Advanced Therapies For Parkinson's Disease

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Disclosures

- **Currently working on clinical trials with:**
- **Ely-Lilly**
- **Axovant.**

Agenda

- Introduce "motor complications" in Parkinson's disease
  - Wearing-off / motor fluctuations
  - Dyskinesias
- List medication strategies to manage motor complications
- Discuss advanced therapies for management of motor complications

Beyond the honeymoon

- The first years of PD therapy are marked by a good and sustained response to treatment.
- With progression, some motor complications may take place, e.g.; motor fluctuations and levodopa-induced dyskinesia
- Overall 10 % of patients with Parkinson's per year develop such motor complications.

Aquino & Fox, Mov Disord 2014

What are motor fluctuations?

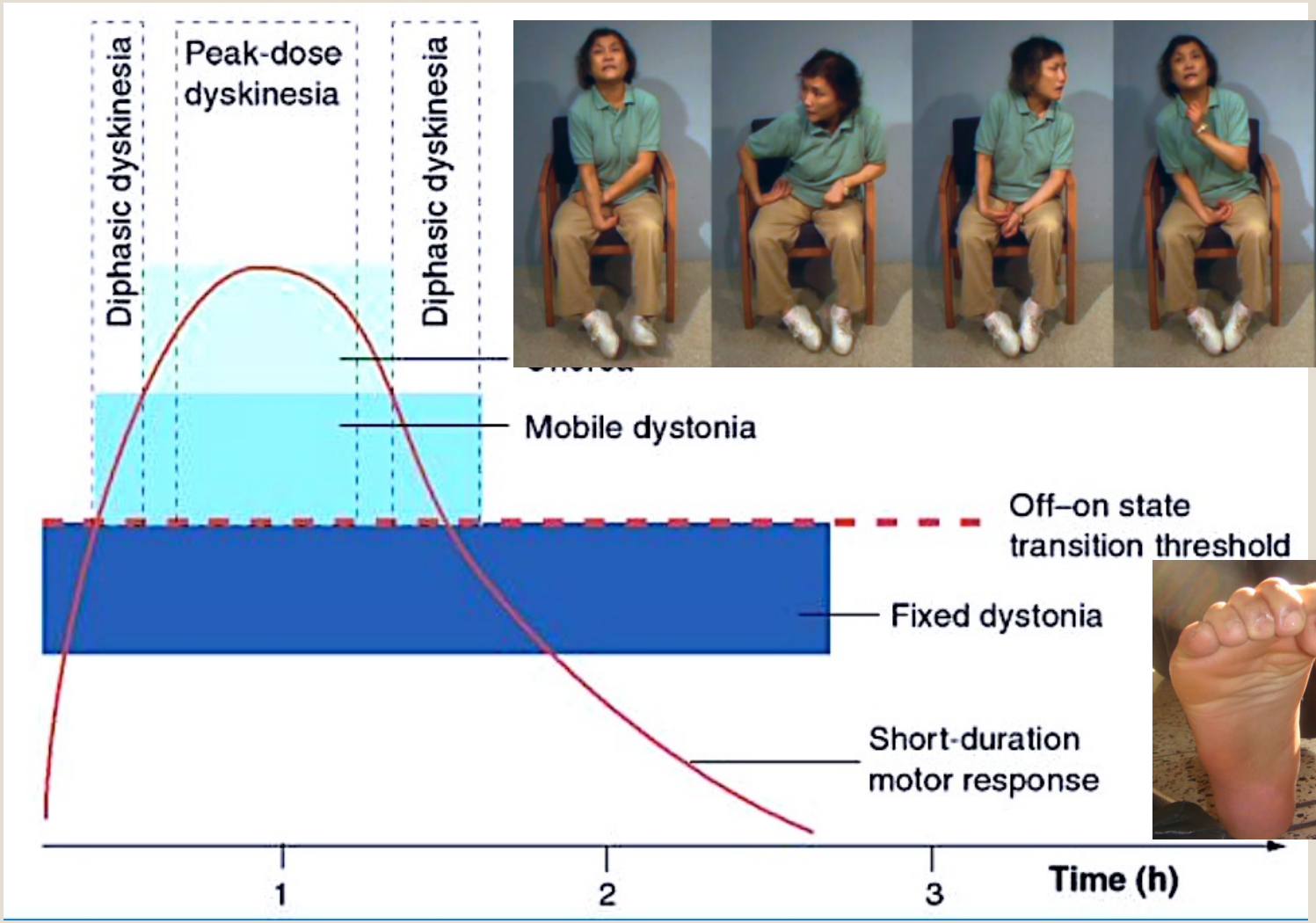
Motor fluctuations	Clinical presentation
Predictable wearing-off	Expected re-emergence of parkinsonian symptoms at the end of LD dose.
Unpredictable, sudden offs	Acute episodes of immobility unrelated to the timing of LD dose.
Dose failure, delayed or partial on response	LD dose failing to provide the expected benefit or benefit delayed by minutes or hours.
On-off fluctuations / 'yo-yoing'	Rapid cycling between being 'on' and mobile with dyskinesia, to being 'off' and immobile

