



**BEACH  
BRAIN**

# **Management of Idiopathic Parkinsons Disease**

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BSc (Hons) MBBS (Lond) FRACP (Aus)

***Sri Lanka September 2023***



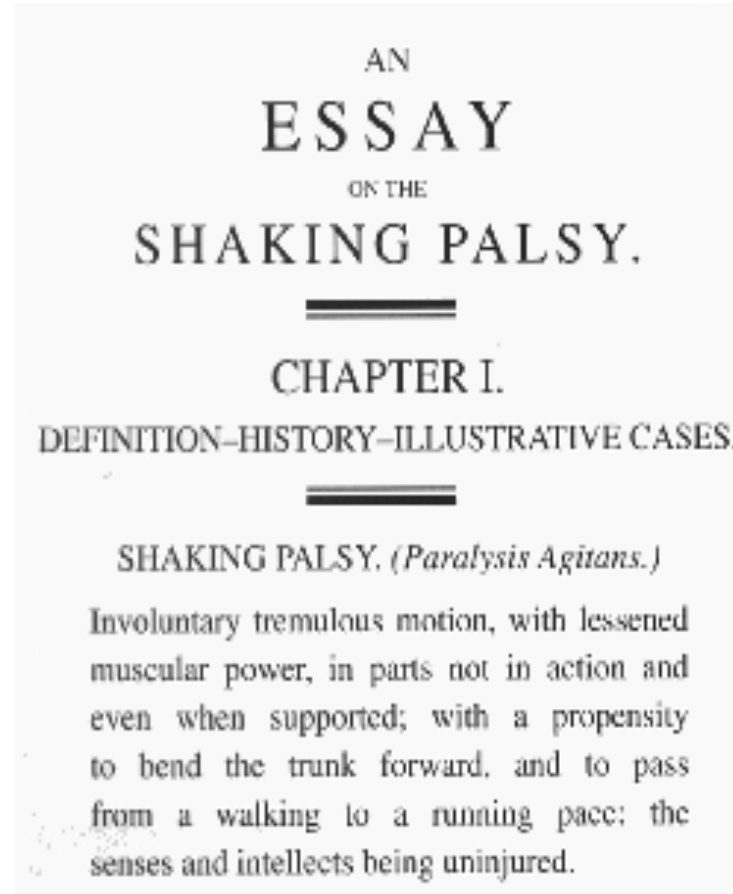
# BB BEACH BRAIN



# Learning Objectives

- Treatments of early motor features of IPD
- Recognising non motor symptoms (NMS) of IPD
- Rationale for symptom specific treatments of NMS
- Advancing stage therapies in IPD
- Role of Rehabilitation and Multidisciplinary team in improving QOL

# Dr J PARKINSON 1755-1824



***English Born, English Bred, Forgotten by the English and the World at large ! ( J G Rowntree -Neuroscientist, 1912)***

# Very common disease

- Incidence approximately 100 -180 per 100000
- Increased frequency with age
  - 0.4% people over 40
  - 3-4 % over 85

# Risk of Mortality

- Parkinson's disease causes a shortened life span
- Dopamine replacement has little effect on the non-dopaminergic motor and variable effect on non motor symptoms which are important causes of mortality
- 2.2 fold increase in all cause mortality compared to the general population
- Leading cause of death pneumonia, cardiovascular disease, cerebral vascular events and neoplasia

# Criteria for Motor symptoms IPD: “TRAP”

- Tremor
- Rigidity
- Akinesia
- Postural instability



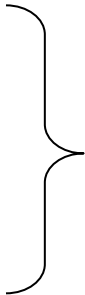
# Risk Factors associated with PD

- Increased risk

- Age
- Family history
- Exposure
  - Well water
  - Pesticides (Rotenone-NW Vic)
- Head injury
- REM behavior disorder
- Constipation
- Depression

- Decreased risk

- Caffeine
- Cigarettes



**these are more likely  
early disease symptoms**

# Secondary Parkinsonisms

- Post-encephalitic
- Post-traumatic
- **Vascular**
- Hydrocephalus
- Space-occupying lesion
- Toxic
  - Manganese
  - MPTP
  - Carbon monoxide
  - Cyanide
  - Carbon disulfide

- **Drug-induced**
  - DA-receptor blockers
  - **Antipsychotics**
  - **Anti-emetics**
  - CA-channel blockers
  - Anticonvulsants
  - Phenytoin
  - Valproic acid
  - Antiarrhythmics
  - Amiodarone
  - Others
  - Lithium

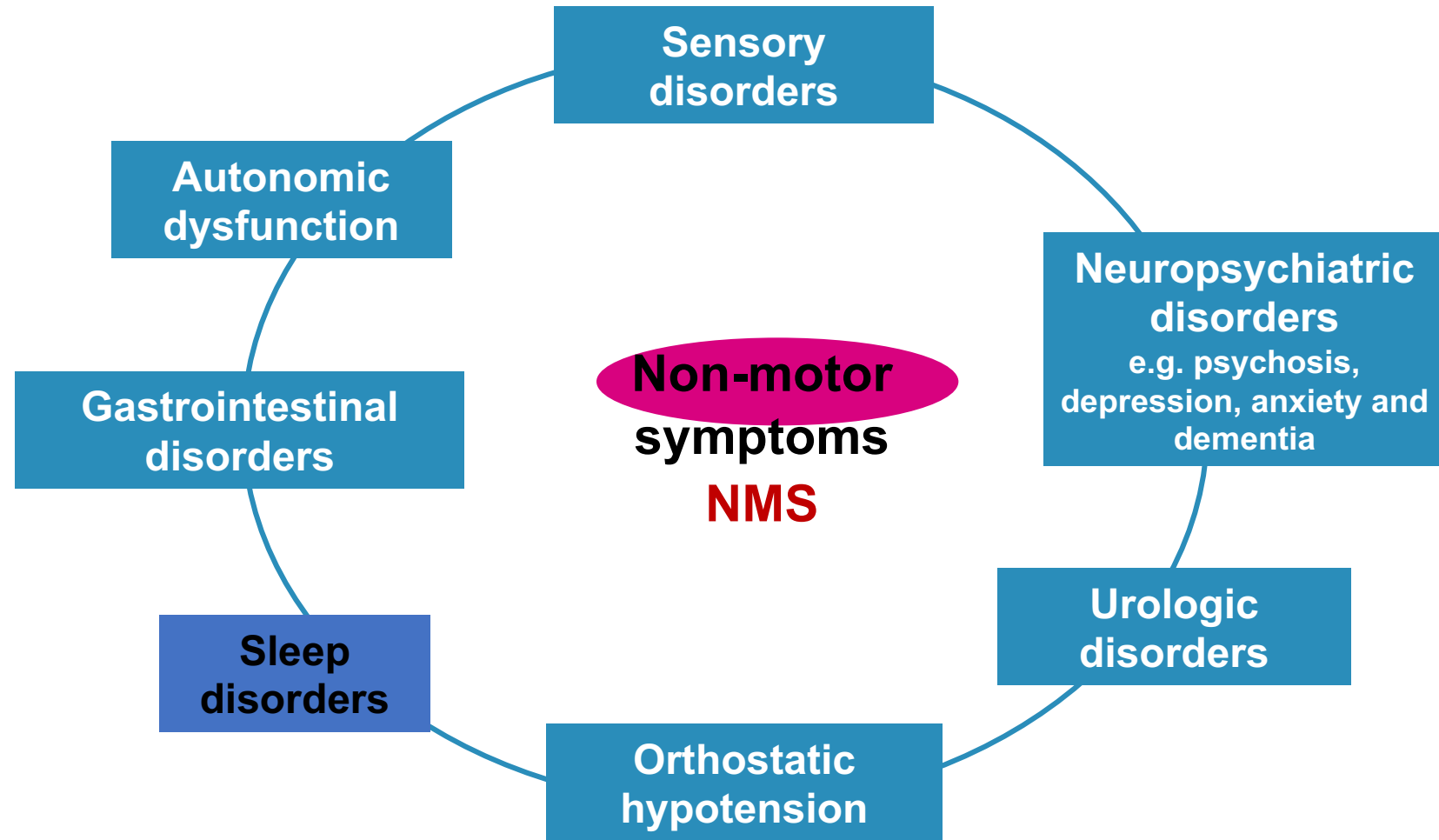
# The story of Phil

- Has a 10 year history of Parkinson's disease
- Under the care of a neurologist in Brisbane: infrequent visits
- Initially developed **resting tremor** on the right
- **Slowing, stiff**, shuffling gait
- Started on Madopar with good effect
- Intolerant of pramipexole as well as other Parkinson's meds
- Now **falling**; 12 in the past year only intermittently using 4ww
- Struggling to get going in the morning
- Frequent freezing and difficulty getting out of the house
- Difficulty with fine motor tasks: handwriting, cutlery etc

# Non Motor Symptoms

- Often precede motor symptoms (sometimes by several decades)
- Are poorly recognised
- Are debilitating
- Are poorly treated

# Non-motor symptoms (NMS) of Parkinson's disease:



# Non Motor Symptoms

- Hyposmia 25 -90 %
  - Precede diagnosis
  - Increases risk by 10 times
- Fatigue 60 %
  - Precedes diagnosis
- Somnolence
  - Precede diagnosis
  - Increase risk by 3.3 times
- Depression 25 %
  - Precede diagnosis
  - Increase risk 2.4 times
- Rapid eye movement sleep behavioural disturbance 30%
  - Precede diagnosis by 15 years+
- Constipation
  - Precedes diagnosis
  - Increase risk 3 to 5 times
- Erectile dysfunction
  - Precedes diagnosis
  - Increase risk 4 times
- Pain ( especially unilateral)
  - Precede diagnosis
  - Increase risk 34 %

# Late symptoms

- Treatment resistant axial symptoms 5 – 10 years after onset
  - Freezing /postural instability / falls 90 % by 15 years
  - Dysphagia 50 % by 15 year
- Psychiatric disturbance 5 to 10 years
  - Anxiety
  - Visual hallucinations
- Autonomic disturbance
  - Postural hypotension 15 %
  - Sialorrhea 30 %
  - Urinary urgency 35 %
  - Nocturia 35 %
  - Sexual dysfunction 20 %
- Cognitive impairment
  - Mild cognitive impairment 35 % at diagnosis 50 % at 5 years
  - Dementia 80 % at 20 years post onset

# Non motor systems questionnaire

Have you experienced any of the following in the last month?

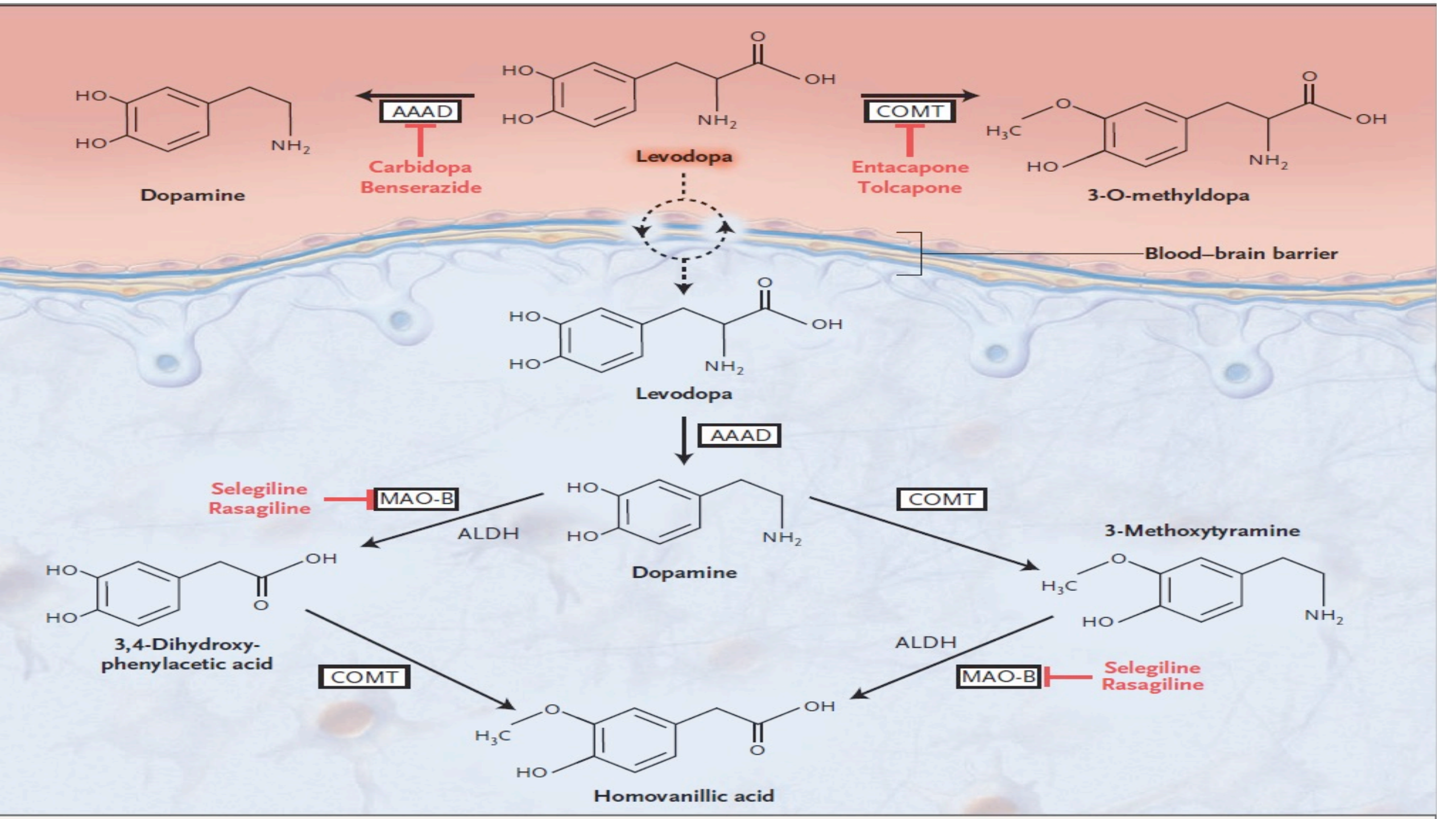
	Yes	No		Yes	No
1 Dribbling of saliva during the daytime.	<input type="checkbox"/>	<input type="checkbox"/>	16 Feeling sad, 'low' or 'blue'.	<input type="checkbox"/>	<input type="checkbox"/>
2 Loss or change in your ability to taste or smell.	<input type="checkbox"/>	<input type="checkbox"/>	17 Feeling anxious, frightened or panicky.	<input type="checkbox"/>	<input type="checkbox"/>
3 Difficulty swallowing food or drink or problems with choking.	<input type="checkbox"/>	<input type="checkbox"/>	18 Feeling less interested in sex or more interested in sex.	<input type="checkbox"/>	<input type="checkbox"/>
4 Vomiting or feelings of sickness (nausea).	<input type="checkbox"/>	<input type="checkbox"/>	19 Finding it difficult to have sex when you try.	<input type="checkbox"/>	<input type="checkbox"/>
5 Constipation (less than three bowel movements a week) or having to strain to pass a stool.	<input type="checkbox"/>	<input type="checkbox"/>	20 Feeling light-headed, dizzy or weak standing from sitting or lying.	<input type="checkbox"/>	<input type="checkbox"/>
6 Bowel (faecal) incontinence.	<input type="checkbox"/>	<input type="checkbox"/>	21 Falling.	<input type="checkbox"/>	<input type="checkbox"/>
7 Feeling that your bowel emptying is incomplete after having been to the toilet.	<input type="checkbox"/>	<input type="checkbox"/>	22 Finding it difficult to stay awake during activities such as working, driving or eating.	<input type="checkbox"/>	<input type="checkbox"/>
8 A sense of urgency to pass urine makes you rush to the toilet.	<input type="checkbox"/>	<input type="checkbox"/>	23 Difficulty getting to sleep at night or staying asleep at night.	<input type="checkbox"/>	<input type="checkbox"/>
9 Getting up regularly at night to pass urine.	<input type="checkbox"/>	<input type="checkbox"/>	24 Intense, vivid or frightening dreams.	<input type="checkbox"/>	<input type="checkbox"/>
10 Unexplained pains (not due to known conditions such as arthritis).	<input type="checkbox"/>	<input type="checkbox"/>	25 Talking or moving about in your sleep, as if you are 'acting out' a dream.	<input type="checkbox"/>	<input type="checkbox"/>
11 Unexplained change in weight (not due to change in diet).	<input type="checkbox"/>	<input type="checkbox"/>	26 Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move.	<input type="checkbox"/>	<input type="checkbox"/>
12 Problems remembering things that have happened recently or forgetting to do things.	<input type="checkbox"/>	<input type="checkbox"/>	27 Swelling of the legs.	<input type="checkbox"/>	<input type="checkbox"/>
13 Loss of interest in what is happening around you or in doing things.	<input type="checkbox"/>	<input type="checkbox"/>	28 Excessive sweating.	<input type="checkbox"/>	<input type="checkbox"/>
14 Seeing or hearing things that you know or are told are not there.	<input type="checkbox"/>	<input type="checkbox"/>	29 Double vision.	<input type="checkbox"/>	<input type="checkbox"/>
15 Difficulty concentrating or staying focussed.	<input type="checkbox"/>	<input type="checkbox"/>	30 Believing things are happening to you that other people say are not.	<input type="checkbox"/>	<input type="checkbox"/>



