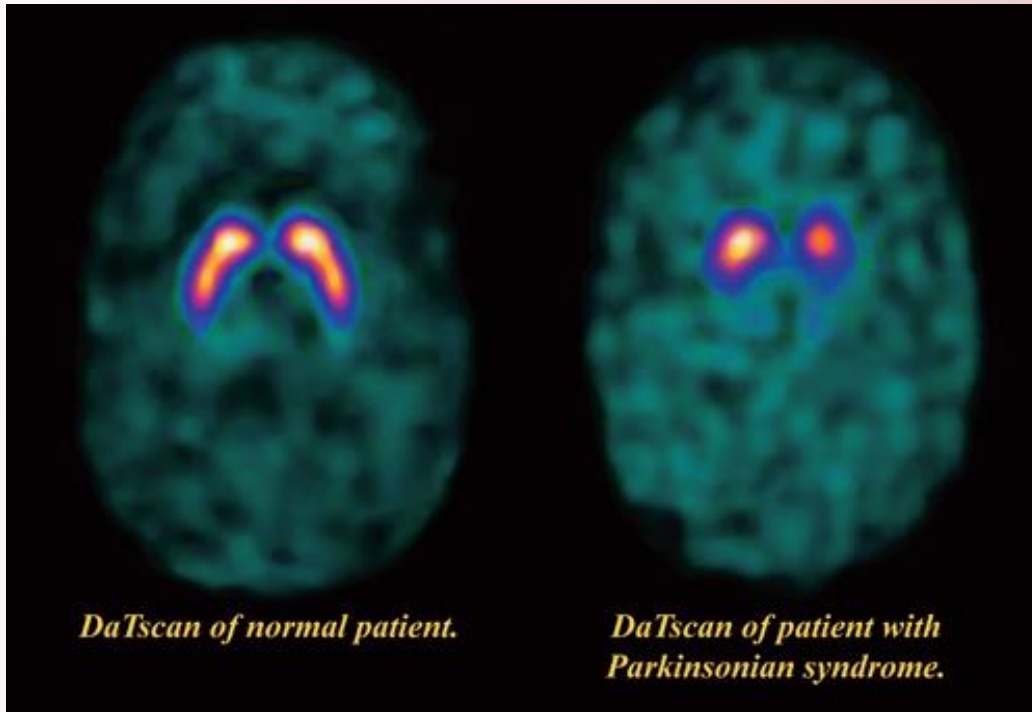
•**BRADYKINESIA**

•**RIGIDITY**

•**TREMOR**

•**POSTURAL INSTABILITY**

PLUS ONE OR MORE OF:



DATscan provides a (semi-)quantitative measure of pre-synaptic dopamine levels:

Good in theory but low sensitivity

Best seen as an ancillary test > diagnostic test

Diagnosis of PD:
Remains a clinical one

UK PDS Brain Bank Criteria:

•**BRADYKINESIA**

•**RIGIDITY**

•**TREMOR**

•**POSTURAL INSTABILITY**

PLUS ONE OR MORE OF:

What makes me suspicious? (and why)

- Symmetrical signs/symptoms



DRUG-INDUCED

- Prominent/early urinary symptoms



**AUTONOMIC FAILURE:
MULTIPLE SYSTEM
ATROPHY (MSA)**

- Early falls / “Wheelchair” sign



**POSTURAL INSTABILITY:
PROGRESSIVE
SUPRANUCLEAR PALSY (PSP)**

Diagnosis of PD:
Remains a clinical one

FOR NOW...

UK PDS Brain Bank Criteria:

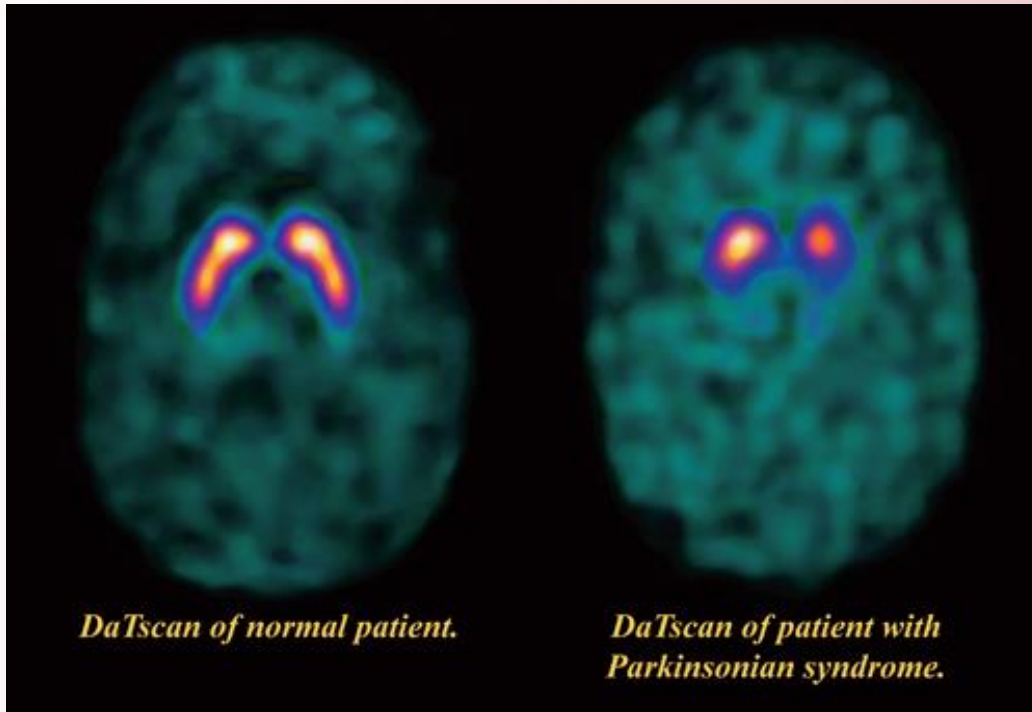
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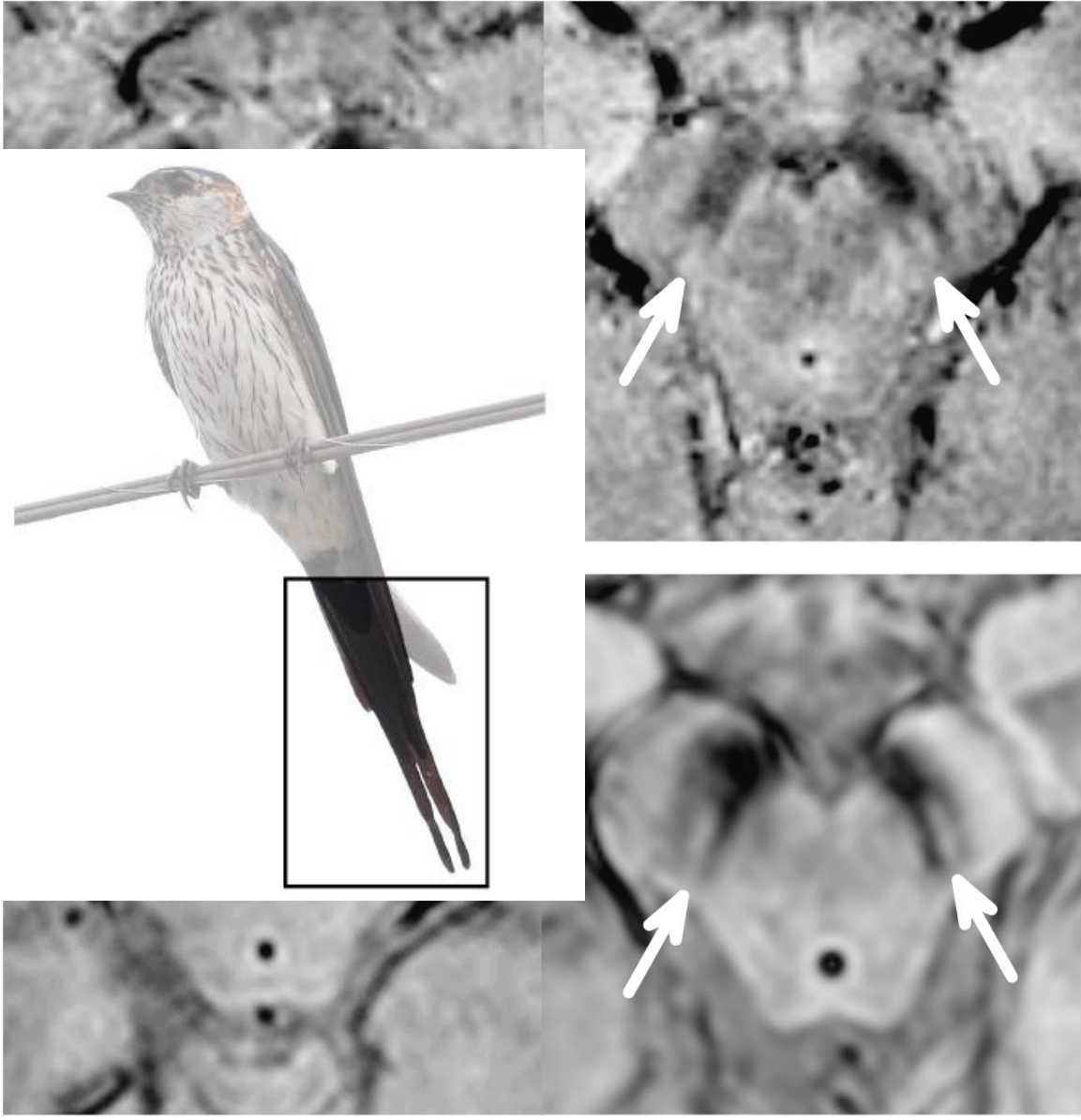
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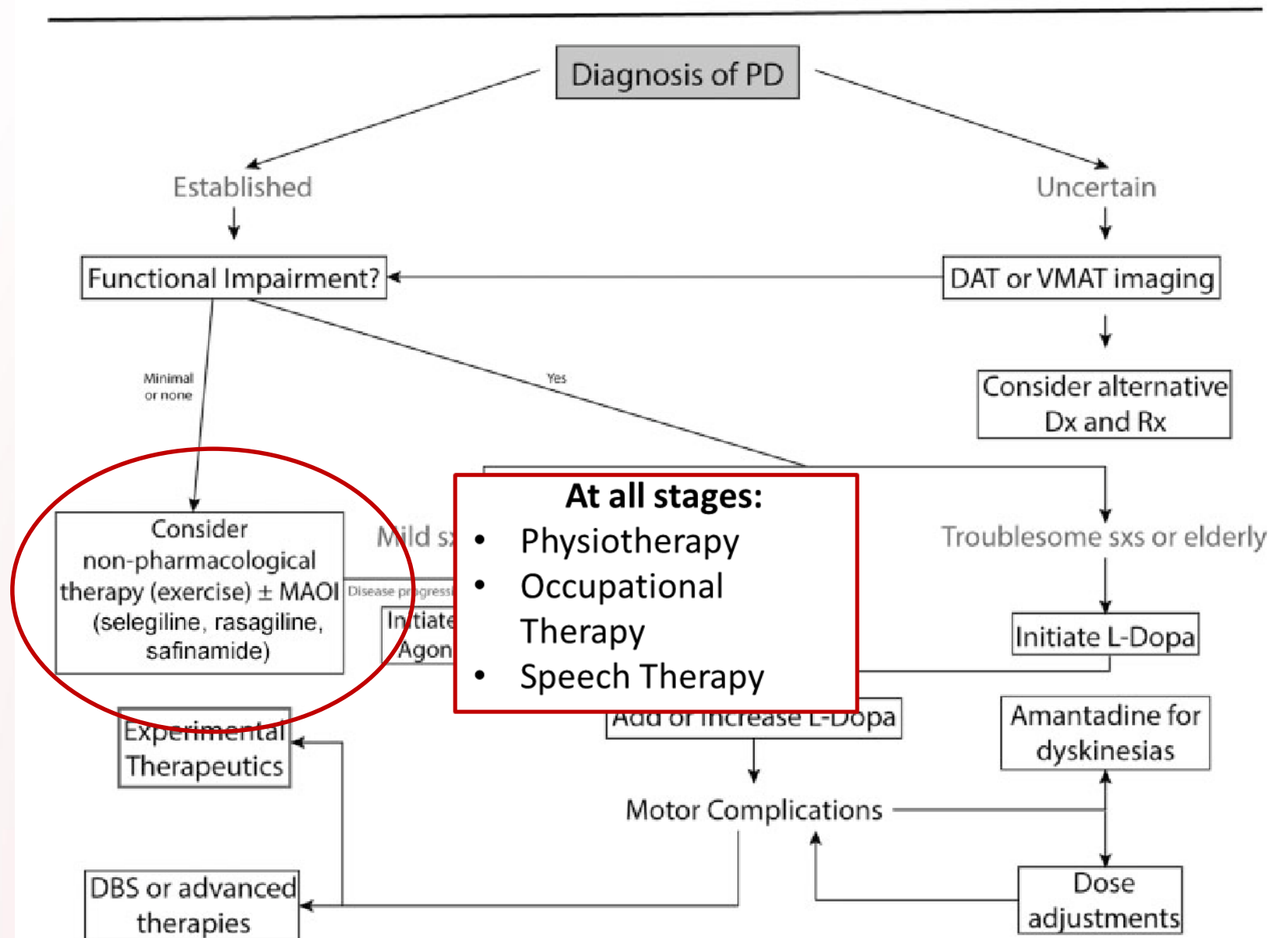