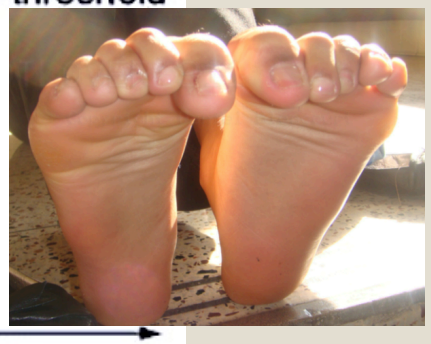
What are dyskinesias?

- **Dyskinesias are involuntary movements that occur in PD, usually in association with medications.**

- **Commonly described as irregular jerking, wiggling, twitching, rocking.**

Subtypes of dyskinesia





Aquino & Fox, 2014

Mechanisms of motor complications

Presynaptic

- Progressive loss of dopaminergic cells
- Impaired dopamine storage
- Conversion of LD in other cells with erratic release/uptake

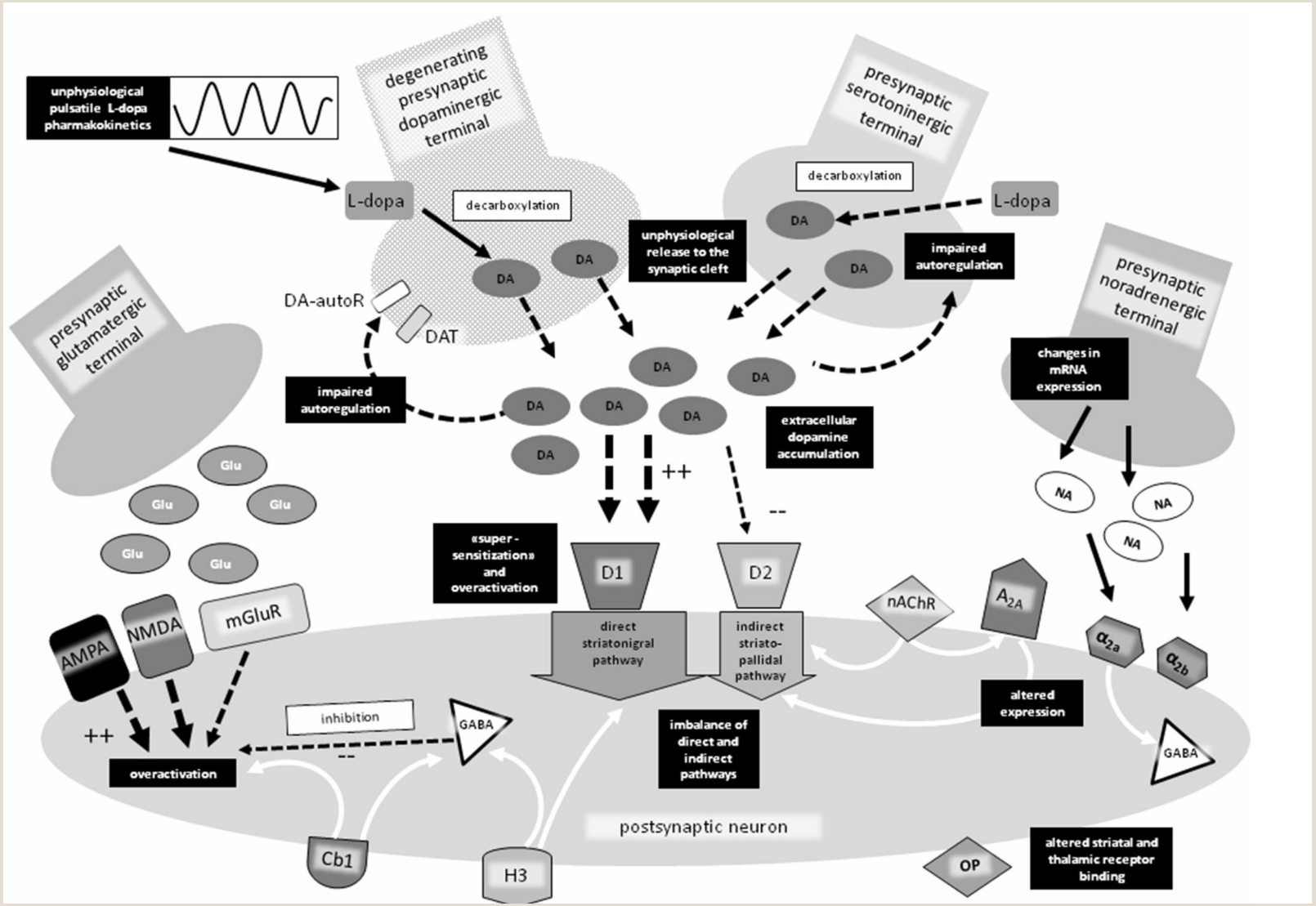
Peripheral

- Bioavailability of LD
- Gastrointestinal absorption
- Passage across blood brain barrier
- Genetic variants in levodopa metabolizing enzymes

Postsynaptic

- Pulsatile dopaminergic stimulation
- Maladaptative synaptic plasticity, e.g.; glutamate
- Non-dopaminergic systems: serotonergic, opioid, alpha$_2$ adrenoceptors, cannabinoids, cholinergic and histaminergic.