# Back to Phil.....

- Cognitive decline mainly short term memory
- Poor sleep: difficulty rolling in bed, frequent nightmares, nocturia x4
- Daytime sleepiness and hypersomnolence
- Soft voice and food occasionally stuck in his throat
- Constipated and regularly dizzy when standing
- Loss of taste and smell
- Weight loss and muscle wasting
- Son moved in with him as he is struggling on his own. No community supports or carers allowance, phil is still driving

# Pharmacotherapy Options



The cornerstone to the management of Parkinson's Disease is Levodopa

# Kampavata ('shaking palsy')



- Described a more than two thousand years ago in ancient India
- *mucuna pruriens* (velvet bean) originally used as aphrodisiac but found to be effective for Kampavata
- L-dopa extracted in 1932

# Experimental parkinsonism in monkey reserpine model



# Levodopa long term complications

- Motor complications
  - 'Wearing off' phenomenon
  - Delayed 'on'
  - No 'on'
  - 'on-off' phenomenon
- Dyskinesia
  - Peak dose chorea
  - Dystonia
  - Biphasic dyskinesia
  - Wearing off dyskinesia

# Motor complications of PD

Wearing off



Probable central  
mechanism

On-Off (sudden off)

Delayed on



Probable peripheral  
mechanism

Dose Failure



# The Gut and IPD

## **Mouth**

Pooling of saliva and problems with movements needed to brush teeth can cause dental dysfunction. Motor effects cause jaw tremors.

## **Oesophagus**

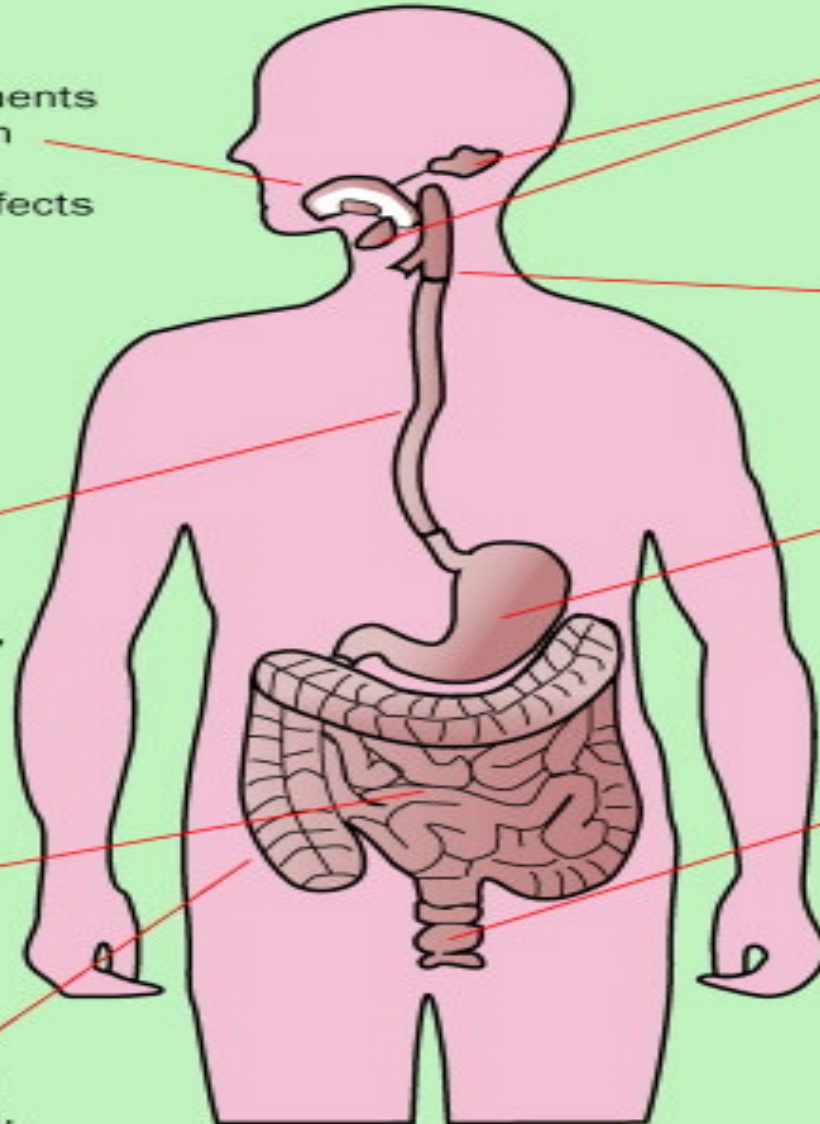
Symptoms of oesophageal dysphagia include slow oesophageal transit, segmental oesophageal spasm, spontaneous contractions of proximal oesophagus, air trapping, aperistalsis, and gastro-oesophageal reflux

## **Small intestine**

Dilatation

## **Colon**

Colonic dysmotility, constipation, megacolon, volvulus, and bowel perforation.



## **Salivary glands**

Reduced saliva production, but low swallowing frequency causes drooling.

## **Pharynx**

Oropharyngeal dysphagia increases risk of aspiration.

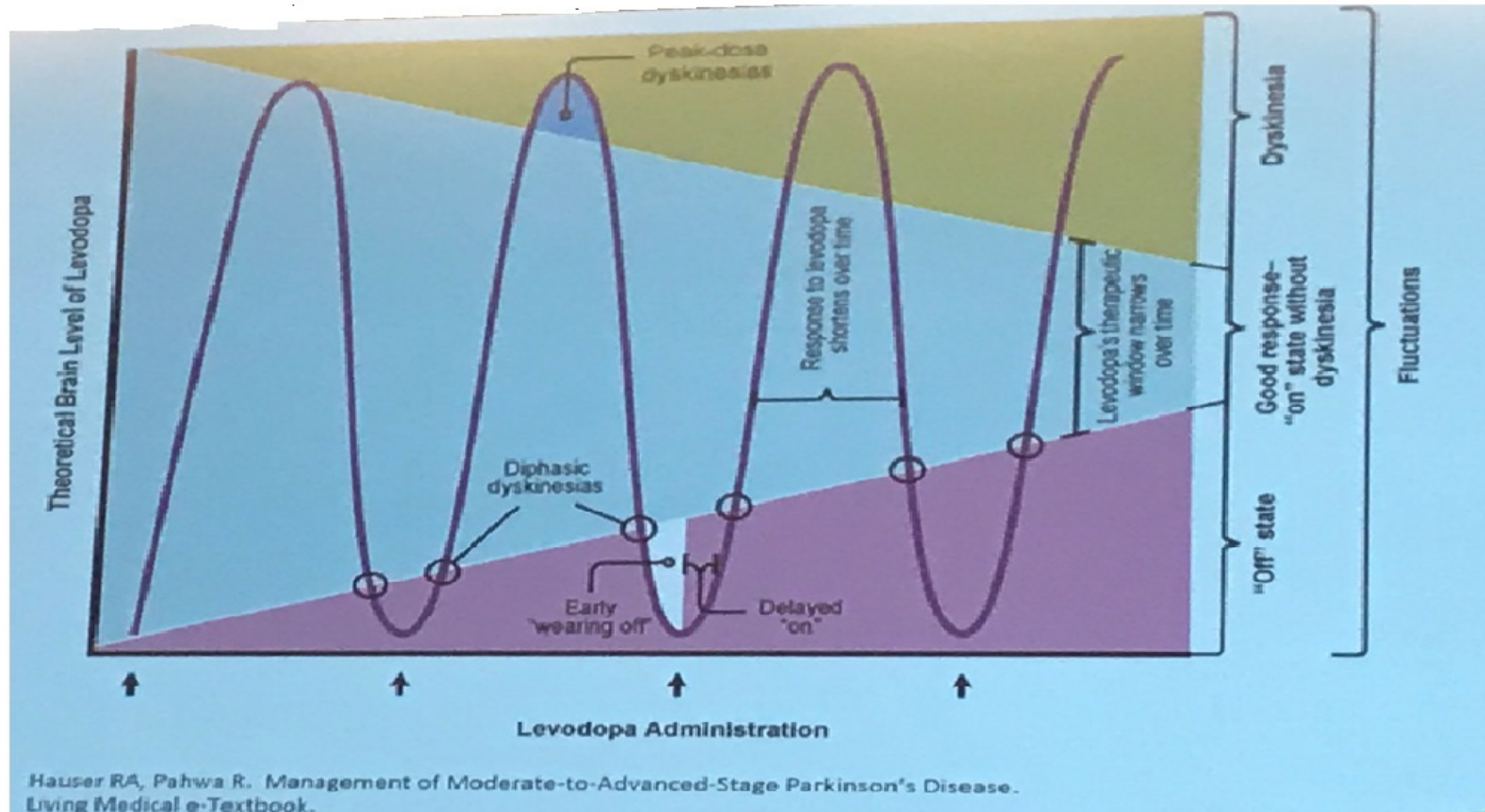
## **Stomach**

Impaired gastric emptying (gastroparesis) cause nausea, bloating, early satiety, and weight loss.

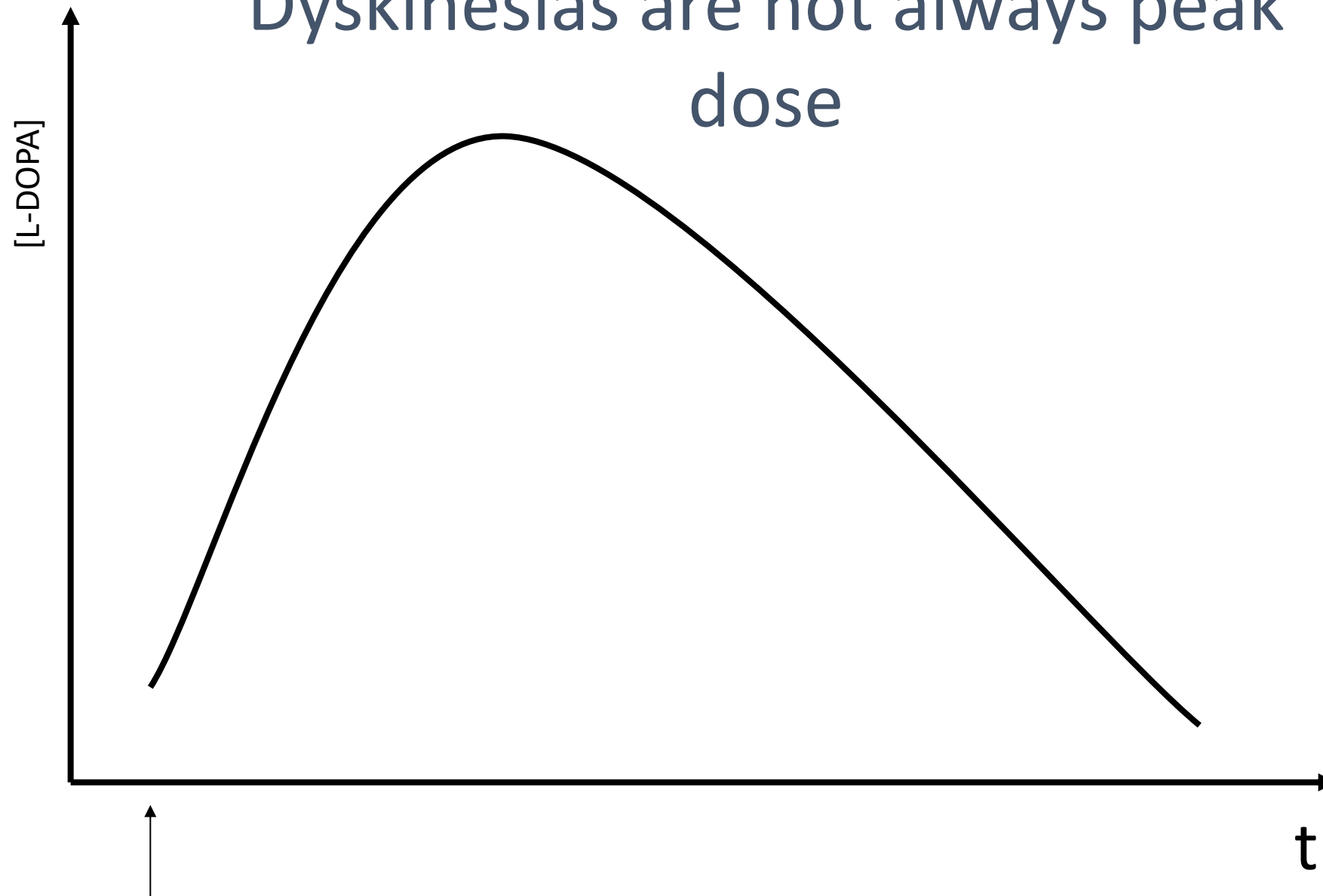
## **Rectum**

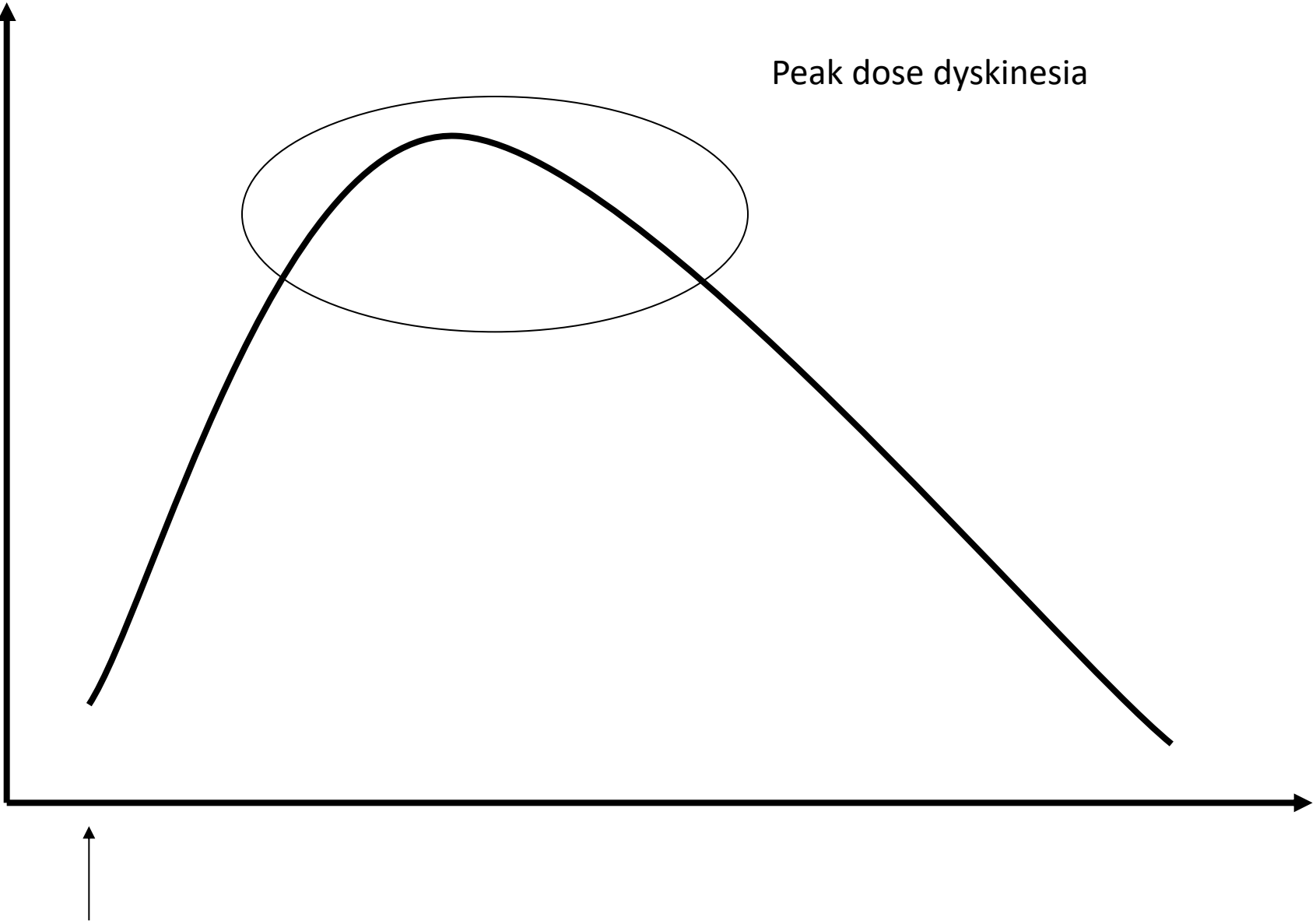
Anorectal dysfunction leads to difficulty with defecation