Nigrosome-1
imaging
SWI (T2*) at 3T
In PD (A – patient)
Versus Control (B)

Loss of the “Swallow
tail” indicating loss of
dopaminergic neurons
in SNpc

**PROVIDES POSITIVE
DIAGNOSTIC
EVIDENCE OF PD**

Treatment of PD: Overview

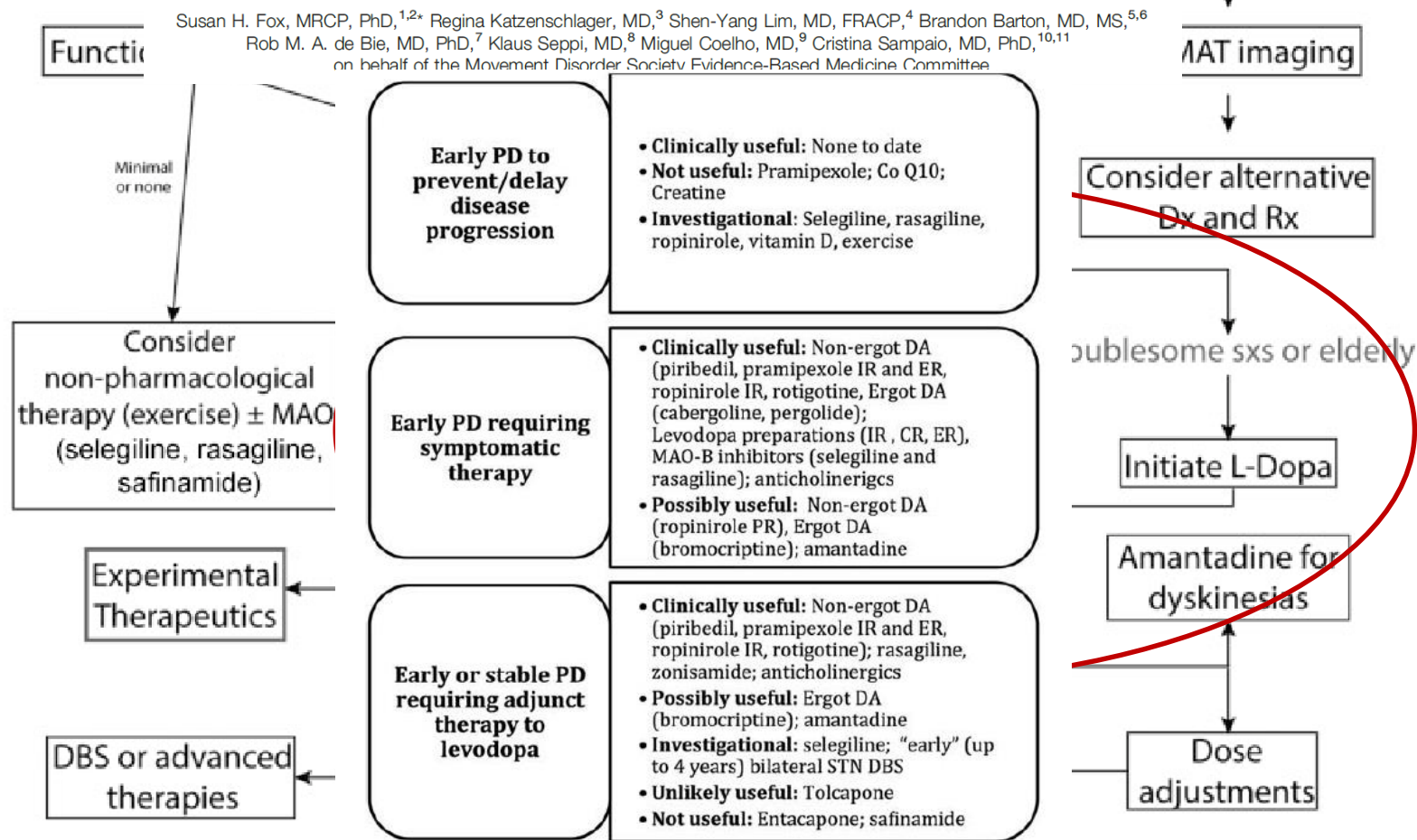


Treatment of PD: Overview

REVIEW

International Parkinson and Movement Disorder Society Evidence-Based Medicine Review: Update on Treatments for the Motor Symptoms of Parkinson's Disease

Susan H. Fox, MRCP, PhD,^{1,2*} Regina Katsenschlager, MD,³ Shen-Yang Lim, MD, FRACP,⁴ Brandon Barton, MD, MS,^{5,6}
Rob M. A. de Bie, MD, PhD,⁷ Klaus Seppi, MD,⁸ Miguel Coelho, MD,⁹ Cristina Sampaio, MD, PhD,^{10,11}
on behalf of the Movement Disorder Society Evidence-Based Medicine Committee



Pharmacotherapy in early PD:

Relative merits and de-merits

	ORAL AGONIST	TRANSDERMAL AGONIST	LEVODOPA	MAO INHIBITOR	AMANTADINE
AKINESIA	++	++	+++	+	+/-
TREMOR	++	++	++	+	++
PSYCHIATRIC	+ (?PPX)	+/-	+/-	+/-	--
SLEEP	+/-	++	+	+/-	--
IMPULSE CONTROL	--	-	+/-	+/-	+/-
"DISEASE-MODIFYING"	-	-	-	"ADAGIO"	-

Pharmacotherapy in early PD:

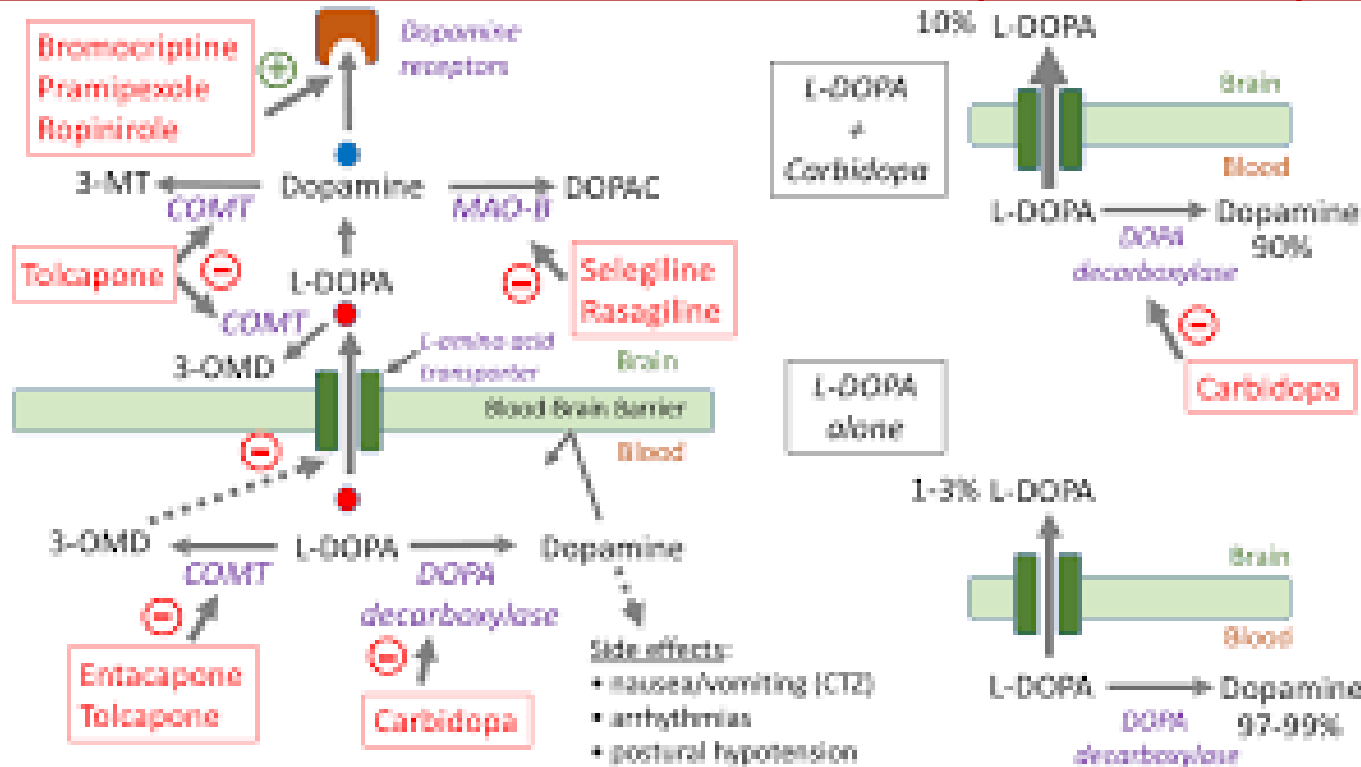
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AKINESIA	++	++	+++	+	+/-
TREMOR	++	++	++	+	++
PSYCHIATRIC	+ (?PPX)	+/-	+/-	+/-	--
SLEEP	+/-	++	+	+/-	--
IMPULSE CONTROL	--	-	+/-	+/-	+/-
"DISEASE-MODIFYING"	-	-	-	"ADAGIO"	-

Pharmacotherapy in early PD:

Relative merits and de-merits

	ORAL AGONIST	TRANSDERMAL AGONIST	LEVODOPA	MAO INHIBITOR	AMANTADINE
AKINESIA	Bromocriptine Pramipexole Ropinirole				
TREMOR					
PSYCHIATRI					
SLEEP					
IMPULSE CONTROL					
"DISEASE-MODIFYING"	-	-	-	"ADAGIO"	-



“To treat or Not to Treat?”
Rationale against delayed therapy in PD

1. Leaves patient with symptoms
2. Although a delay in e.g. dyskinesias can be achieved by using an agonist earlier, this effect is lost at ca. 5 years and comes at the expense of motor control
3. The incidence of dyskinesias is dose-dependent – in early disease low levels of therapy required therefore the incremental exposure to “exogenous” dopamine is small
4. Evidence from PD MED: Initiating Levodopa associated with better patient-rated (e.g. QOL) outcomes
5. For the “average” patient the incidence of developing motor complications is similar to that of developing dementia – dementia has a far more significant impact on QOL
6. We are improving in our management of motor complications in complex phase PD

PD-MED and Levodopa v DA agonist v MAOi as first Rx

Lancet 2014; 384: 1196-205 PD MED Collaborative Group*

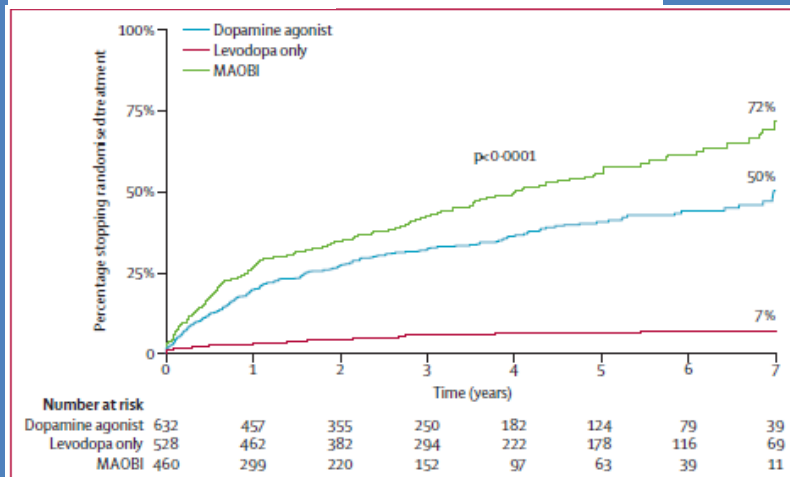


Figure 2: Proportion of patients stopping treatment with allocated drug class
MAOBI=monoamine oxidase type B inhibitors.

At 7 years LID relates were slightly higher in LD-initiated group, but motor fluctuations were not. LED was higher in the non-LD groups at 7 years. QOL measures at all time points showed a small but significant benefit favouring LD.

	Levodopa vs levodopa-sparing		Dopamine agonist vs MAOBI		MID*
	Estimate† (95% CI)	p value	Estimate‡ (95% CI)	p value	
Mobility	1.8 (0.5 to 3.0)	0.005	1.4 (0.0 to 2.9)	0.05	3.2
ADL	1.9 (0.7 to 3.0)	0.002	0.3 (-1.1 to 1.7)	0.7	4.4
Emotional wellbeing	-0.2 (-1.1 to 0.7)	0.7	0.3 (-0.8 to 1.4)	0.6	4.2
Stigma	1.3 (0.2 to 2.3)	0.02	1.3 (0.0 to 2.5)	0.06	5.6
Social support	0.1 (-0.6 to 0.8)	0.8	0.8 (-0.1 to 1.7)	0.07	11.4
Cognition	1.0 (0.0 to 2.0)	0.05	1.7 (0.5 to 2.9)	0.005	1.8
Communication	0.9 (0.0 to 1.8)	0.05	0.5 (-0.6 to 1.5)	0.4	4.2
Bodily discomfort	1.4 (0.3 to 2.4)	0.01	0.7 (-0.6 to 2.0)	0.3	2.1
Summary index	1.0 (0.3 to 1.7)	0.008	0.8 (0.0 to 1.7)	0.05	1.6
EQ-5D utility score	0.03 (0.01 to 0.05)	0.0002	0.004 (-0.01 to 0.02)	0.6	..

PDQ=Parkinson's disease questionnaire. MAOBI=monoamine oxidase type B inhibitor. ADL=activities of daily living.
*MID= minimally important difference. †Positive numbers favour levodopa. ‡Positive numbers favour MAOBI.

Table 2: Estimated average differences between levodopa and levodopa-sparing groups, and between dopamine agonist and MAOBI, in the different PDQ-39 subscales and in EQ-5D utility score

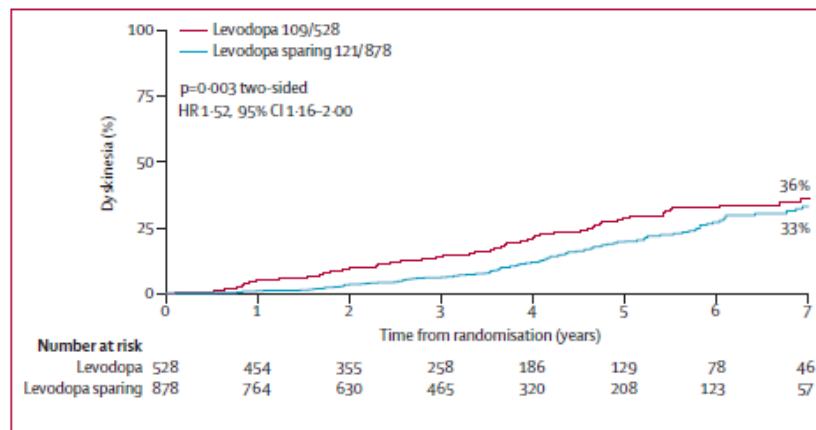
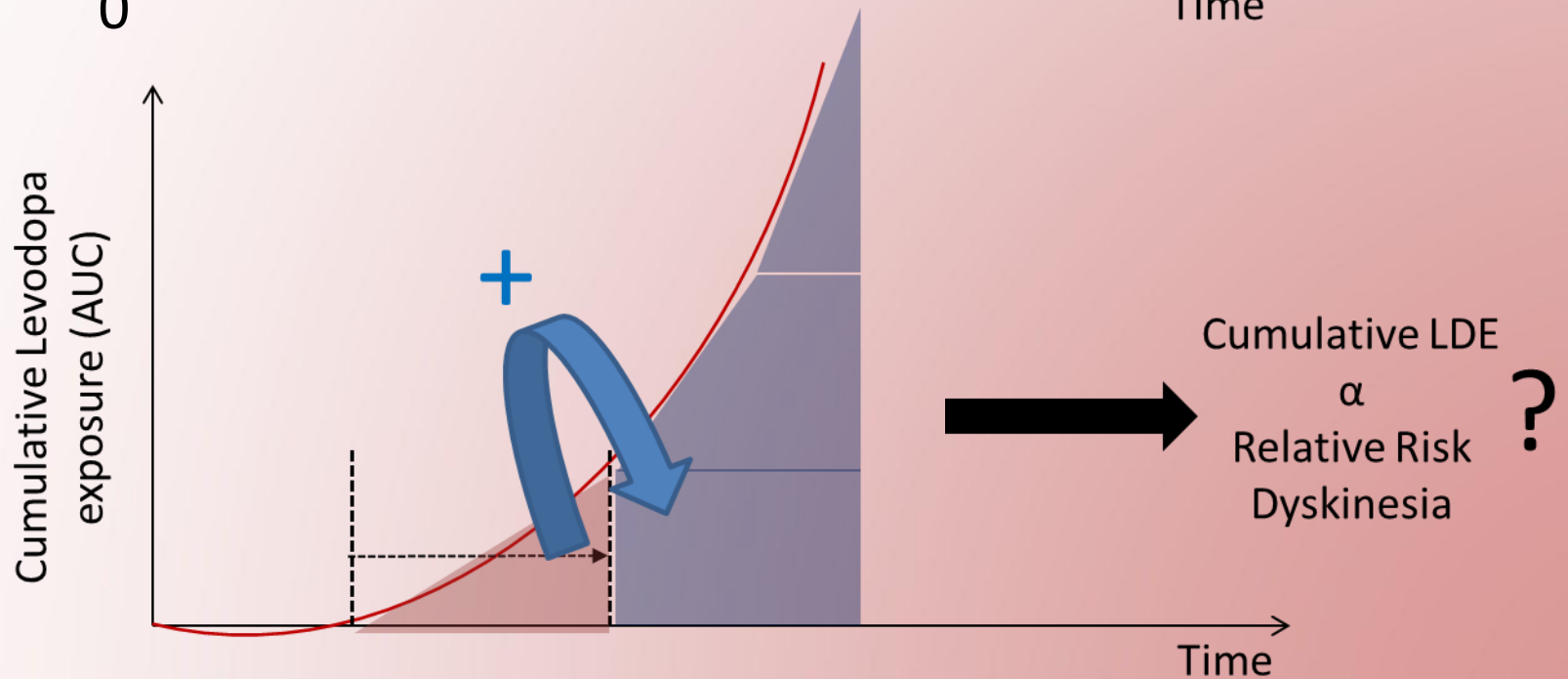
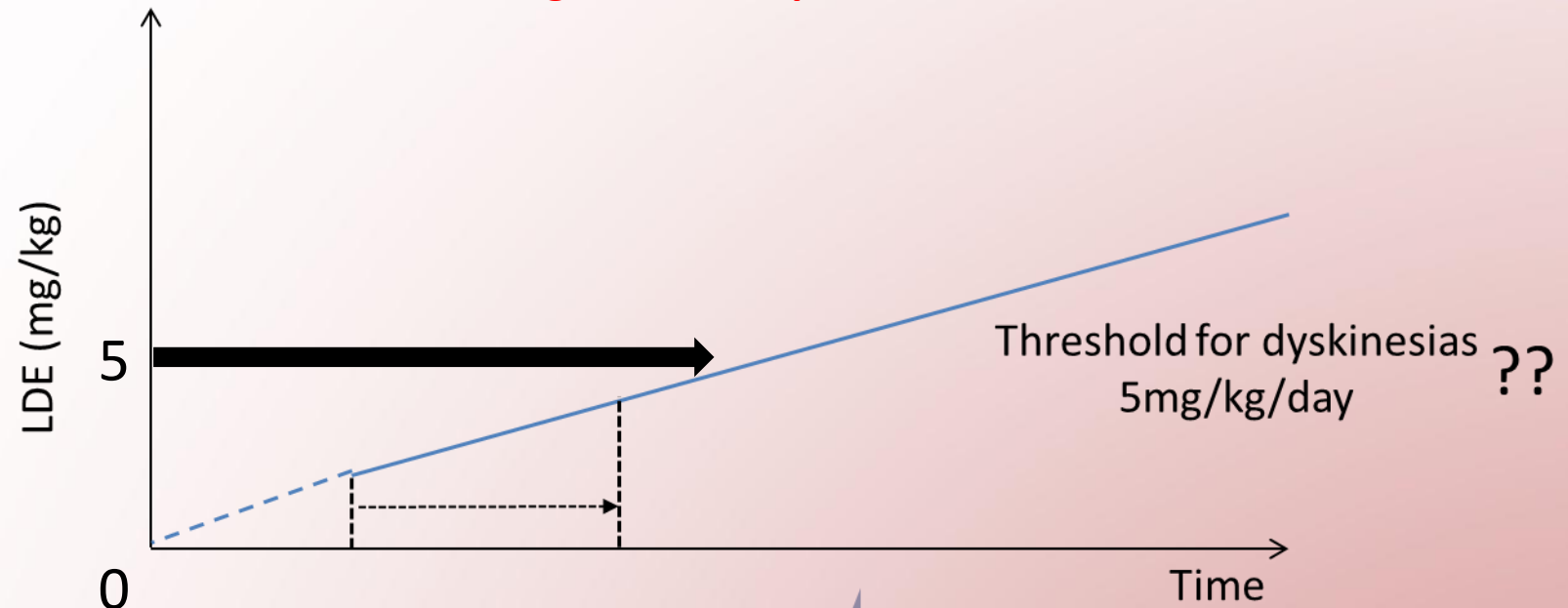