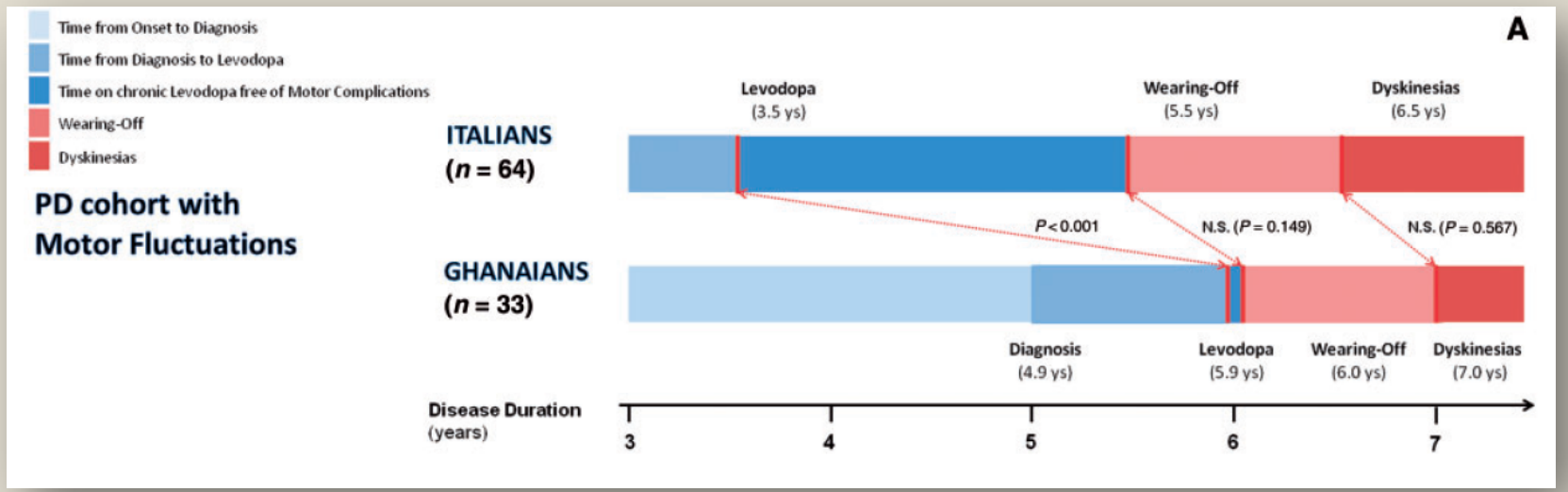
Schaeffer & Berg, 2014



Cilia R, et al, Brain 2014