# Motor Fluctuations

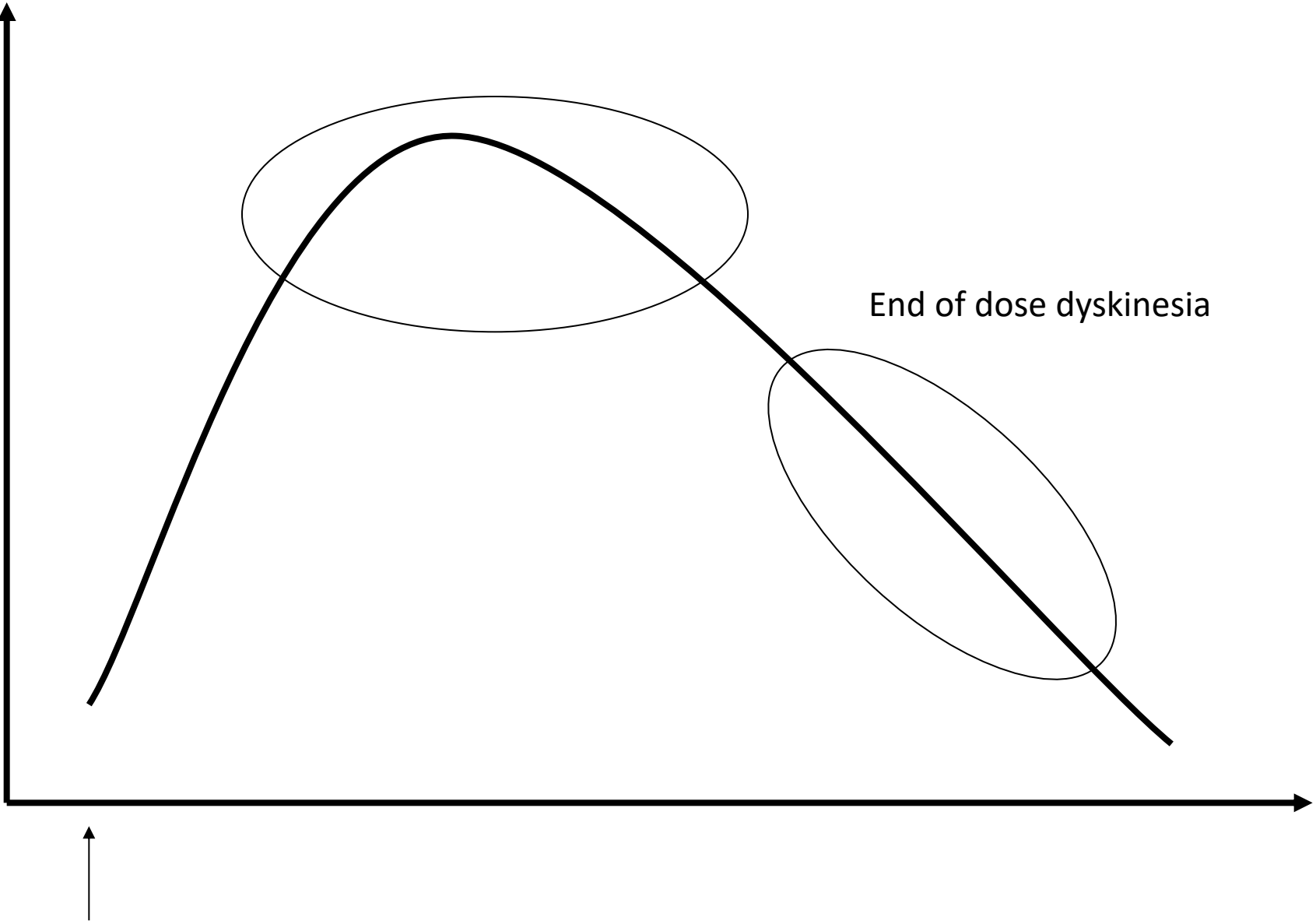


Dyskinesias are not always peak  
dose





Peak dose dyskinesia



End of dose dyskinesia

# Dyskinesia

## Peak dose

- 30-60 min post LDOPA
- Chorea
- Entire body
- Often not aware

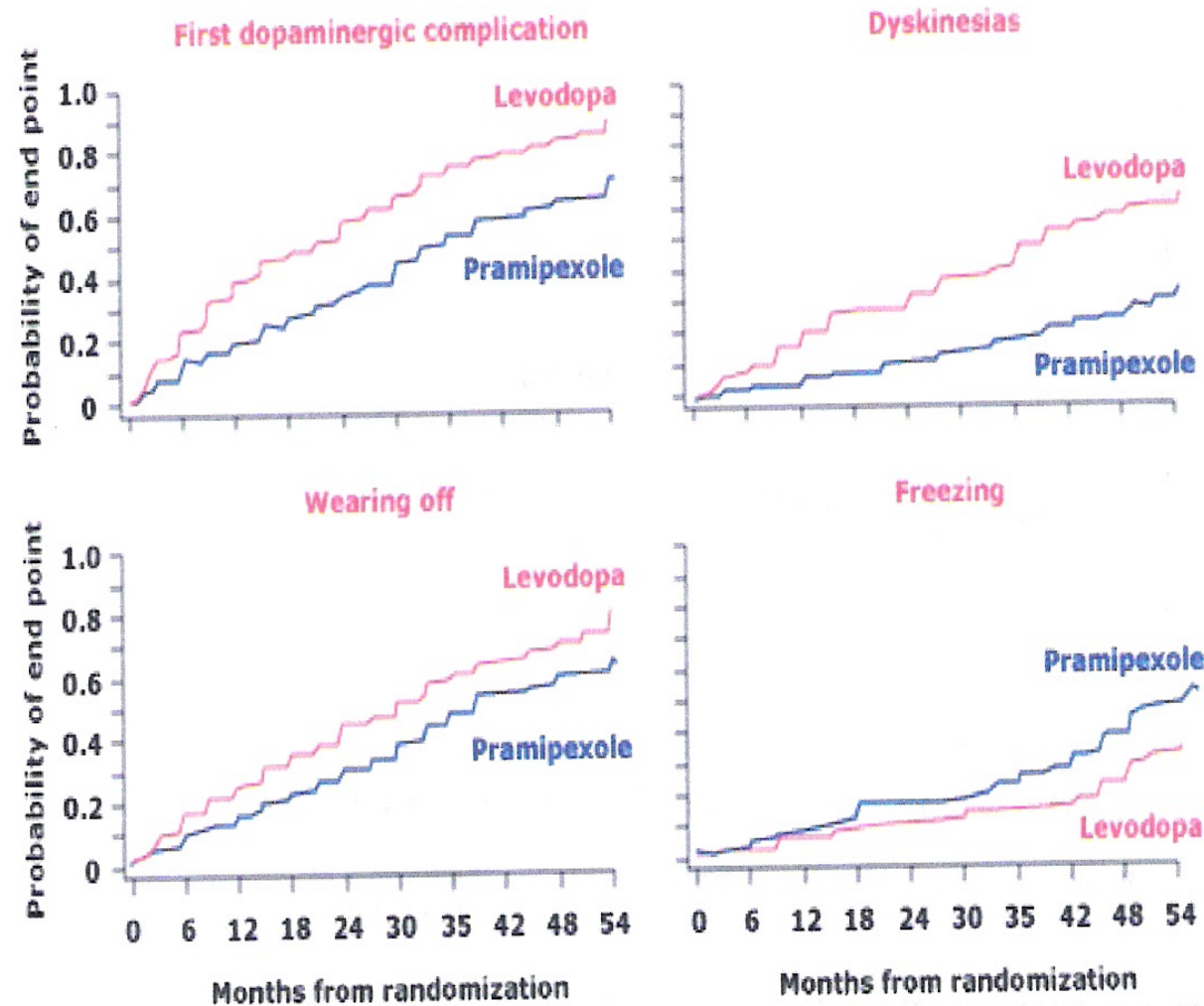
## End of dose

- 3-4 hours post LDOPA or early morning
- Dystonia
- Often foot or restless lower limbs
- Often painful

Is Levodopa Toxic?

# Pramipexole vs Levodopa as initial treatment for PD

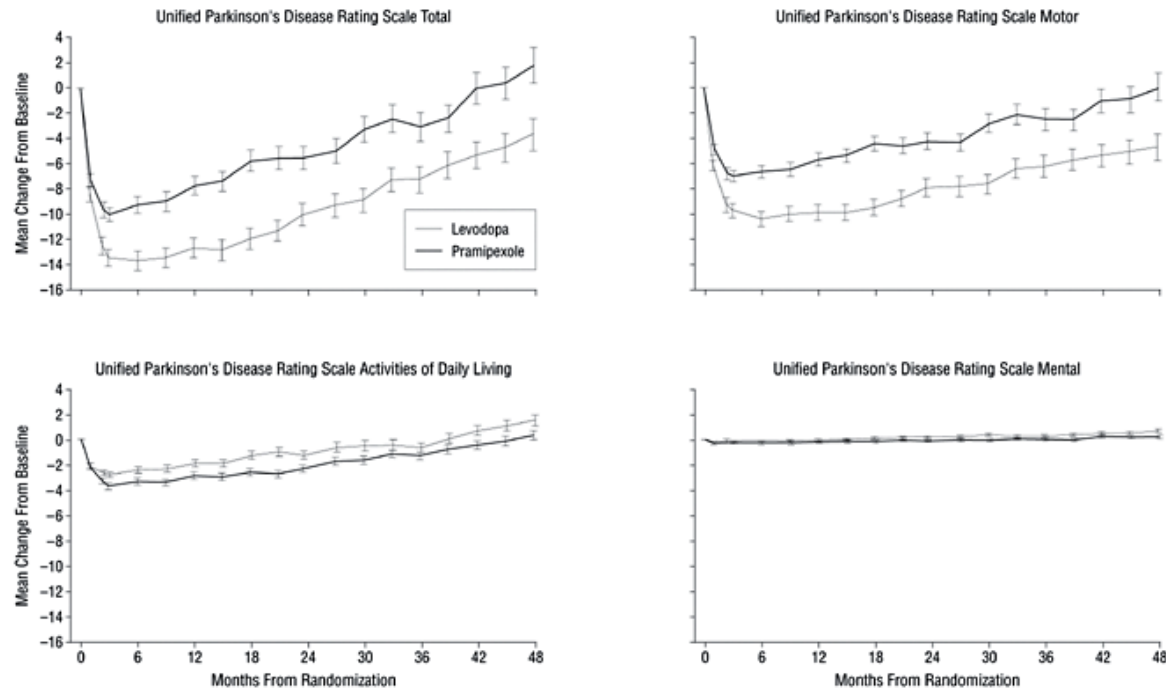
The Parkinsons Study Group: Arch Neurol 2004;61:1044





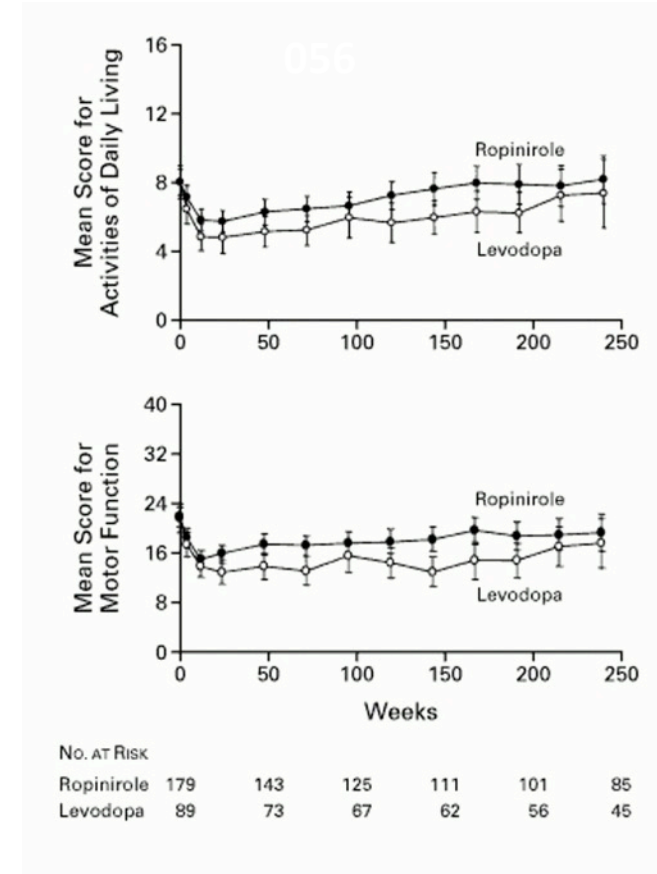
# Efficacy

Mean (SE) total (parts I + II + III), motor, activities of daily living, and mental Unified Parkinson's Disease Rating Scale scores during the course of the trial by treatment assignment



The Parkinson Study Group, Arch Neurol 2004;61:1044-1053.