Figure 5: Risk of developing dyskinesia in levodopa and levodopa-sparing groups

“To treat or Not to Treat?”
Rationale against delayed therapy in PD

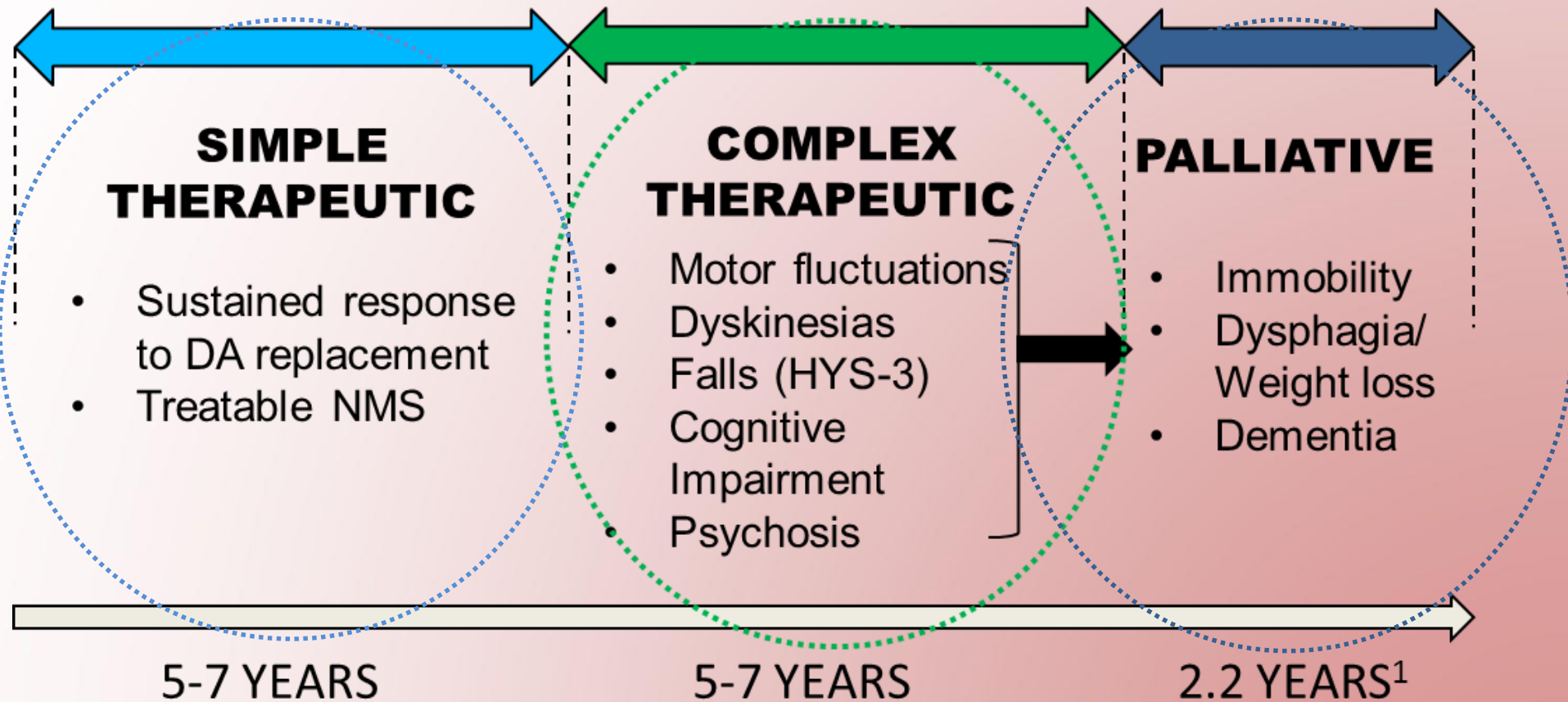
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Modelling motor complication risk in PD



When the going gets Tougher
What defines Progression in PD?:

Talking about (and modelling) the Natural history



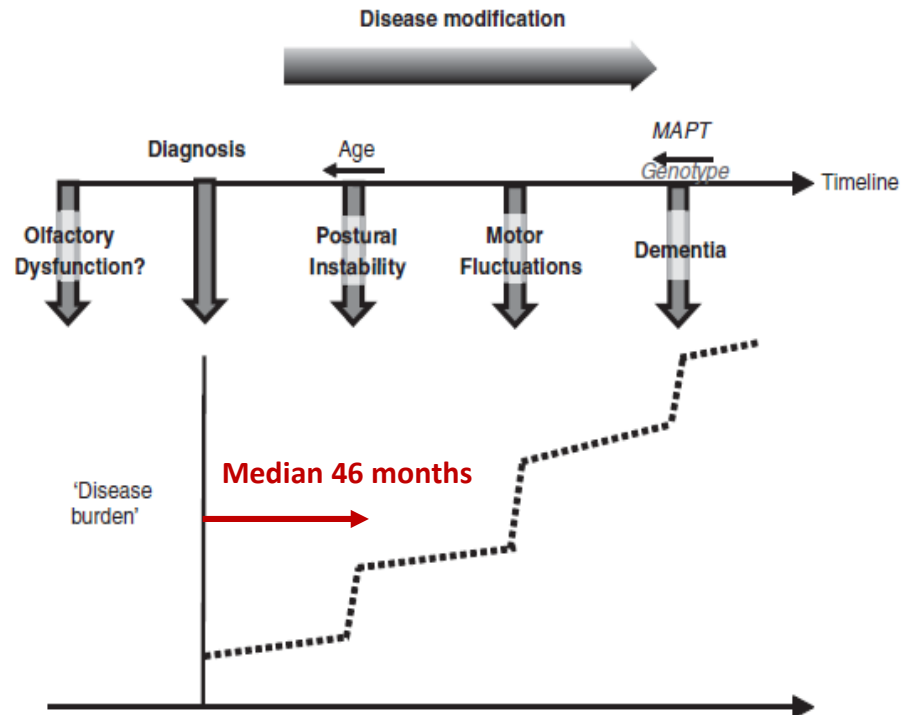
Posture/Gait

Tremor

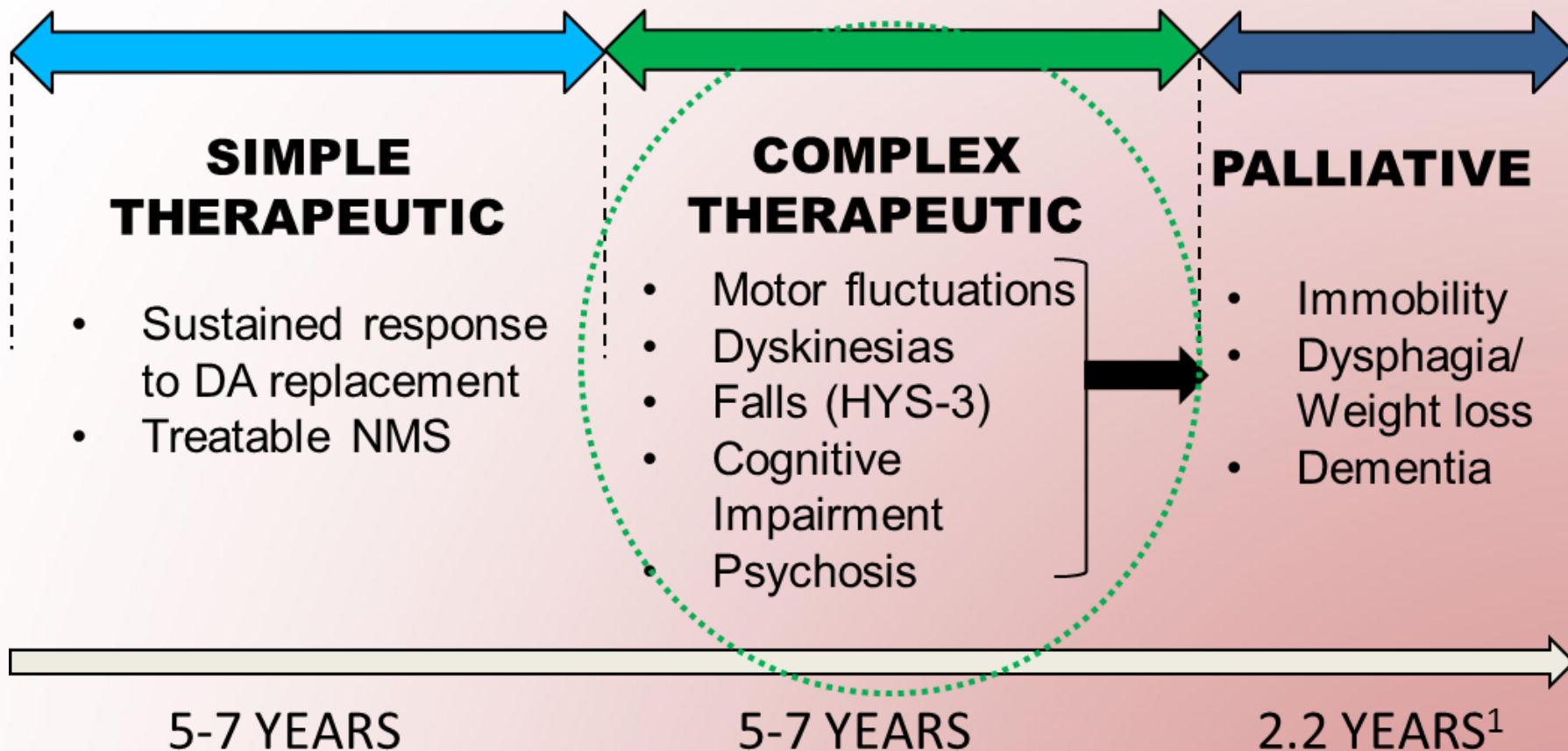
Bradykinesia

“Vector Model” of Progression – Postural/Gait disturbance evolves more rapidly – less responsive to (current) therapy

“Milestone Model” may be of utility in e.g. defining outcome measures in trials of putative disease-modifying treatments



THERAPY IN THE “COMPLEX PHASE” OF PD



Our major advances in improving management of patients with PD have been around better identifying, assessing and their condition when it enters the complex phase

International Parkinson and Movement Disorder Society Evidence-Based Medicine Review: Update on Treatments for the Motor Symptoms of Parkinson's Disease

Susan H. Fox, MRCP, PhD,^{1,2*} Regina Katschenschlager, MD,³ Shen-Yang Lim, MD, FRACP,⁴ Brandon Barton, MD, MS,^{5,6}
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on behalf of the Movement Disorder Society Evidence-Based Medicine Committee