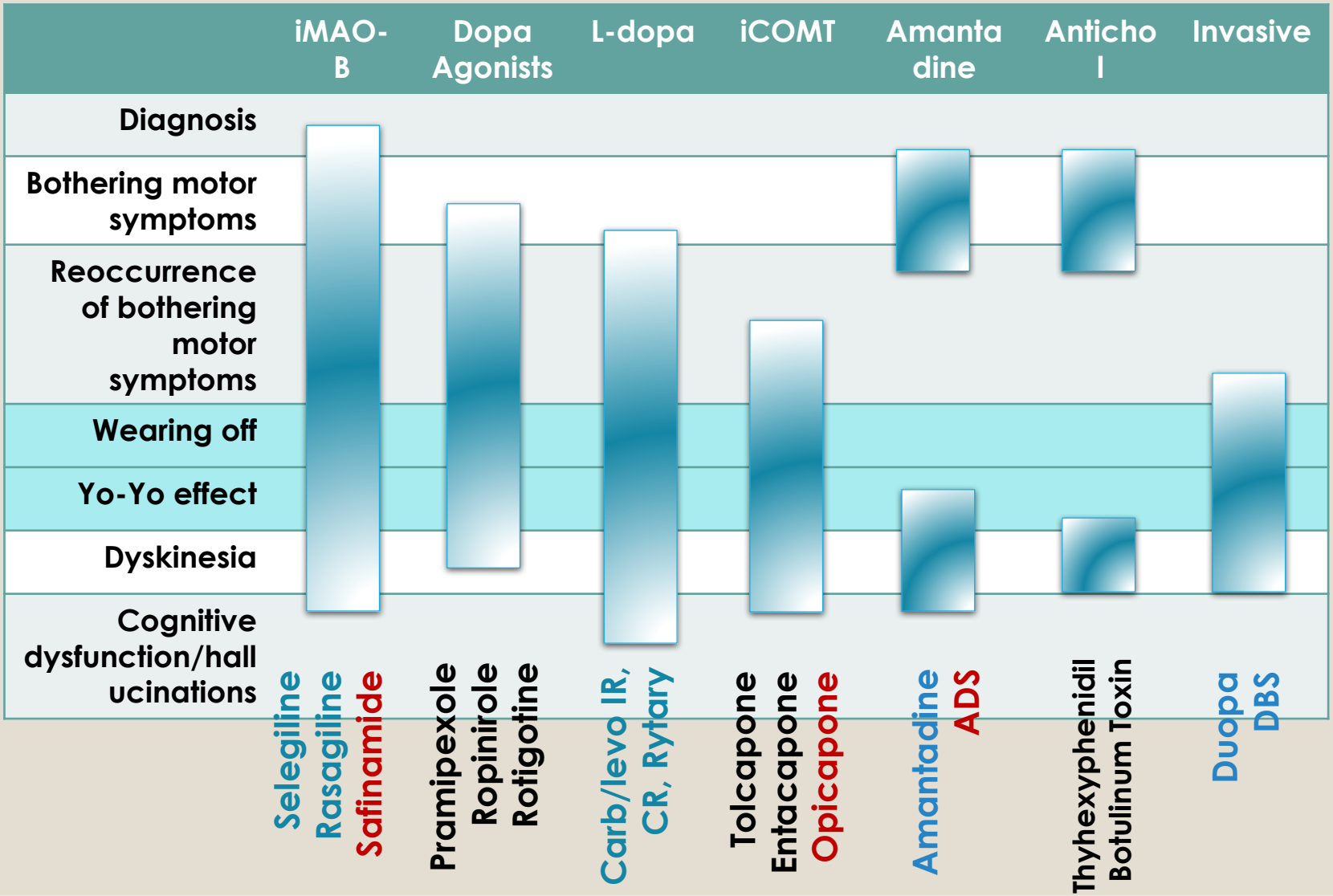
What if we delay PD treatment?