Pramipexole

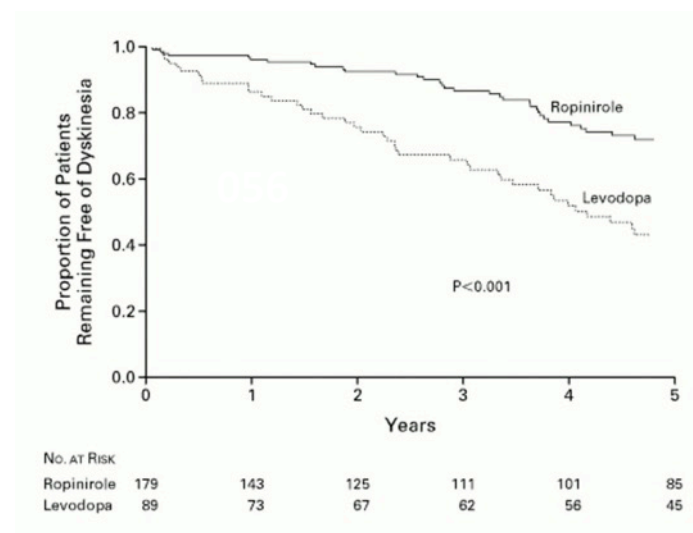
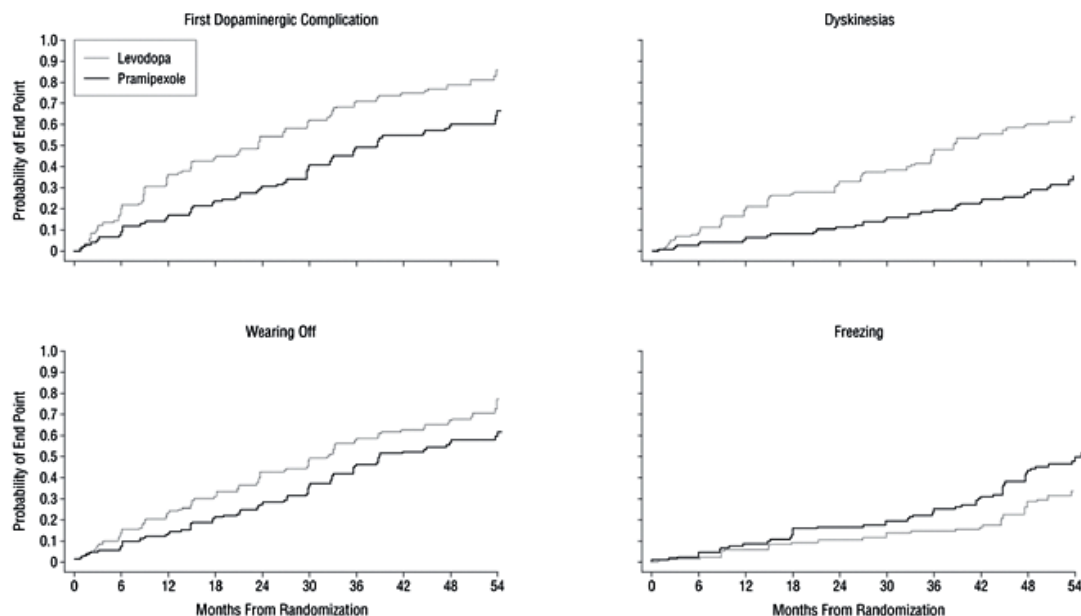


Rascol O et al. N Engl J Med 2000;342:1484-1491

Ropinirole

# Dyskinesias

Cumulative probability of reaching the first dopaminergic complication



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

The Parkinson Study Group, Arch Neurol 2004;61:1044-1053.

Pramipexole

Ropinirole

Levodopa gives better symptom relief but greater dyskinesia

# Impulse Control Disorders in Parkinson Disease

## *A Cross-Sectional Study of 3090 Patients*

*Daniel Weintraub, MD; Juergen Koester, PhD; Marc N. Potenza, MD, PhD;  
Andrew D. Siderowf, MD, MSCE; Mark Stacy, MD; Valerie Voon, MD;  
Jacqueline Whetteckey, MD; Glen R. Wunderlich, PhD; Anthony E. Lang, MD, FRCPC*

Mov Dis 2010

3090 patients

ICD Total: 13.6%

- Gambling: 5.0%
- Sexual: 3.5%
- Buying: 5.7%
- Eating: 4.3%

# Dopamine Agonist Withdrawal Syndrome in Parkinson Disease

Arch Neurol 2010;67:58-63

*Christina A. Rabinak, BSE; Melissa J. Nirenberg, MD, PhD*

- 26 patients, DA withdrawal (15 ICD)

5 developed DAWS:

- Anxiety
- Panic attacks
- Agoraphobia
- Depression
- Diaphoresis
- Fatigue
- Pain
- Orthostatic hypotension
- Drug cravings

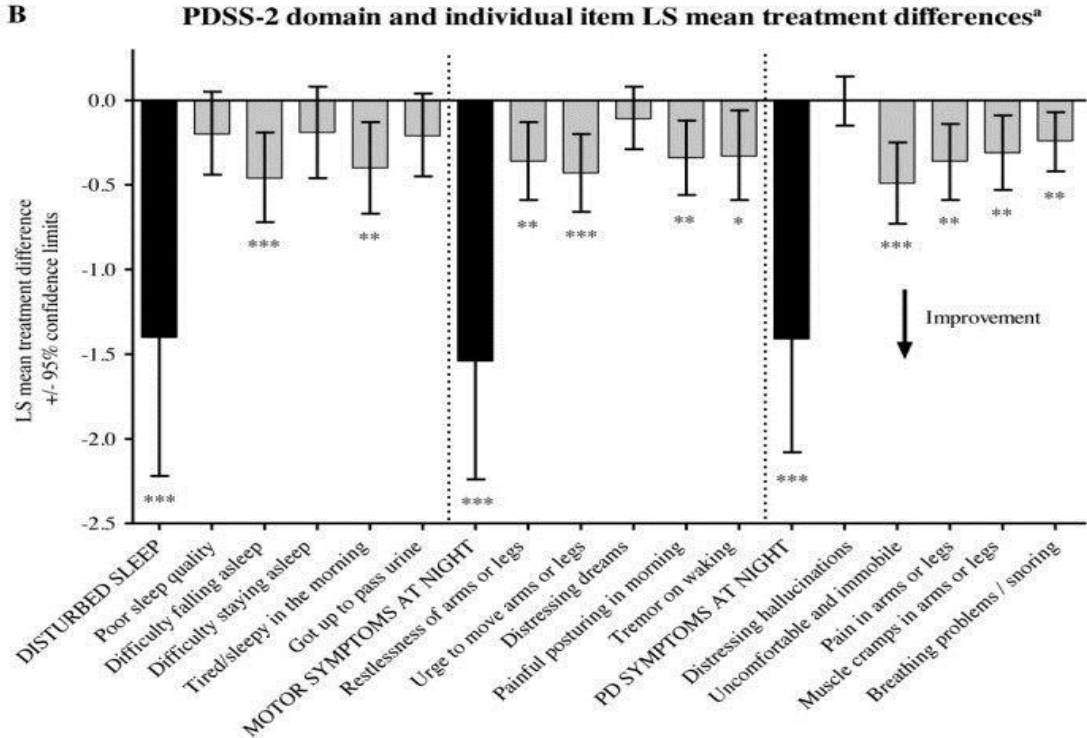
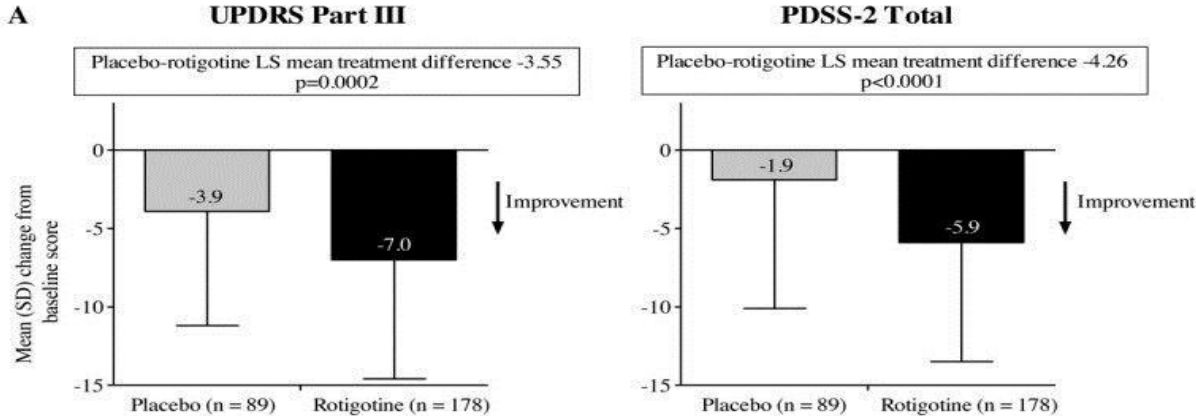
All had ICD

Refractory to levodopa, benzodiazepines, antidepressants

**Responsive to restarting DA**

3 remain on DA with chronic ICD

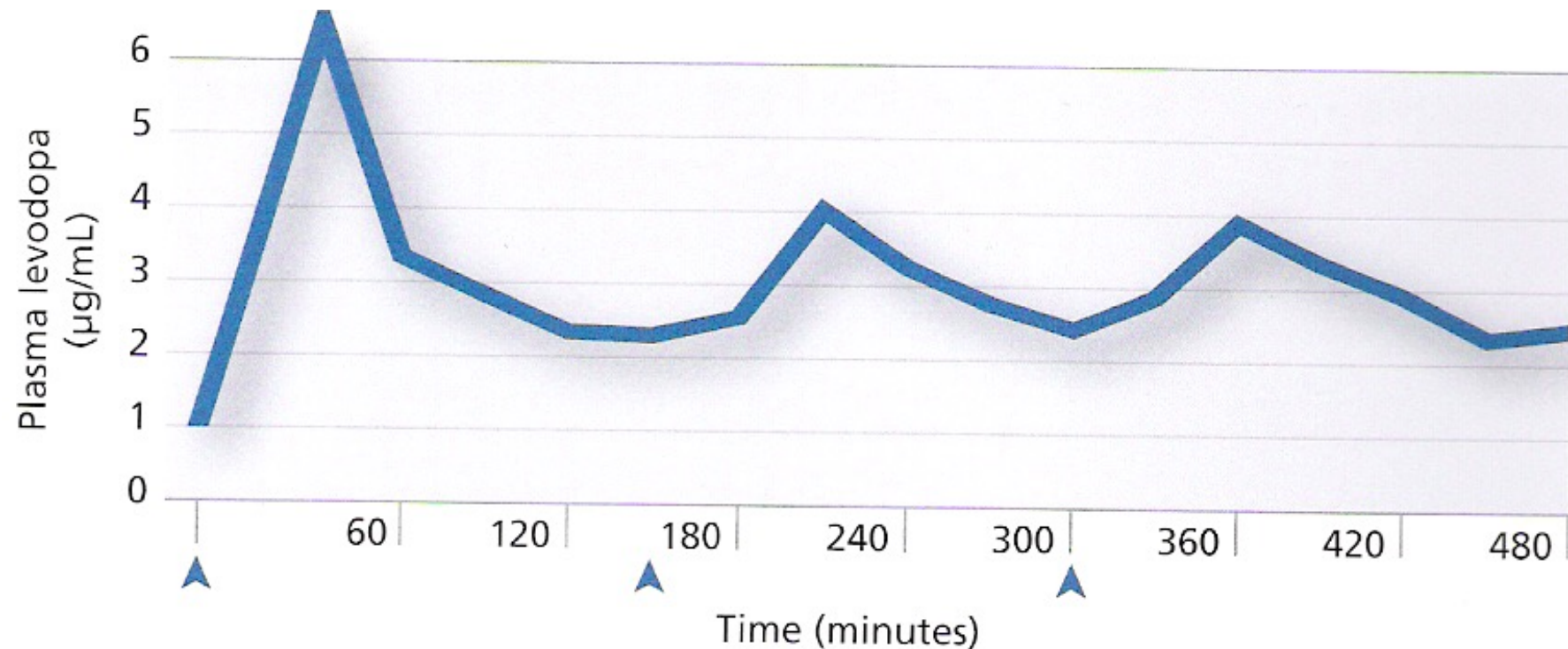
# Rotigotine for NMS (RECOVER trial)



# Dopamine agonists

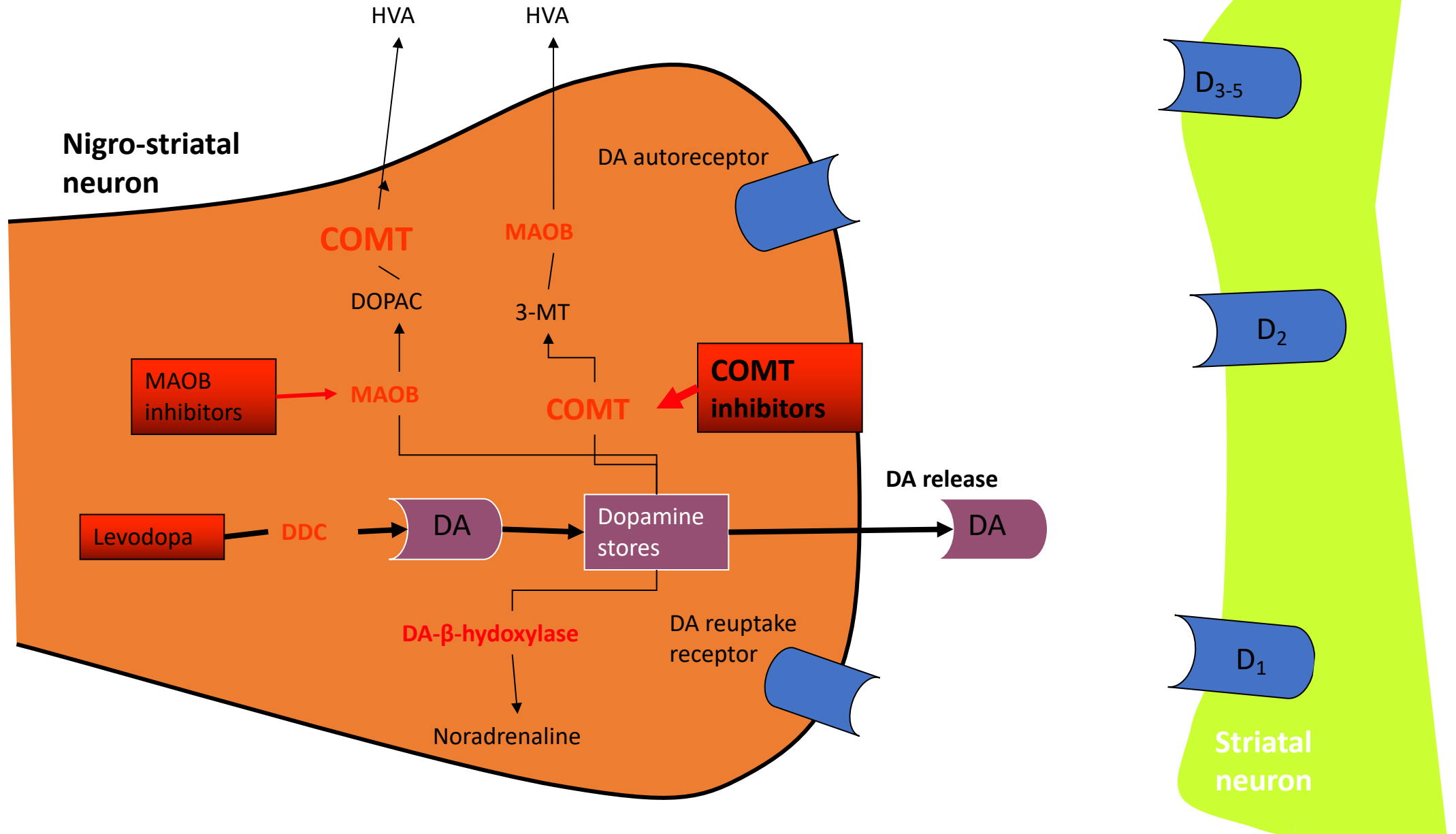
- Reduced risk of dyskinesias
- Weaker antiparkinsonian action
- Nausea, daytime sleepiness, ankle swelling
- Rotigotine best evidence base for NMS
- Get good consent
- Ensure that your indemnity is up to date (ICD)

# Fluctuating levodopa plasma levels



**Figure 2** Plasma dopa level in seven patients receiving sequential oral doses of levodopa with carbidopa. Arrows indicate levodopa administration at average doses of  $211 \pm 40$  mg,  $179 \pm 33$  mg and  $161 \pm 34$  mg. Adapted from Shoulson et al.<sup>12</sup>