ON +
LIDS

ON

OFF

Treating motor fluctuations

- **Clinically useful:** Non-ergot DA (pramipexole; ropinirole; rotigotine; apomorphine intermittent injections, pergolide); levodopa ER; COMT inhibitors (entacapone; opicapone); MAO-B inhibitors (rasagiline, safinamide; zonisamide); LCIG; bilateral DBS surgery (STN or GPi)
- **Possibly useful:** Ergot DA (bromocriptine, cabergoline); istradefylline; tolcapone; Non-ergot DA (apomorphine infusion)

Treating dyskinesia

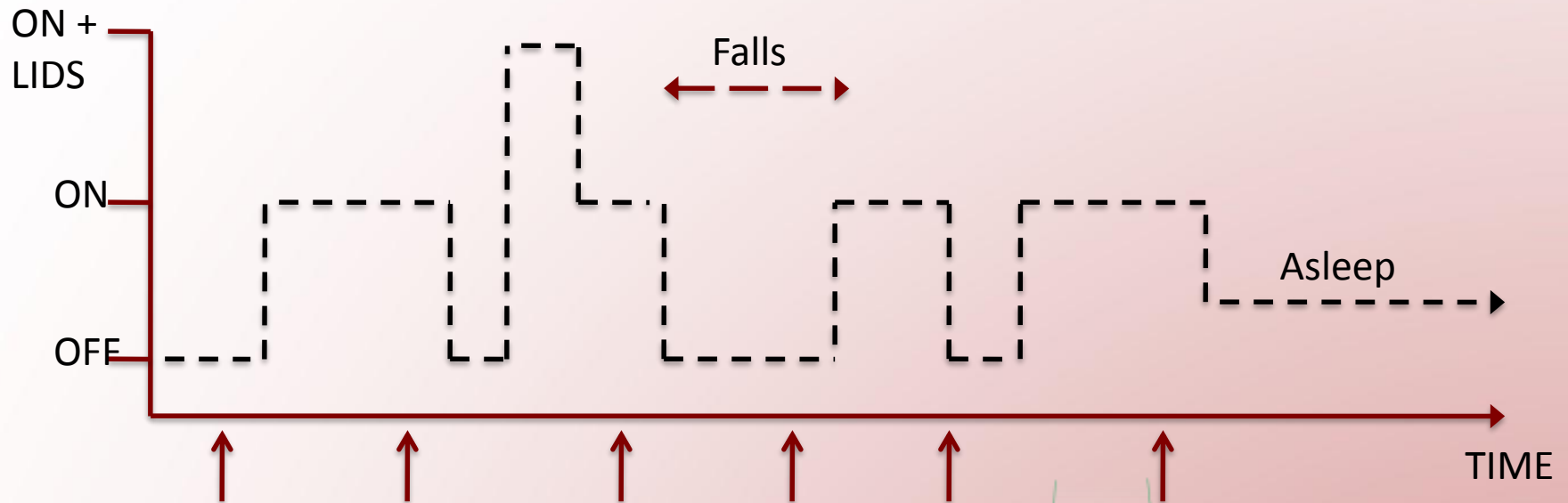
- **Clinically useful:** Amantadine; clozapine; LCIG; bilateral DBS surgery (STN or GPi); unilateral pallidotomy

Treating specific/ general motor symptoms

- **Clinically useful:** Physiotherapy
- **Possibly useful:** Rivastigmine (gait and balance); Exercise-based movement strategy training (gait and balance); formalized patterned exercises (gait and balance); speech therapy (speech and swallowing); occupational therapy; thalamic surgery (DBS or thalamotomy) (tremor)
- **Investigational:** Donepezil (gait and balance); methylphenidate (gait and balance); memantine (gait and balance) cannabidiol; technology-based movement strategies; acupuncture; rTMS; tDCS

Asleep

TIME



Pharmacological options:

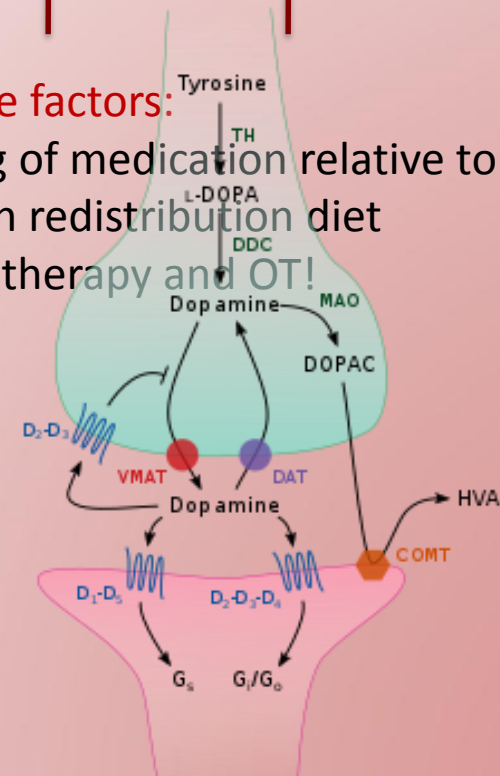
- Increase one or more Levodopa IR doses
- Decrease Levodopa IR spacing
- Combine Agonist with Levodopa (and vice versa)
- Add COMT inhibitor
- Add MAO inhibitor

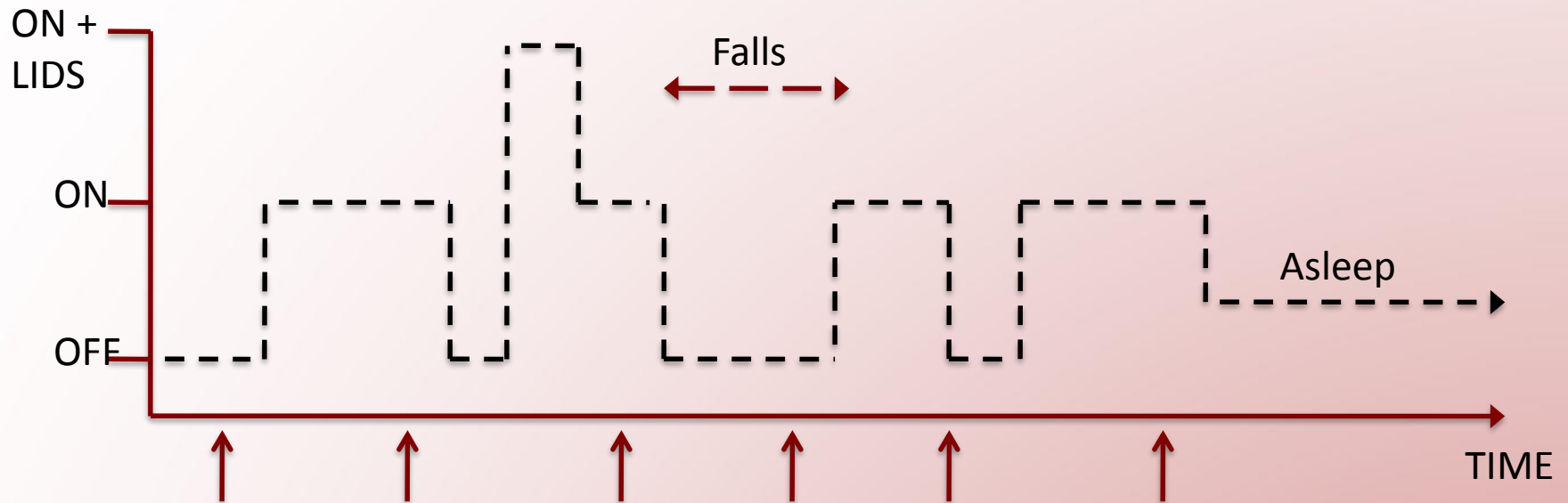
“Rescue” therapy

- Dispersible Madopar
- Apomorphine subcutaneous (“Apo-Go”)

Lifestyle factors:

- Timing of medication relative to meals
- Protein redistribution diet
- Physiotherapy and OT!



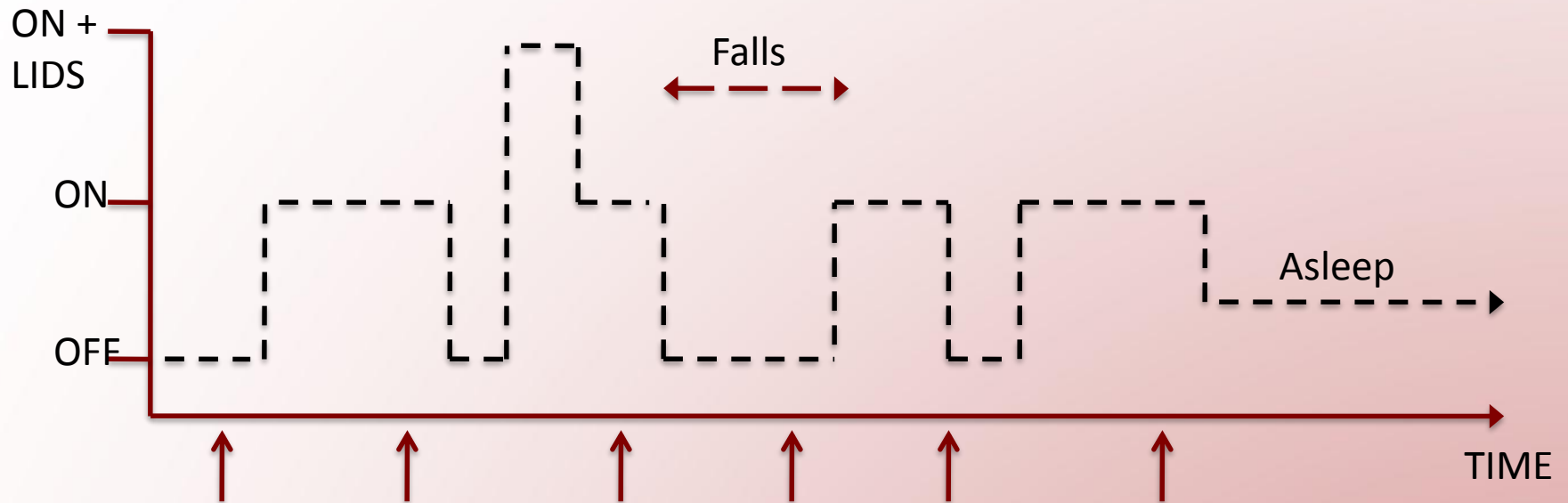


Parkinson's Kinetigraph (PKG)

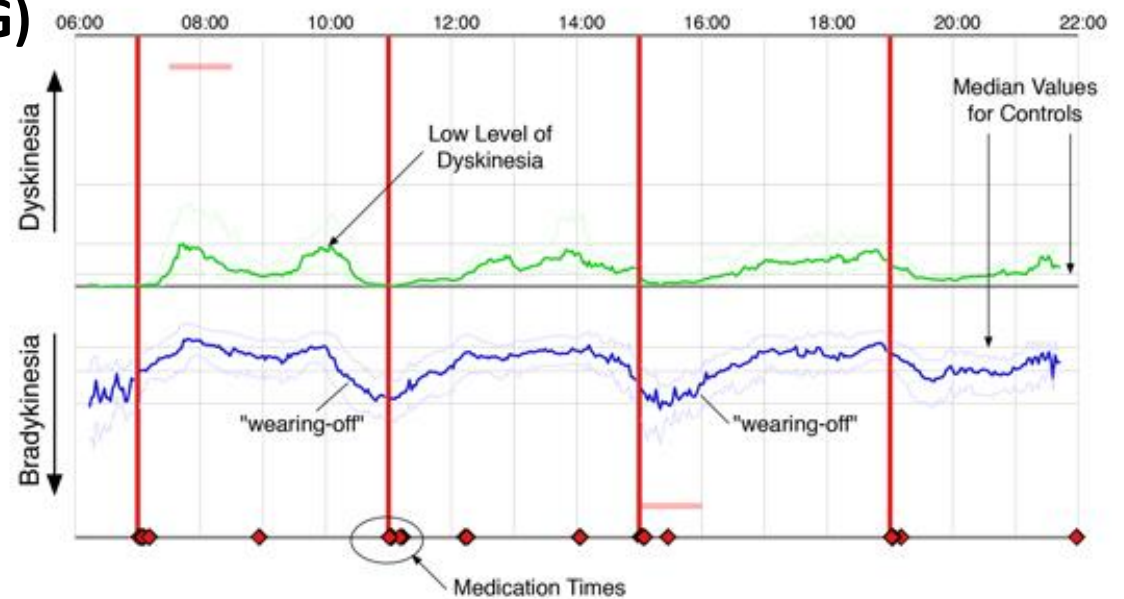


Objective evaluation of motor PD over a 6 day epoch

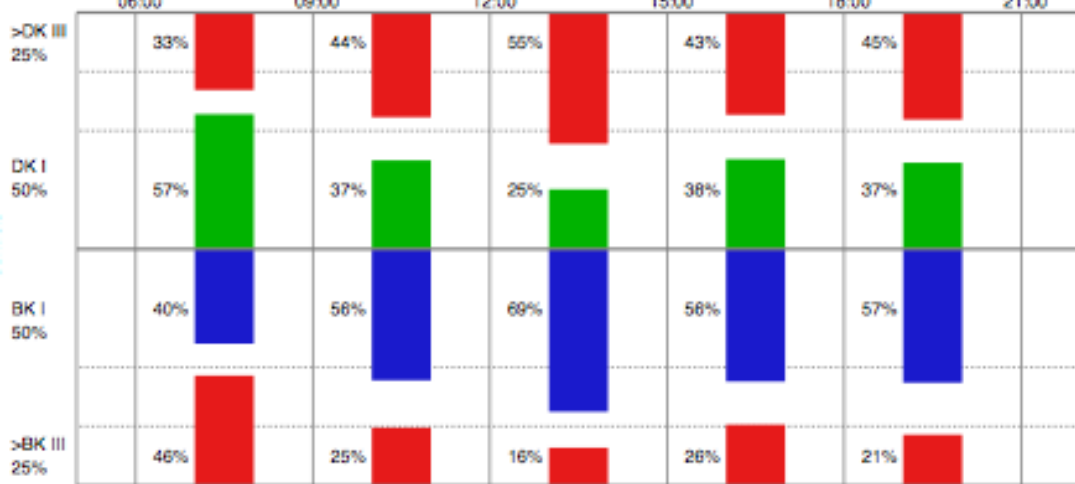
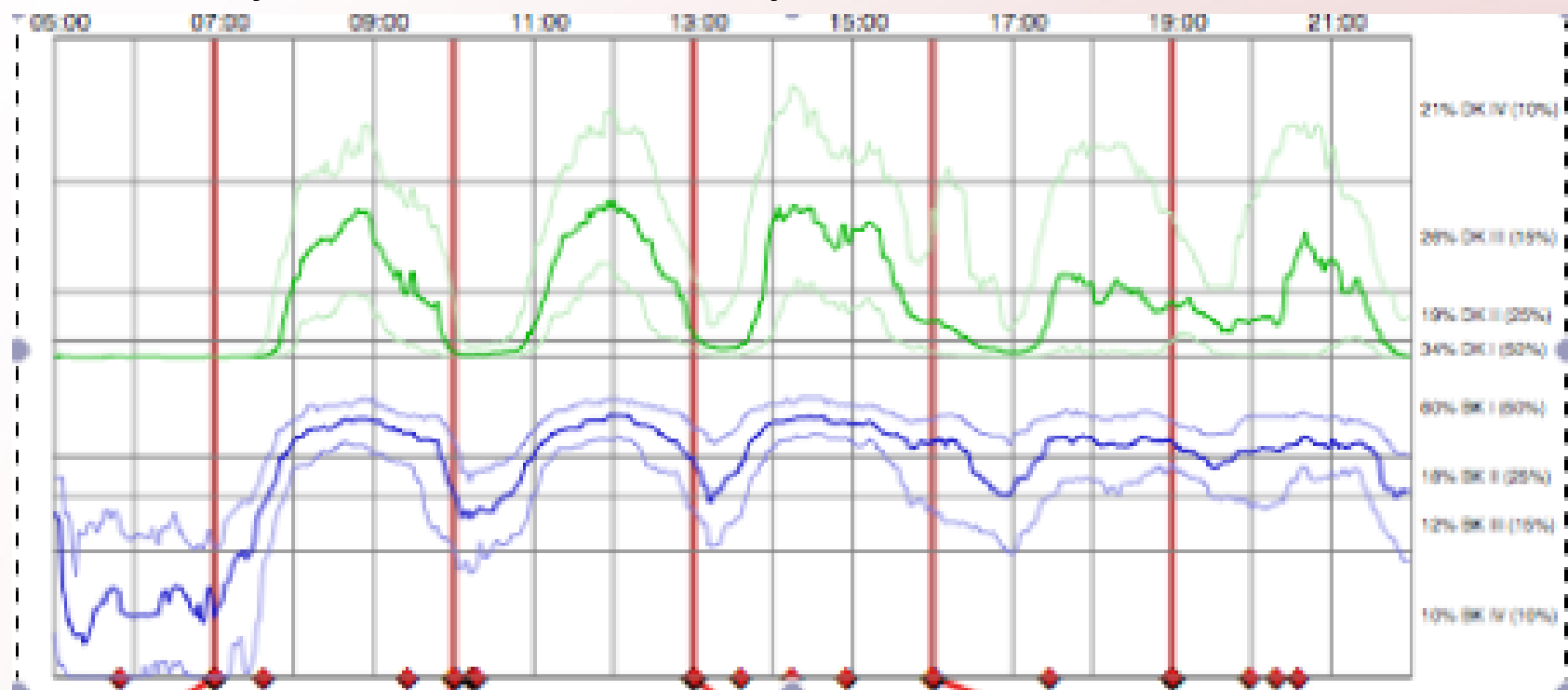
- Medication response
- Wearing Off – predictable vs unpredictable,
- Nature and extent of LIDS
- Where the history and the examination don't match up!



Parkinson's Kinetigraph (PKG)

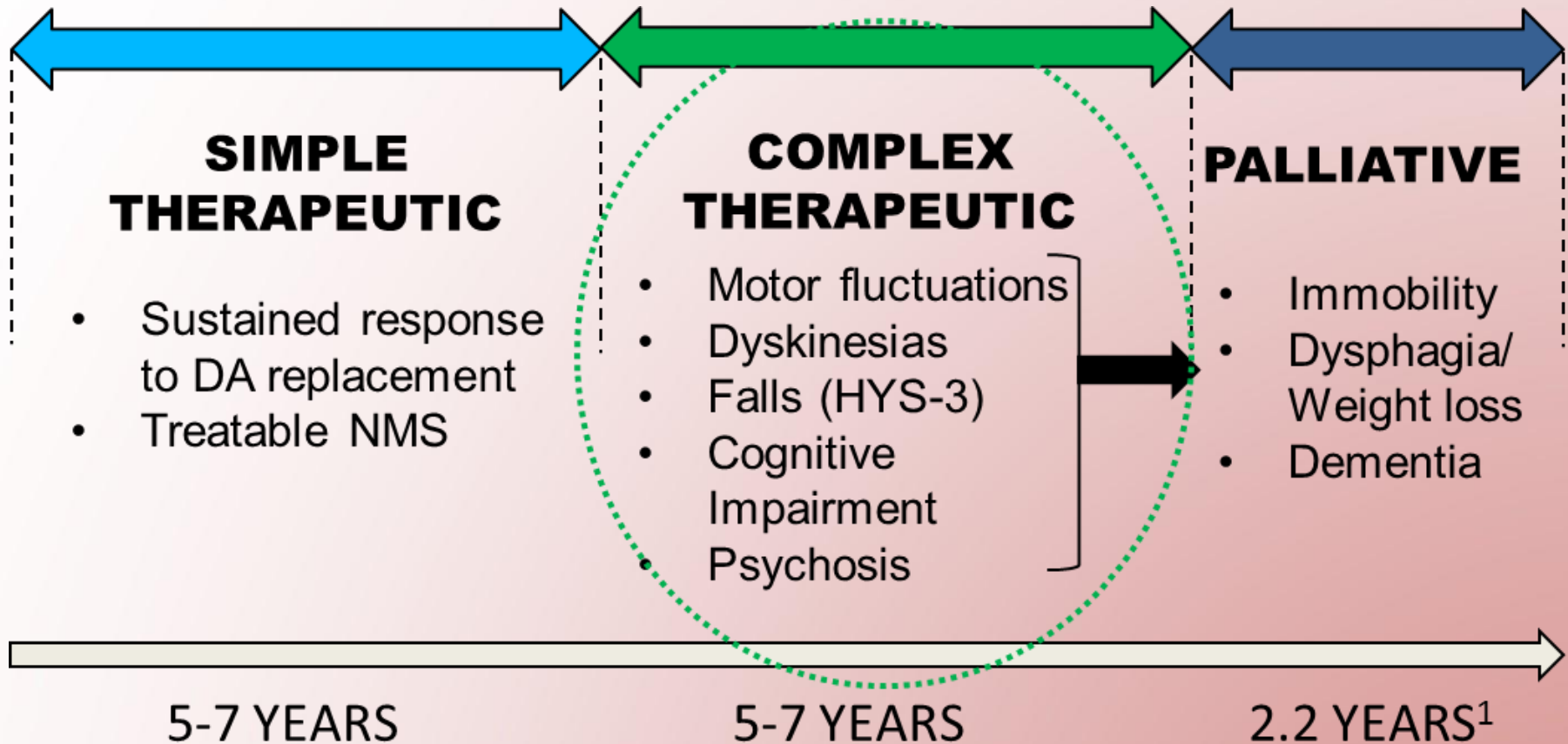


PKG in a 76 year old Female – PD for 17 years



LDE:	1530mg
MDS-UPDRS 3:	40.2
PDQ-39:	46.9
Mean daily On:	0.7
Mean daily Off:	6.3
Mean daily LIDS:	7.0
PKG BK average:	15.4
PKG DK average:	14.5
PKG FDS:	16.4

THERAPY IN THE “COMPLEX PHASE”: Advanced therapies



“5-2-1” CONCEPT:

≥5 doses of Levodopa

≥2h “Off” time

≥1h Troublesome dyskinesia

Is a non-oral therapy or “continuous dopaminergic delivery approach appropriate?