# COMT inhibitors

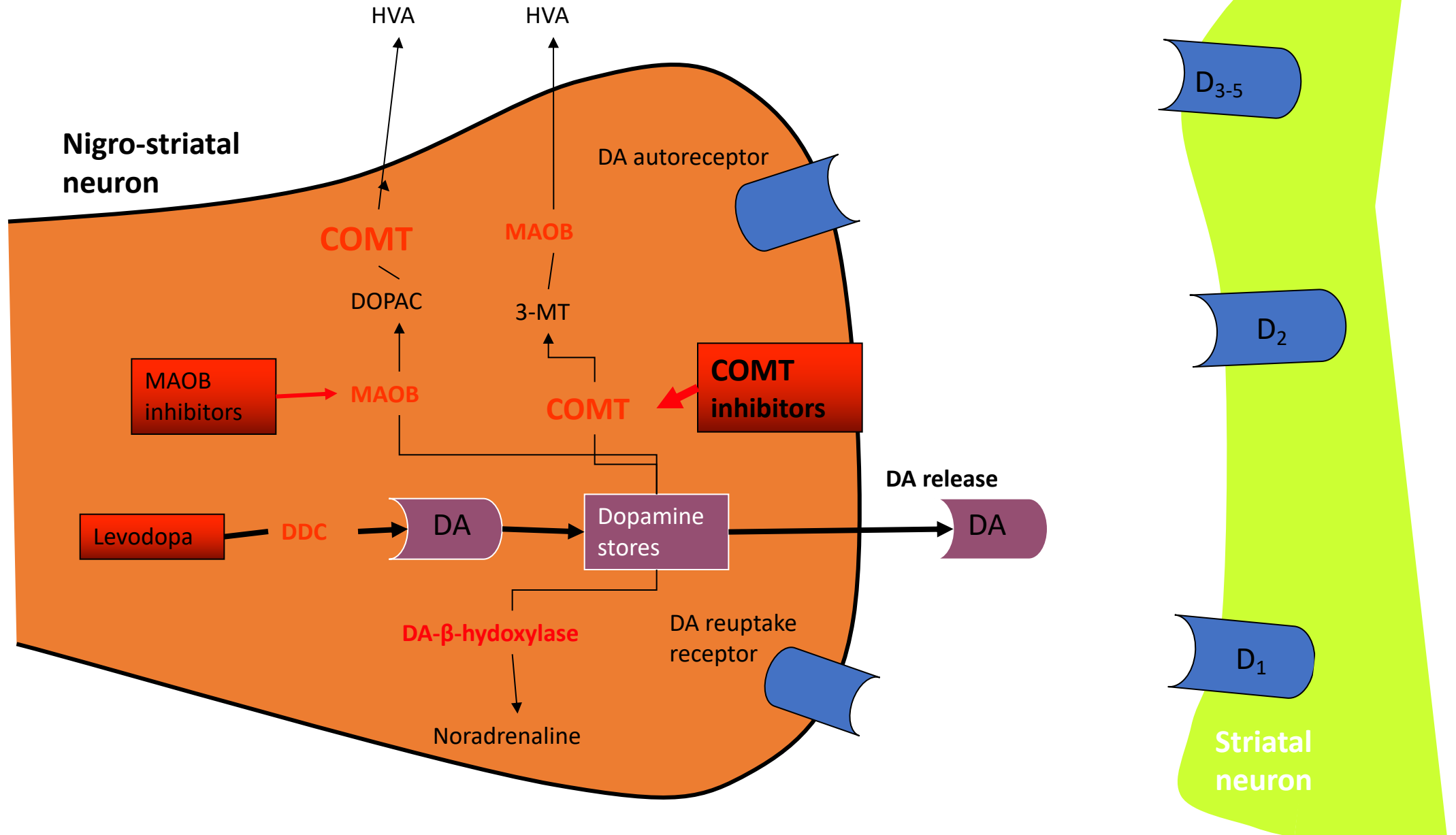




# COMT Inhibitors

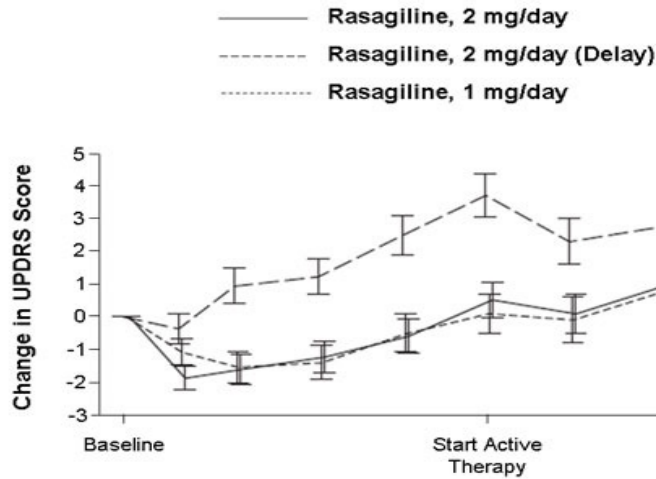
- ▶ Levodopa 'extenders'
- ▶ Useful as add on in motor fluctuations
- ▶ Decreased "off" and increased "on"
- ▶ No effect without motor fluctuations
- ▶ Dopaminergic SEs, mainly dyskinesia

# MAO inhibitors

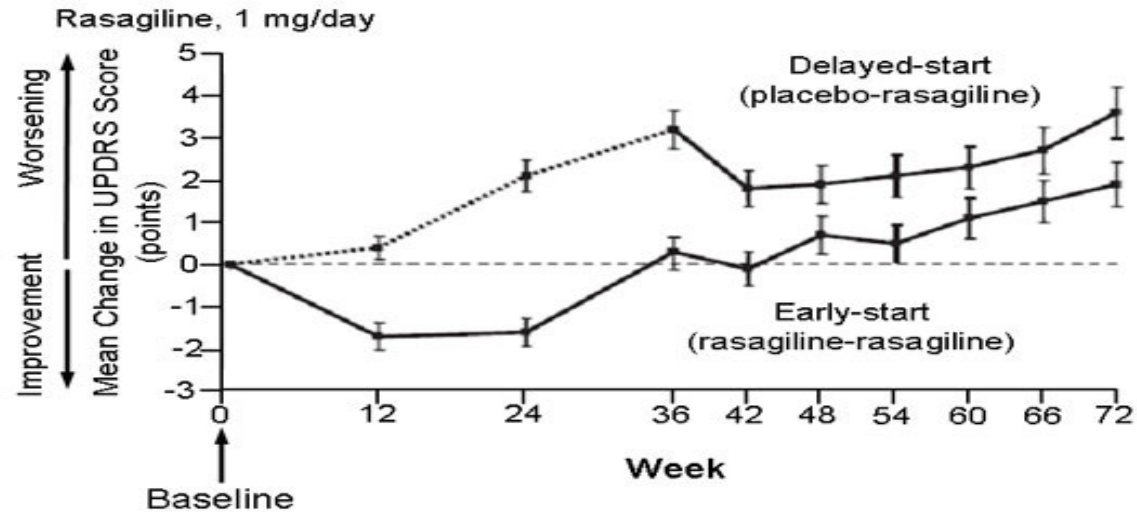


# Disease Modifying?

TEMPO Result: Rasagiline Improves UPDRS for 2 Years<sup>[62]</sup>



ADAGIO Results<sup>[63]</sup>



- Subsequent extended duration studies have defunct this theory
- Safinamide: newer MAOI as adjuvant to L-Dopa to reduce "Off" time

# Amantadine

## **NMDA glutamate receptor antagonist**

- weak anticholinergic
- ↑ dopamine release
- Has symptomatic benefit as monotherapy  
“likely efficacious and clinically useful”

## **Side Effects**

insomnia, livedo reticularis, **confusion**, leg oedema, blurred vision

# Amantadine and dyskinesias

- 24% reduction in dyskinesias
- improved “off” motor performance
- no change in “on” performance

Only agent ever shown to improve dyskinetic and OFF motor symptoms

Clin Neuropharmacol. 2000 Mar-Apr;23(2):82-5.

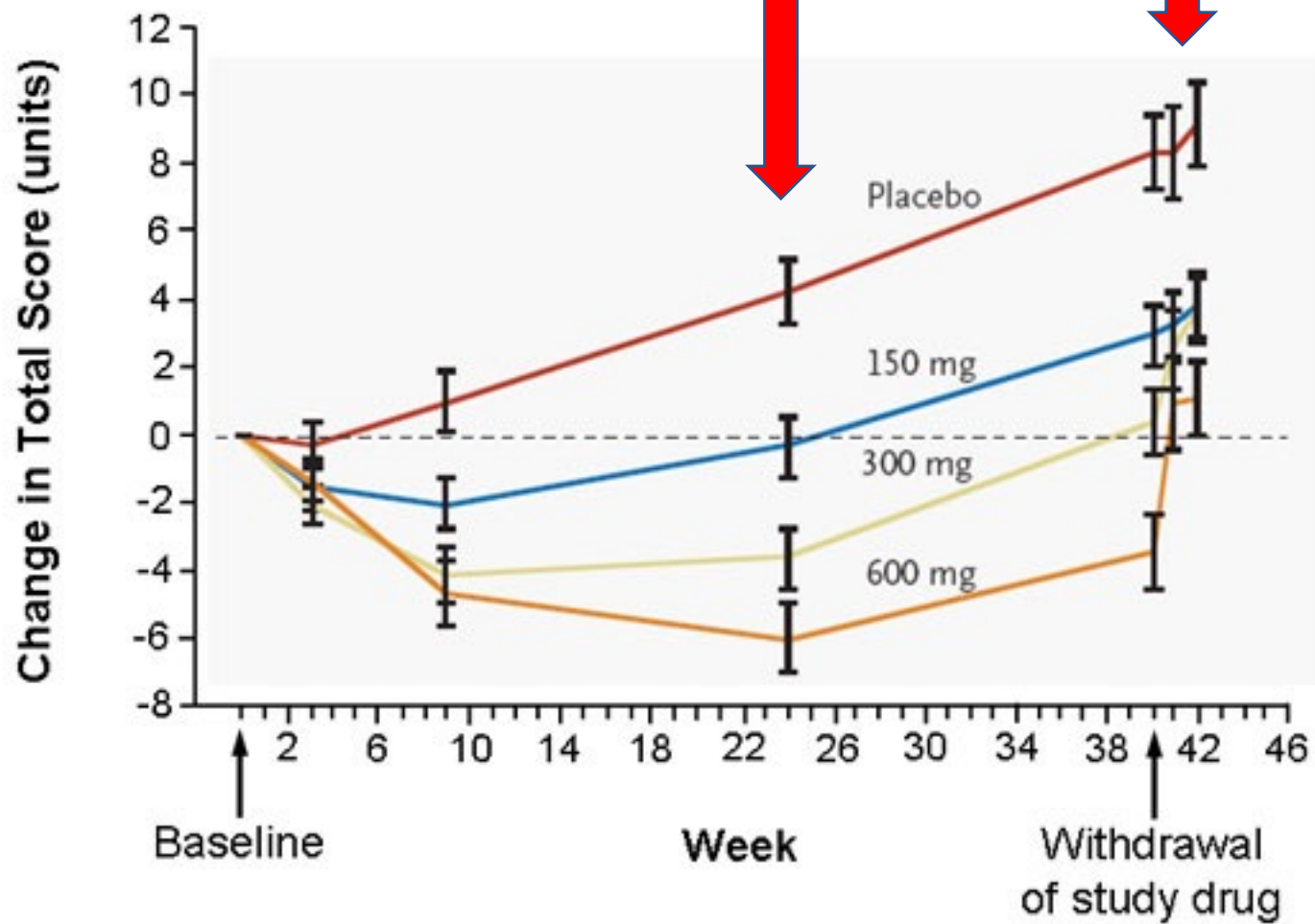
**The effect of amantadine on levodopa-induced dyskinesias in Parkinson's disease: a double-blind, placebo-controlled study.**

[Snow BJ](#), [Macdonald L](#), [Mcauley D](#), [Wallis W](#).

Department of Neurology, Auckland Hospital, New Zealand.

Is Levodopa Toxic?

Changes in Total Scores on the UPDRS<sup>[60]</sup>



Negative scores indicate improvement from baseline.

# Managing EARLY motor fluctuations

Check environmental and PK factors



**L-dopa  
adjustments**

(Efficacious)

Adjust times/  
day

Hallucinations  
Dyskinesia

**DA agonists**

Efficacious

Once daily/slow  
titration

Hallucinations  
Dyskinesia

Leg oedema  
Somnolence  
ICD

**MAOB  
Inhibitors**

Efficacious

One dosage  
Once daily  
No titration

Hallucinations  
Dyskinesia

Serotonin  
syndrome

**COMT Inhibitors**

Efficacious

No titration

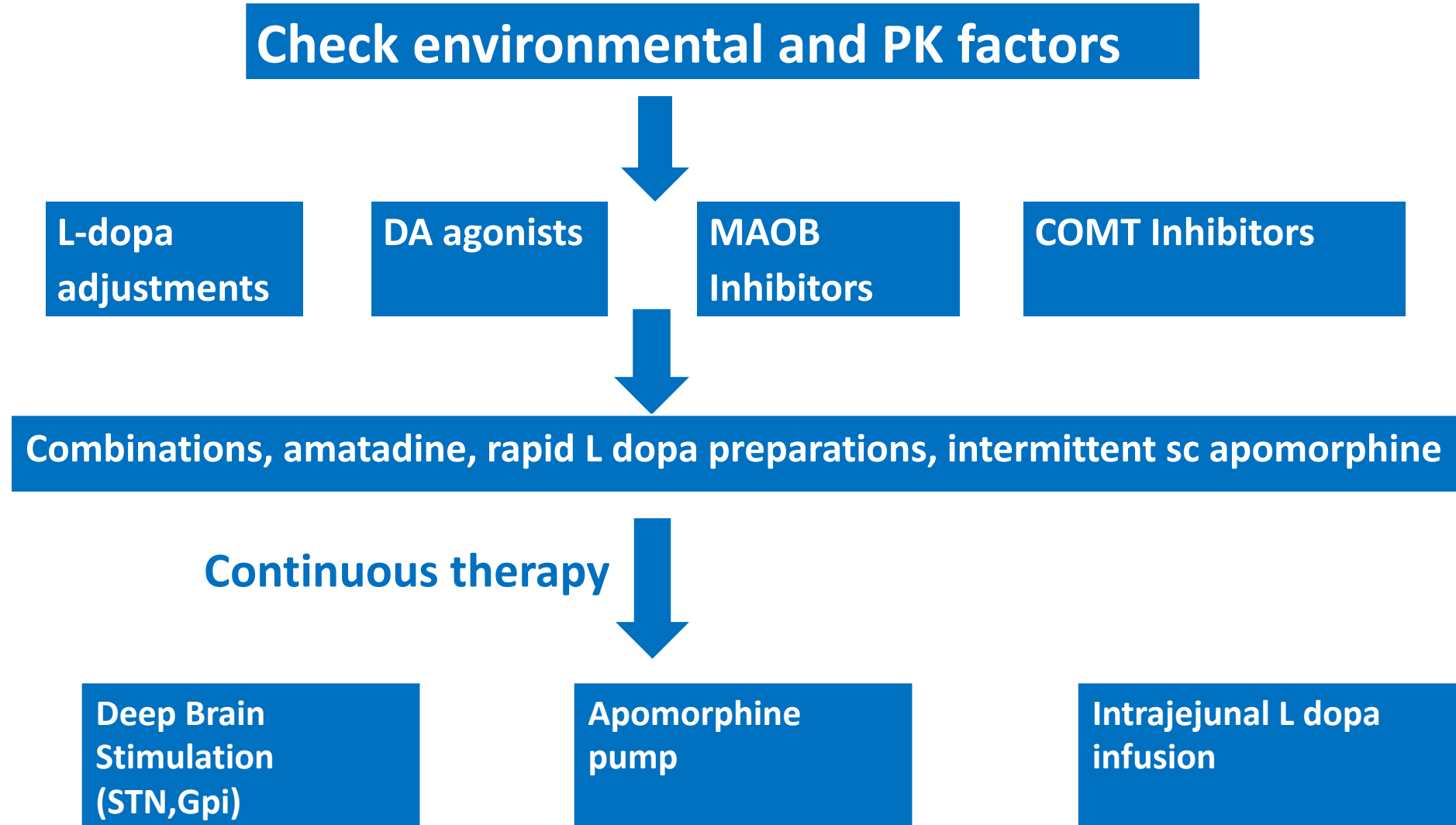
Hallucinations  
Dyskinesia

Diarrhoea

Fox et al  
2011



# Managing more severe fluctuations



# Continuous device assisted stimulation (Not advanced therapy)

1. Apomorphine infusion
2. Intestinal preparation of levodopa (Duodopa)
3. Deep Brain Stimulation (DBS)

# Apomorphine Therapy



A Crono PAR infusion pump is shown against an orange background. The pump has a clear reservoir with markings from 5 to 20 ml. The digital display shows '20 OFF ml/h'. Below the display are three buttons: a blue 'd/p' button, a black stop button, and a red 'ON/OFF' button with a plus sign. The text 'Crono PAR' is printed below the buttons.

Apomine® Solution for Infusion (apomorphine hydrochloride hemihydrate) does not contain morphine. It is not a narcotic, has no painkilling properties and is not habit-forming or addictive.

Please discuss any questions you may have regarding your treatment with Apomine® Solution for Infusion with your healthcare team.

**Apomine®**  
Solution for Infusion  
apomorphine hydrochloride hemihydrate

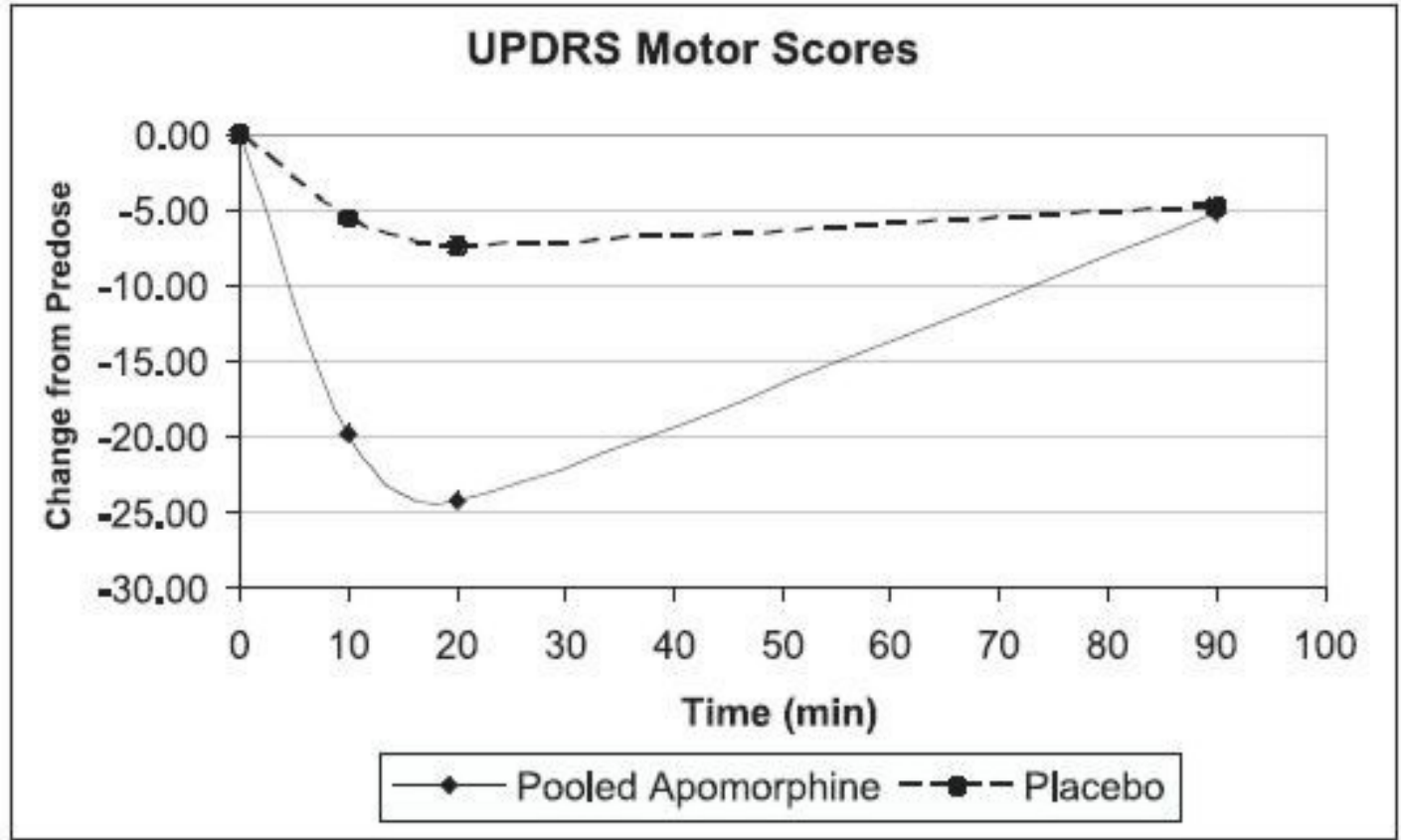


Apomorphine



# Apomorphine

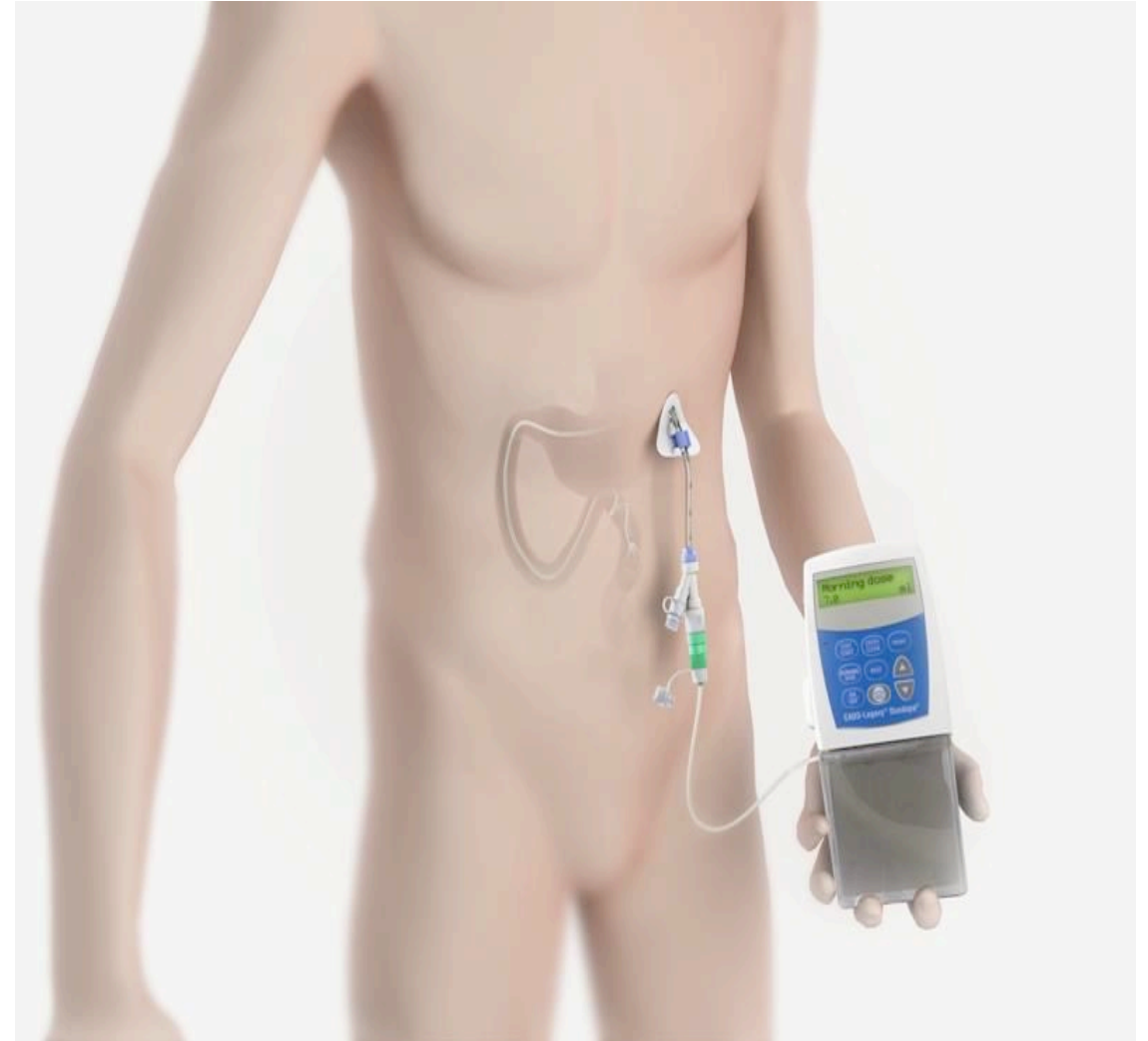
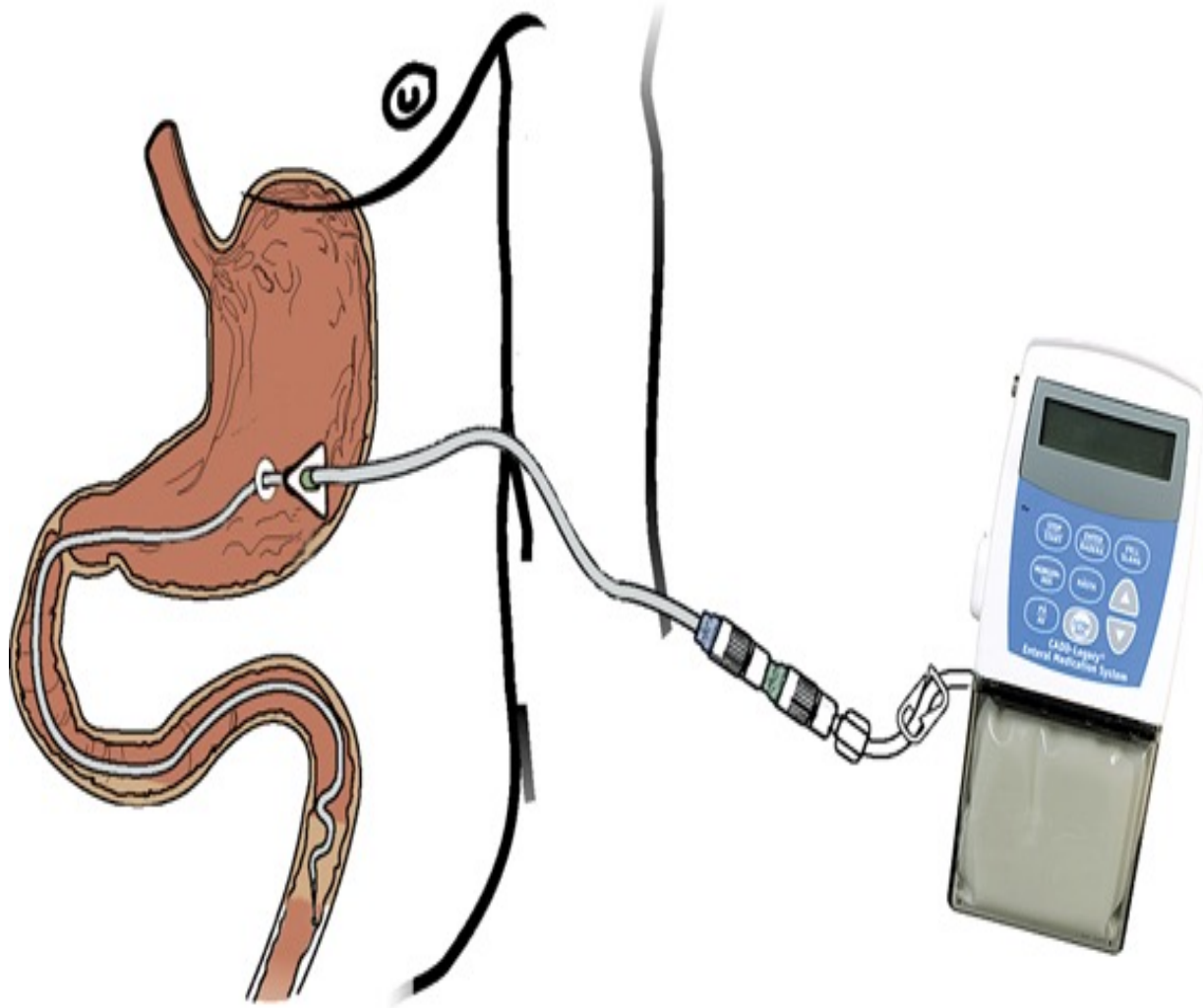
- Apomorphine is a potent injectable dopamine agonist
- Apomorphine cannot be given orally
- the dose of Apomorphine is individually tailored

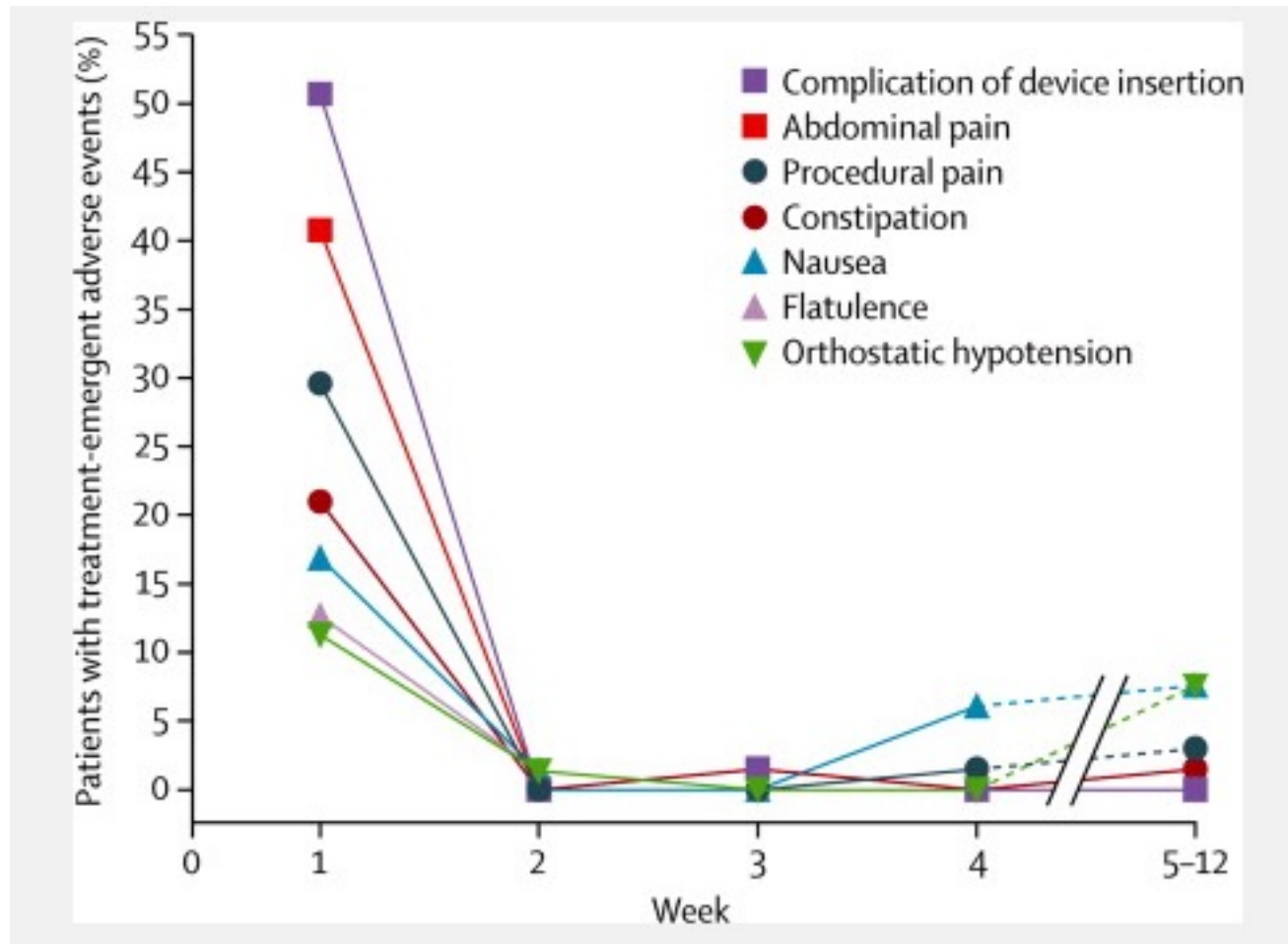


# Side Effects

- Nausea and vomiting
- Nodule formation
- Temporary tiredness
- Neuropsychiatric complications
- Haemolytic anaemia