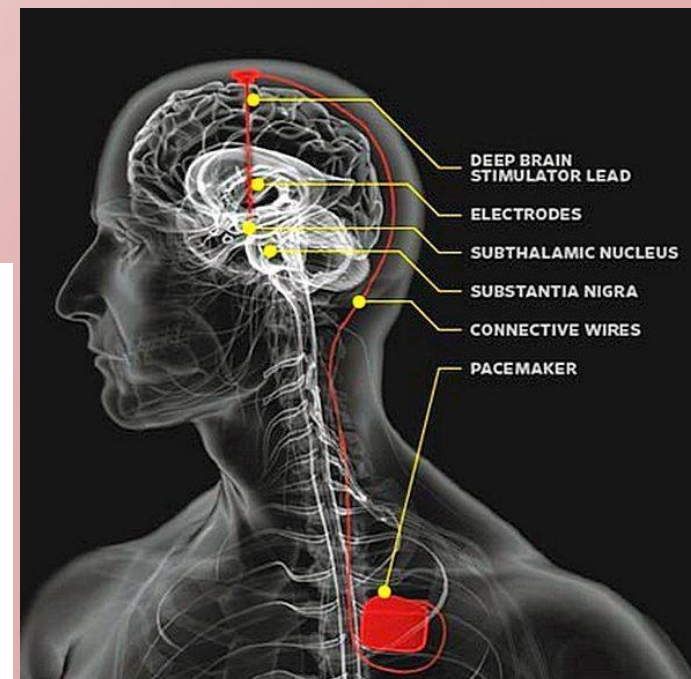
THERAPY IN THE “COMPLEX PHASE”: Advanced therapies

3 current options:

























- **DEEP BRAIN STIMULATION (PREF – SUBTHALAMIC NUCLEUS)**
- **SUBCUTANEOUS APOMORPHINE BY INFUSION**
- **INTRAJEJUNAL DUODOPA**



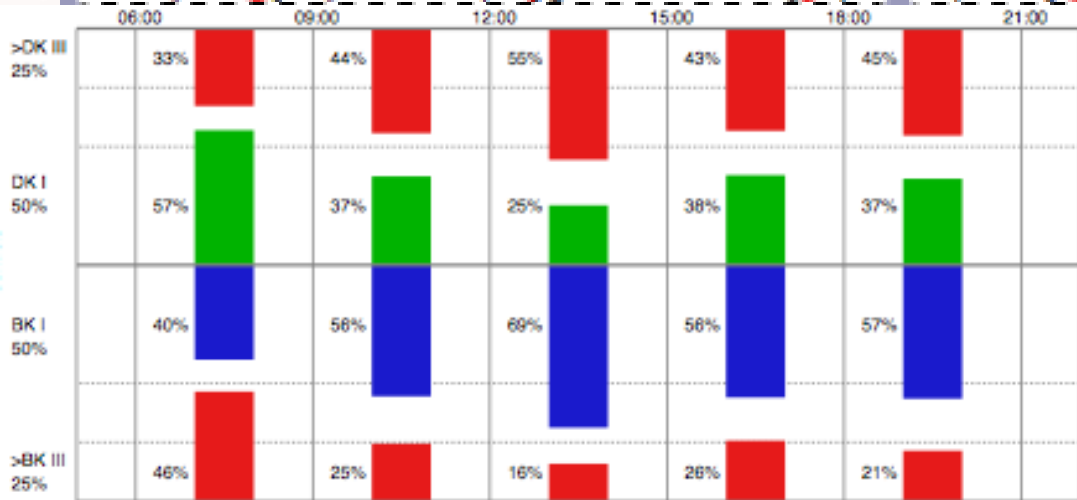
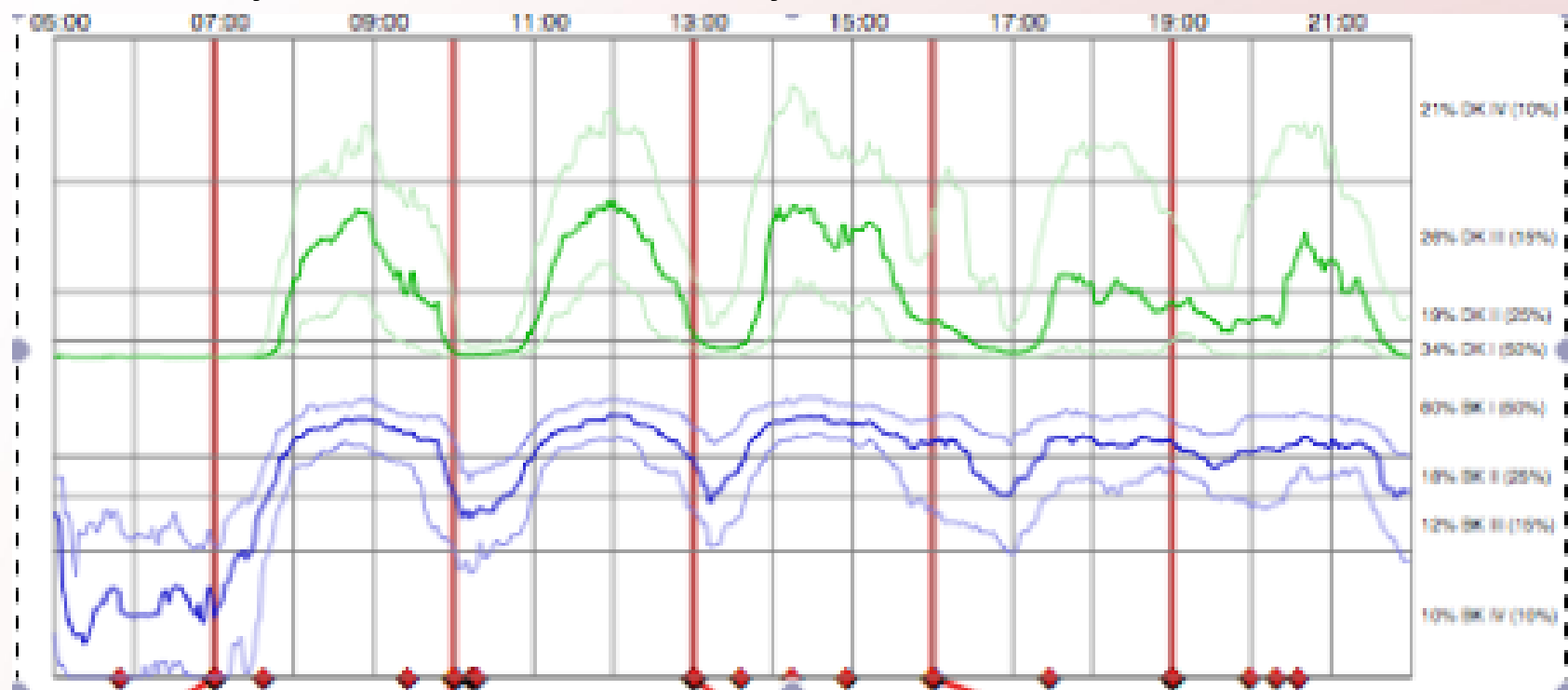
Duodopa®
LEVODOPA/CARBIDOPA INTESTINAL GEL



**THERAPY
IN THE
“COMPLEX
PHASE”:
Advanced
therapies**

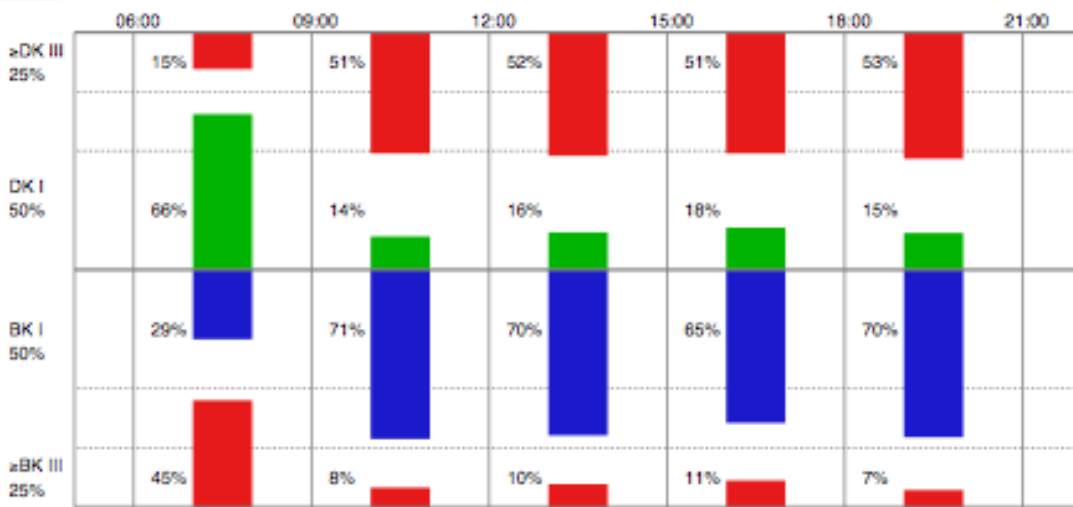
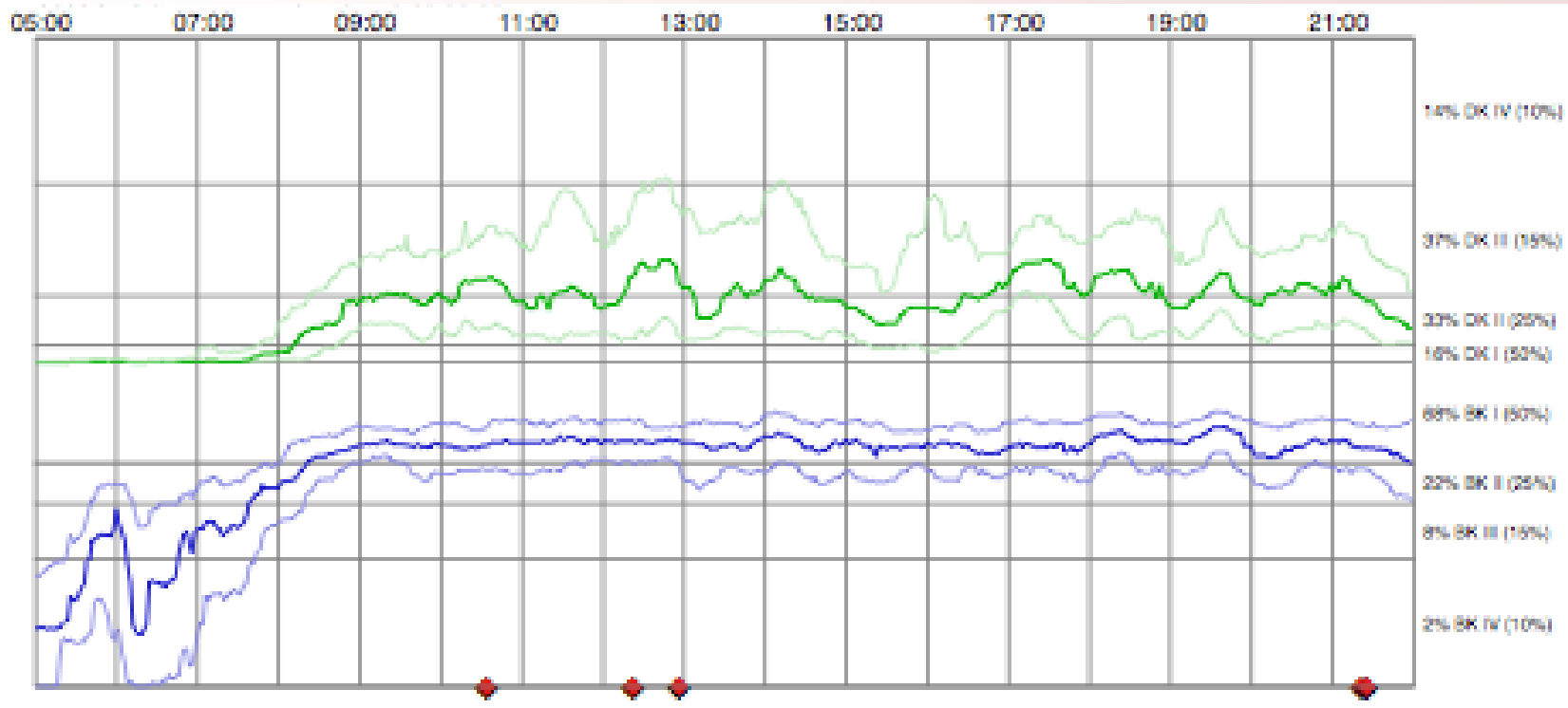
	Apomorphine Pump	Duodopa Pump	DBS
Dementia, slight- moderate			
Dementia, severe			
Psychosis			
Depression, anxiety			
Tremor, pharmacoresistant			
No social support			
Patient not determined			
Patient wants to be independent			