# DUODOPA



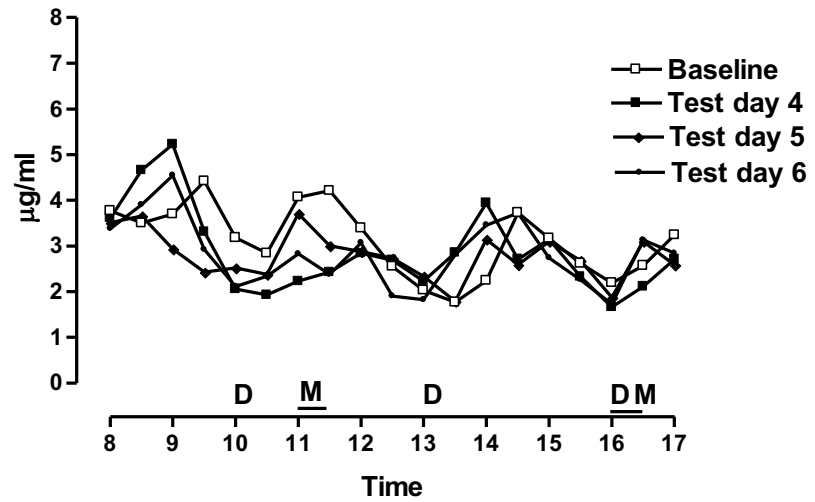


Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study  
 Lancet Neurology 2014;13:141-149

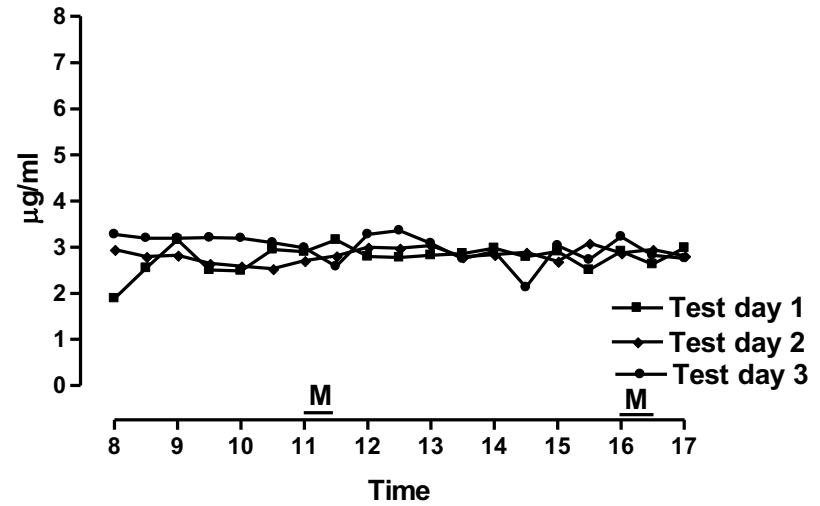


# Plasma Levodopa Concentrations

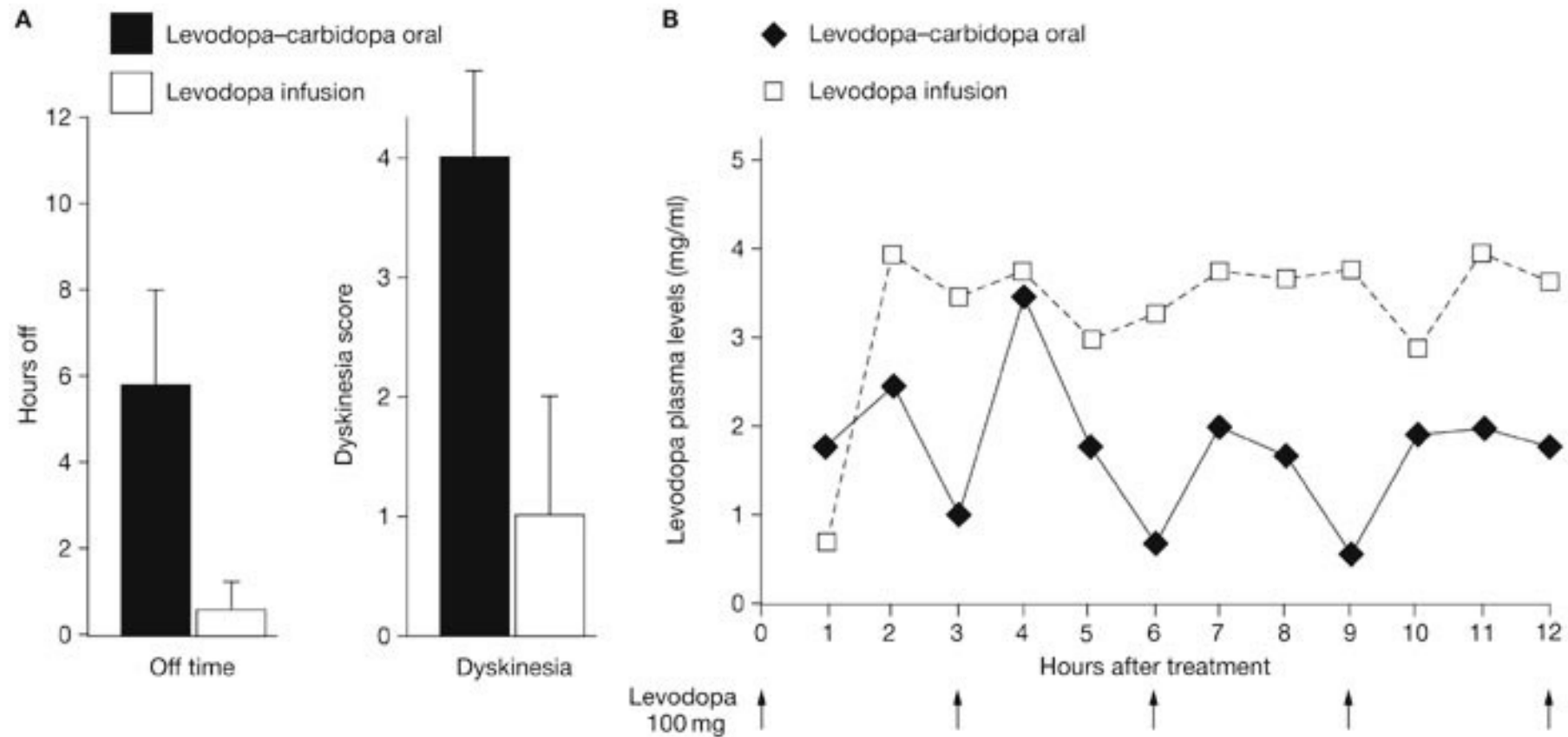
**Patient 03 Sinemet  
plasma levodopa**



**Patient 03 Duodopa  
plasma levodopa**

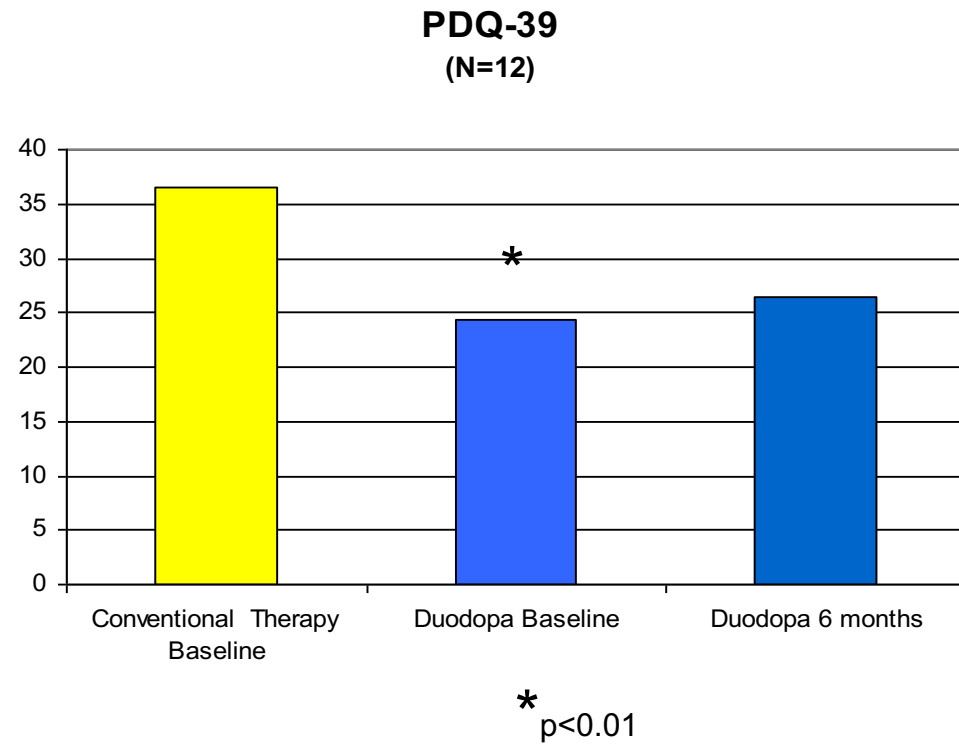


**Figure 3** Effect of intrainestinal levodopa infusion on motor complications in Parkinson's disease

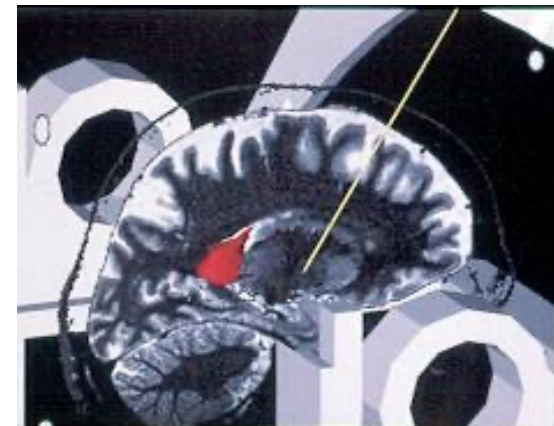
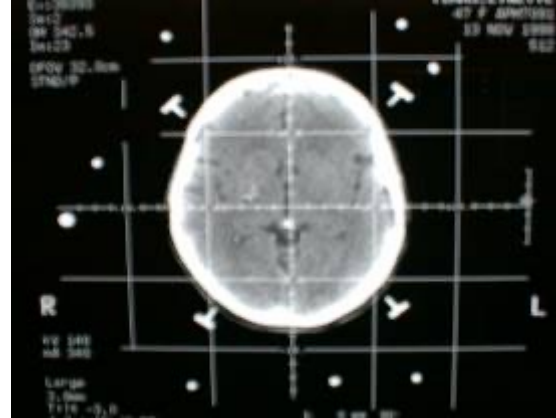


Olanow CW *et al.* (2006) Drug Insight: continuous dopaminergic stimulation in the treatment of Parkinson's disease *Nat Clin Pract Neurol* 2: 382–392 10.1038/ncpneuro0222

# 6 Months Follow Up: PDQ-39



# Deep Brain Stimulation



## Treadmill exercise in PD rodent models

Treadmill exercise → early PD alpha-synuclein model

Exercising > sedentary rats

1. Recovery corticostriatal synaptic plasticity (long term potentiation)
2. Associated with BDNF increase and striatal dendritic spine formation ↑
3. Alpha-synuclein spreading ↓ in the Substantia Nigra pc

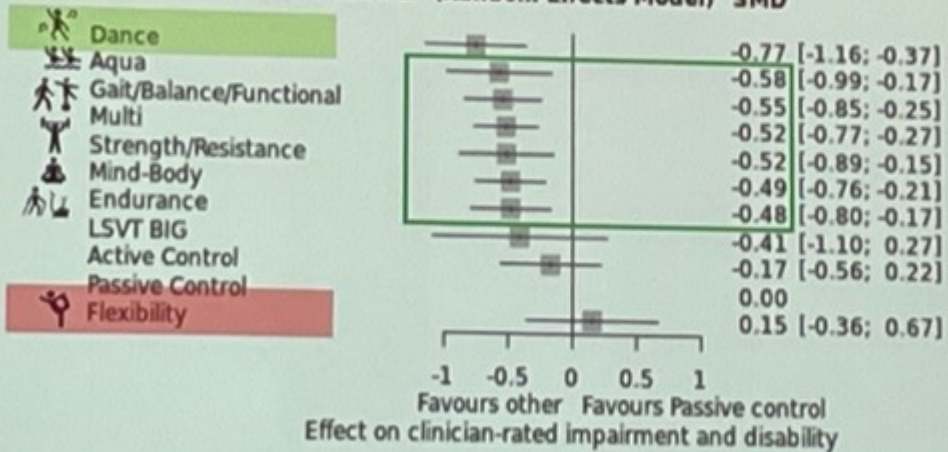
# Exercise in IPD

## EBM intervention

## Which exercise type is best for motor symptoms?

Network meta-analysis ( 71 RCTs, N=3196)

Contrast to Passive control (Random Effects Model) SMD

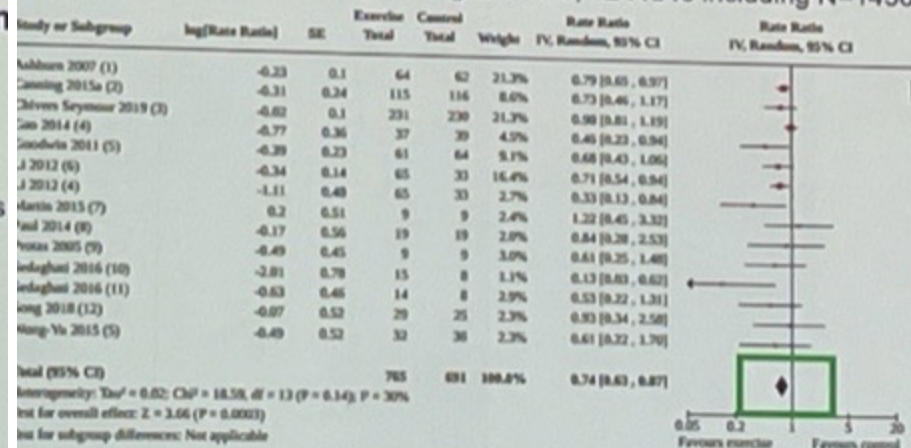


Many types of exercise have moderate effect sizes



## Exercise effective in alleviating falls?

Tai Chi, balance and strengthening exercise, 12 RCTs including N=1456



Reduction of fall rates 26%

Mild/moderate PD  
 Minimal cognitive decline  
 Relatively low risk of FOG



# What was the intervention?

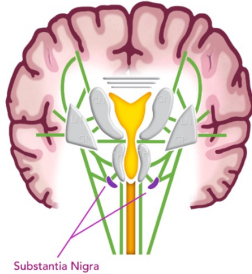
- **Multidisciplinary intervention**
  - Physiotherapy
  - Occupational therapy
  - Speech and Language therapy
  - Dietician
  - Access to both inpatient and day rehabilitation programs

# Occupational therapy intervention for Parkinson's disease

- Exercise
- Environmental cues
- Self management and behavioral strategies
- Strong evidence for motor performance, postural stability and balance
- Moderate evidence for quality of life

# Patient Education

Extrapyramidal System  
*Automatic System*



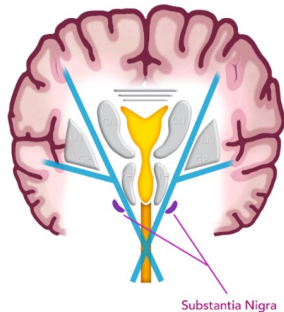
## Automatic System

Movements performed automatically,  
Without conscious effort.

- Blinking
- Swallowing
- Swinging arms when walking



Pyramidal System  
*Intentional System*



## Intentional System

Intentional, purposeful movements.

- Driving down highway when raining
- Exercising
- Learning to play piano





# Intentional System: Speech/Voice

- Stimulability

<b><u>BASELINE STATUS:</u></b>			
Sustained/a/Trial 1:	7	seconds	60-65 dB
Sustained/a/Trial 2:	8	seconds	61-65 dB
Reading:			dB
<b><u>STIMULABILITY:</u></b>			
Sustained/a/Trial 1:	14	seconds	88-92 dB
Sustained/a/Trial 2:	11	seconds	82-89 dB

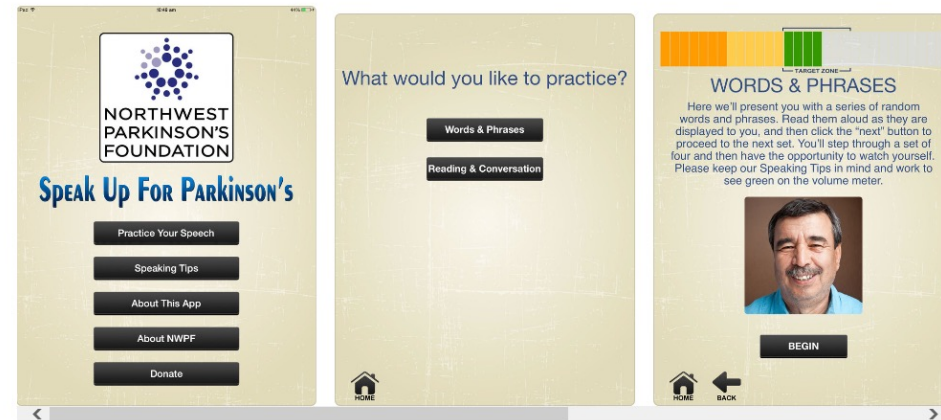
I didn't know I still had it in me!

- App



**Speak Up For Parkinson's** 4+  
Sandcastle  
Free

## iPad Screenshots



## Description

The Speak Up for Parkinson's app is a useful tool for Parkinson's patients to practice their speech. The approach pays special attention to the volume of the patient's voice, a key factor that helps to address several of the challenges faced with Parkinson's. Two practice tools are included: 1) Words & Phrases - a series of random

## Treadmill exercise in PD rodent models

Treadmill exercise → early PD alpha-synuclein model

Exercising > sedentary rats

1. Recovery corticostriatal synaptic plasticity (long term potentiation)
2. Associated with BDNF increase and striatal dendritic spine formation ↑
3. Alpha-synuclein spreading ↓ in the Substantia Nigra pc

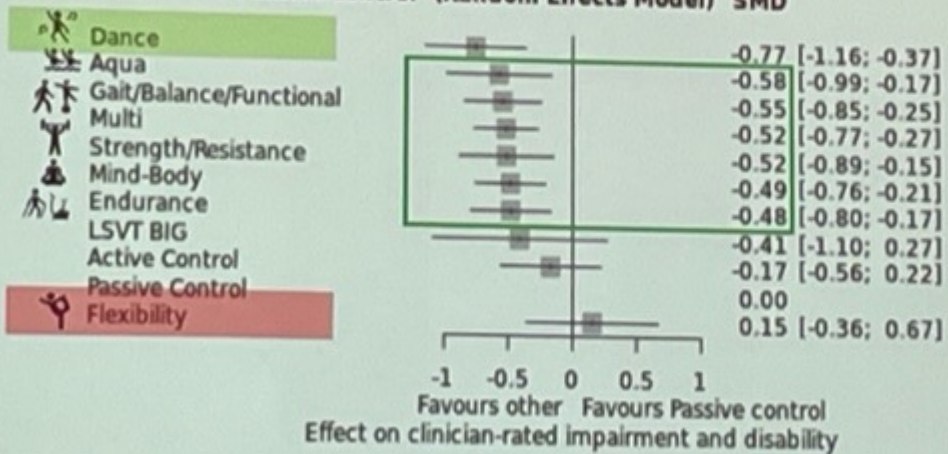
# Exercise in IPD

## EBM intervention

## Which exercise type is best for motor symptoms?

Network meta-analysis ( 71 RCTs, N=3196)

Contrast to Passive control (Random Effects Model) SMD

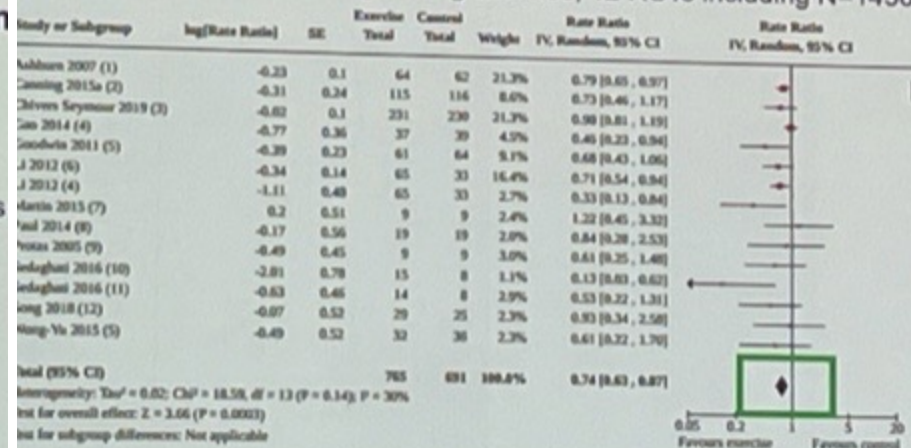


Many types of exercise have moderate effect sizes



## Exercise effective in alleviating falls?

Tai Chi, balance and strengthening exercise, 12 RCTs including N=1456



Reduction of fall rates 26%


Mild/moderate PD  
 Minimal cognitive decline  
 Relatively low risk of FOG



## Utilisation of the multidisciplinary team

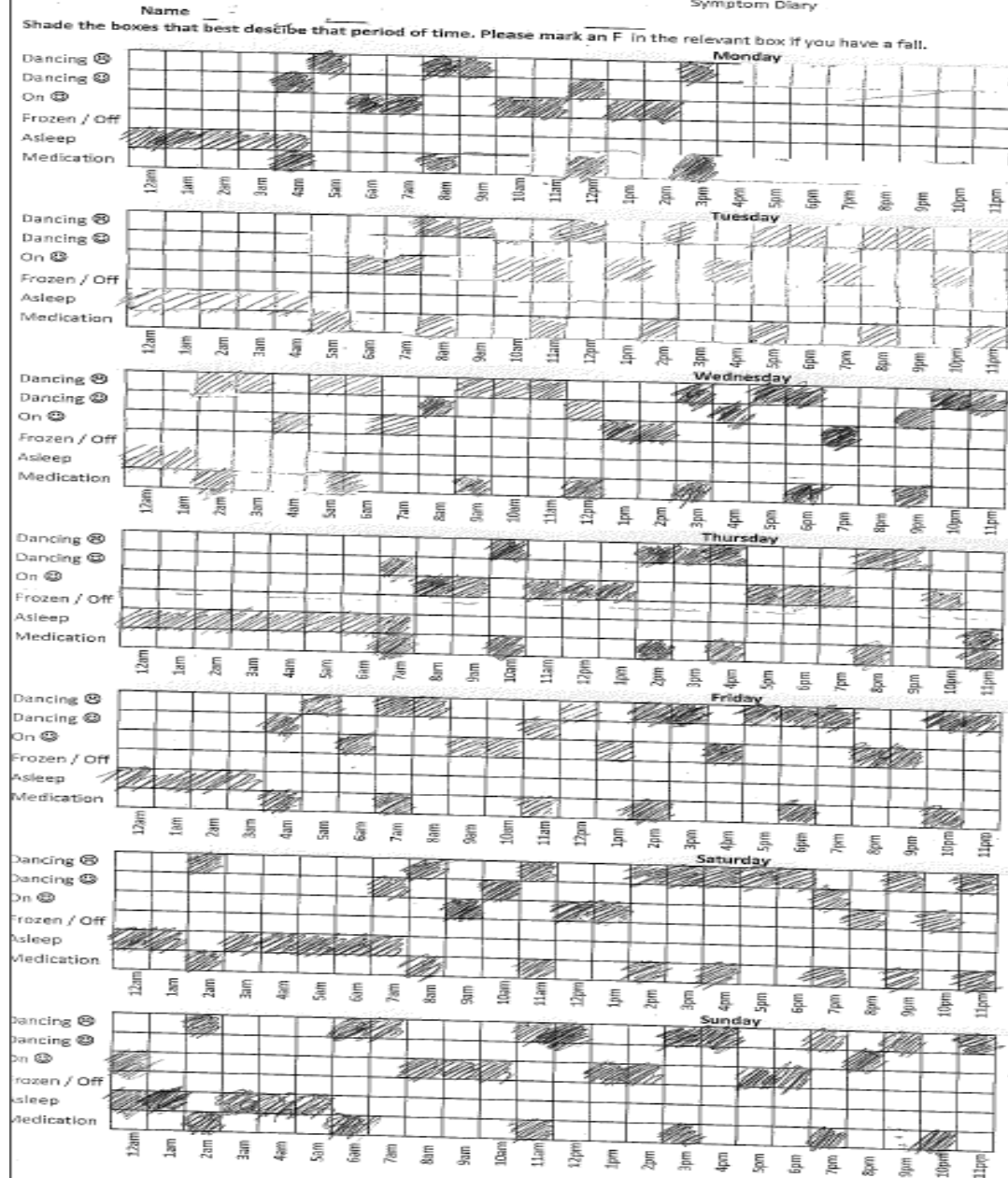
- Primary goal is RIGHT TREATMENT IN THE RIGHT PLACE AT THE RIGHT TIME FOR THAT PERSON
- Treatment plans are coordinated as a team with referral on to appropriate existing community services that can provide targeted therapies.
- Sharing of information and understanding of how the breadth of the patients motor and non-motor symptoms may be impacting across discipline specific areas assists effective and efficient service delivery.
- Progressive disease = monitoring and adapting plan over time as Patient's needs change
- Education empowers the patient to better manage their own health and potentially reduce or prevent further decline

# The multidisciplinary team in action

 <b>Maleny Soldiers Memorial Hospital</b> MOVEMENT DISORDER CLINIC Your Summary Date: _____		<i>Patient Label</i>	
<b>Movement Disorder Type/ Symptoms:</b>			
<b>Medication Changes</b>		<b><u>Your Feedback</u></b>	
<b>Skin Care</b>			
<b>Nutrition</b>			
<b>Memory &amp; Thinking</b>			
<b>Physical &amp; Daily Activities</b>			
<b>Social Support</b>			
<b>Swallowing &amp; Speech</b>			
<p style="text-align: center;"><u>Please bring ALL Medications or Webster Pack to each clinic appointment - Thank You</u></p> <p style="text-align: center;">Your next review will be in _____</p> <div style="text-align: center; border: 1px solid black; padding: 2px;">           Clinic Phone Number: 5420 5000         </div>			

# "Horses for course"

Week Starting 4/10/18



Comments

Comments  
Bad afternoon, Headache all afternoon.

Comments  
NOT MUCH SLEEP. Tremor wakes me. @

Comments  
Good day for me.

Comments

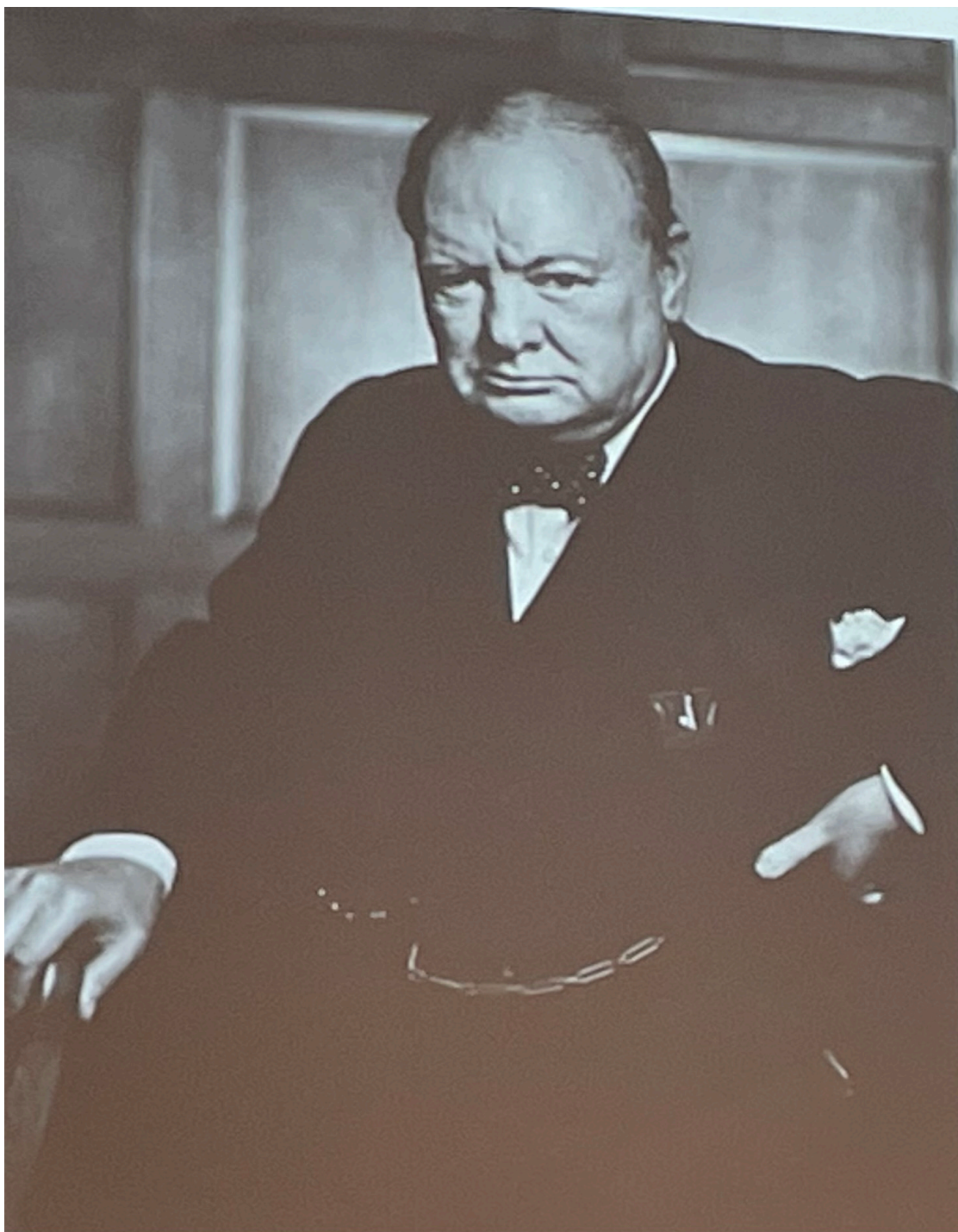
Comments  
Had afternoon out with friends. I was very hot in the premises. Everyone else found it comfortable. Tremor is worse when body hot

Comments

Comments may include mood, non movement symptoms, specific event details, medication changes or extra doses required. This information is all critical for your health practitioners to assist in improving your care plan.

# Summary

- PD is a multisystem disease
- Classic motor symptoms usually not the main contributor to QOL, morbidity and mortality
- Non motor symptoms often predate motor systems by several years (Sleep, cognition, mood disorder, gut issues)
- Levodopa is the mainstay of treatment and need to give a proper trial (>12/52)
- Address non pharmacological issues first when patients run into issues with motor complications
- No disease modifying agents (“cards have been dealt”)
- MDT approach the most beneficial to enhance symptoms, QOL and need for fulltime nursing home/residential care



**Now this is not the end.  
It is not even the  
beginning of the end.  
But it is, perhaps, the  
end of the beginning.**

Winston Churchill 1942