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PKG –response 12 MONTHS POST DUODOPA



LDE:	1276mg
MDS-UPDRS 3:	29.2
PDQ-39:	23.7
Mean daily On:	9.7
Mean daily Off:	4.3
Mean daily LIDS:	0
PKG BK average:	15.2
PKG DK average:	17.1
PKG FDS:	11.9

1530mg
40.2
46.9
0.7
6.3
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14.5
16.4

Non-Motor Aspects of Parkinson's disease:

“PD – Re-dux: A Neuropsychiatric Syndrome”:

The last decade has seen a great increase in our recognition, understanding and treatment of the Non-Motor Aspects of Parkinson's disease

Sensory	Autonomic	Neuropsychiatric
Pain	Thermoregulation	Mood
Akathisia	Pallor	Anxiety, panic attacks
Paresthesias, sensory loss	Sweating, flushing	Depression
Restless legs syndrome	Skin temperature changes	Irritability, hypomania
Internal tremor	Sphincter function	Apathy
Sensory dyspnea	Urinary frequency	Fatigue
	Bloating, abdominal discomfort	Moaning, screaming
	Constipation	Psychotic
	Cardiovascular function	Euphoria, agitation
	Blood pressure changes	Hypomania, mania
	Tachycardia	Hallucinations
	Dysphagia, drooling, dry mouth	Delusions
	Pupillary dilation?	Cognitive changes
	Dyspnea, laryngeal stridor	Sexual function
	Peripheral edema	Hypersexuality
		Aberrant sexual behavior

Some of these symptoms are dopamine dependent, and Levodopa responsive:

Concept of **“Non-Motor Off”**

Non-Motor Aspects of Parkinson's disease:

“PD – Re-dux: *A Neuropsychiatric Syndrome*”:

The last decade has seen a great increase in our recognition, understanding and treatment of the Non-Motor Aspects of Parkinson's disease

Sensory	Autonomic	Neuropsychiatric
Pain	Thermoregulation	Mood
Akathisia	Pallor	Anxiety, panic attacks
Paresthesias, sensory loss	Sweating, flushing	Depression
Restless legs syndrome	Skin temperature changes	Irritability, hypomania
Internal tremor	Sphincter function	Apathy
Sensory dyspnea	Urinary frequency	Fatigue
	Bloating, abdominal discomfort	Moaning, screaming
	Constipation	Psychotic
	Cardiovascular function	Euphoria, agitation
	Blood pressure changes	Hypomania, mania
	Tachycardia	Hallucinations
	Dysphagia, drooling, dry mouth	Delusions
	Pupillary dilation?	Cognitive changes
	Dyspnea, laryngeal stridor	Sexual function
	Peripheral edema	Hypersexuality
		Aberrant sexual behavior

Some of these symptoms are dopamine dependent, and Levodopa responsive:

Concept of **“Non-Motor Off”**

Some may be a consequence of dopaminergic over-stimulation: including Disorders of Impulse control and dopamine dysregulation syndrome

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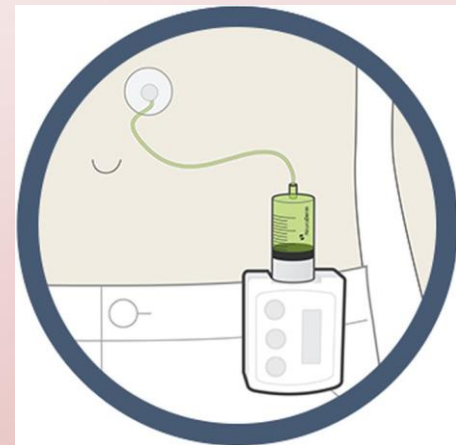
Some are independent of dopaminergic dysfunction and reflect neurodegenerative in other brain regions and other neurotransmitter systems

PIPELINE THERAPIES FOR PD 2018



Getting more from Levodopa:

- Inhalational Levodopa
- Transdermal “Patch-Pump” systems
- Super long-acting Levodopa



Novel therapeutic approaches:

- Neurotrophic factor infusions
- Gene-transfection therapy
- Cell transplantation (but we are a long way from iPSC therapy!)



The Accordion Pill™ - A Drug Delivery Solution for Key Unmet Needs

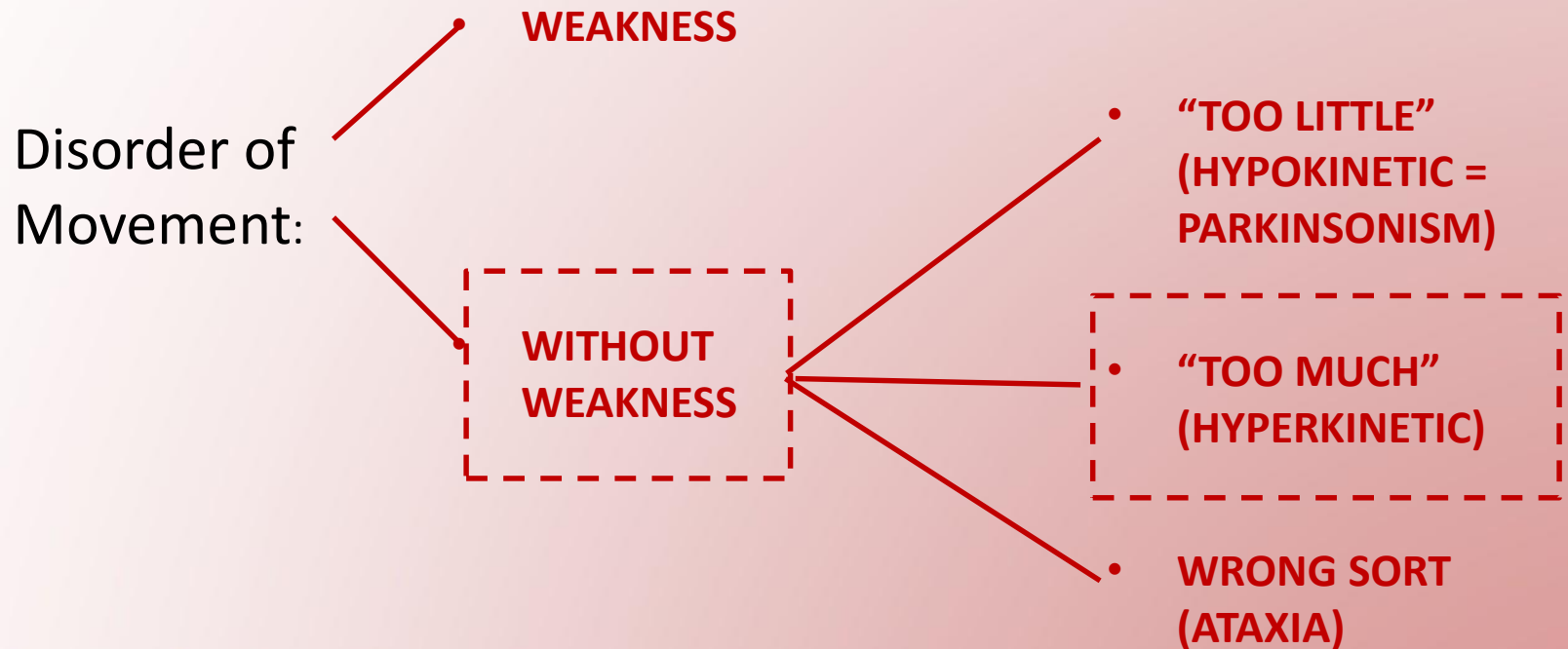


Treatments for Non-Motor PD

- Effective treatment for Gait/Postural disturbance
- Dementia
- Depression

Non-PD Movement Disorders: a quick walk through!

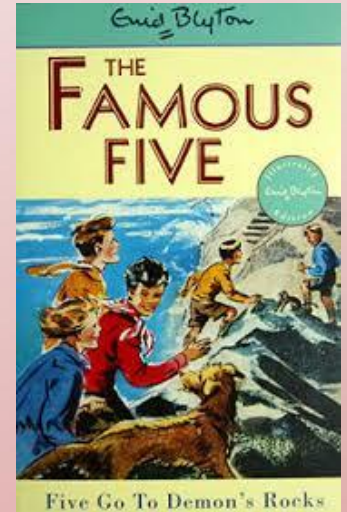
CLASSIFICATION



Non-PD Movement Disorders: a quick walk through!

HYPERKINETIC MOVEMENT DISORDERS

- **TREMOR**
- **DYSTONIA**
- **CHOREA/ATHETOSIS**
- **TICS / Stereotypies**
- **MYOCLONUS**



The small print and the periphery!

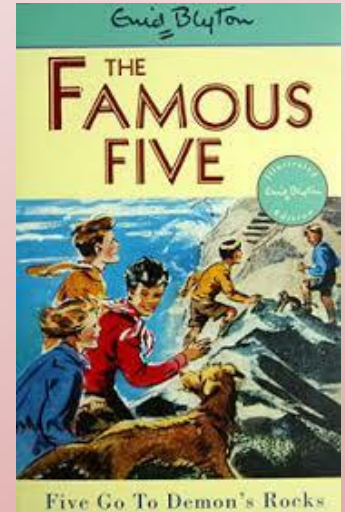
- **RESTLESS LEGS SYNDROME**
- **MYOKYMIA**
- **CRAMPS**
- **NEUROMYOTONIA**

Unfortunately, a lot of the diagnostic work here is pattern recognition but certain patterns are common:

Non-PD Movement Disorders: a quick walk through!

HYPERKINETIC MOVEMENT DISORDERS

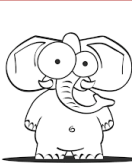
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Unfortunately, a lot of the diagnostic work here is pattern recognition but certain patterns are common:

- **ADULT-ONSET CERVICAL DYSTONIA (“Torticollis”) – Idiopathic**
- **ADULT ONSET CRANIOF-FACIAL (Blepharospasm, Hemifacial spasm) - Idiopathic**
- **OROLINGUAL DYSTONIA/DYSKINESIA – Drug-Induced (Neuroleptics)**

And the other “elephant in the room” – odd, weird, dramatic hyperkinetic disorders are often non-organic (“functional”)



Update on Parkinson's disease and other Movement Disorders

October 2018

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QUESTIONS?