The modern pre-levodopa era of Parkinson's disease: insights into motor complications from sub-Saharan Africa



Fasano, 2014

Available medical strategies



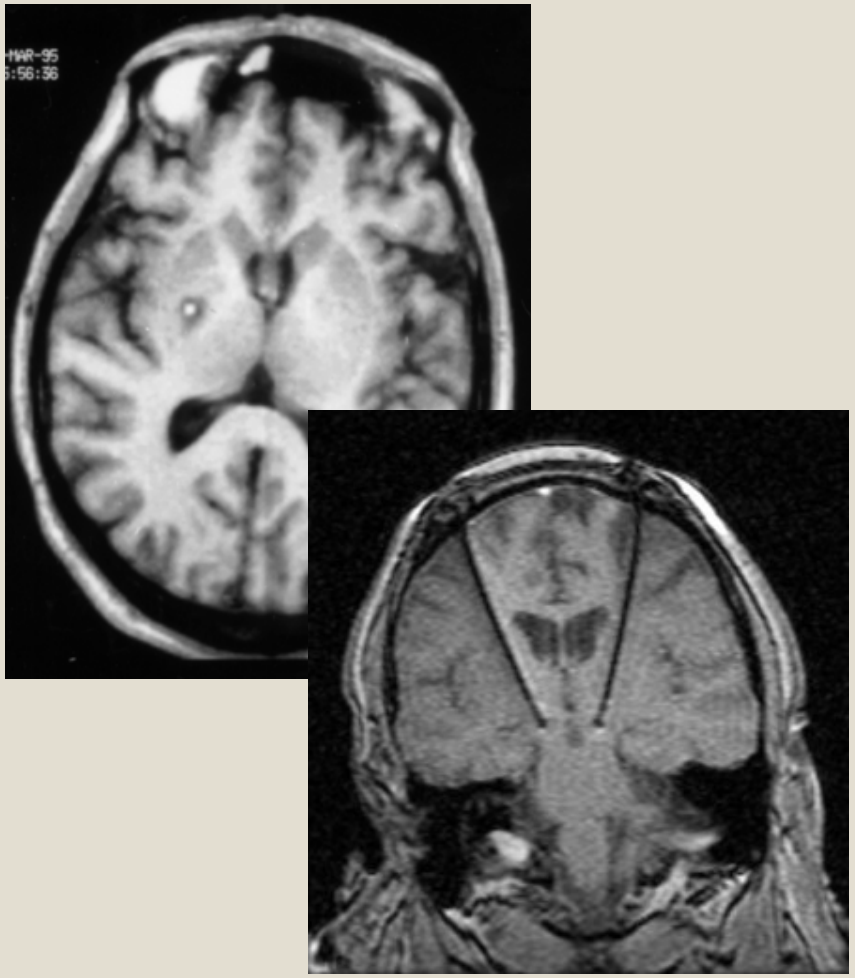
Strategies to manage dyskinesia

- **Reduction of levodopa - at the expense of worsening other PD symptoms.**
- **Amantadine is not always well tolerated.**
- **Clozapine can be an options: rigorous blood monitoring**
- **Because of the several transmitter systems involved (dopaminergic and non-dopaminergic) a wide range of targets can be explored.**

ADVANCED THERAPIES

Surgical therapies for motor complications

- Ablation – pallidotomy or thalamotomy
- Deep brain Stimulation (DBS)
- MRI guided - focused ultrasound (experimental)

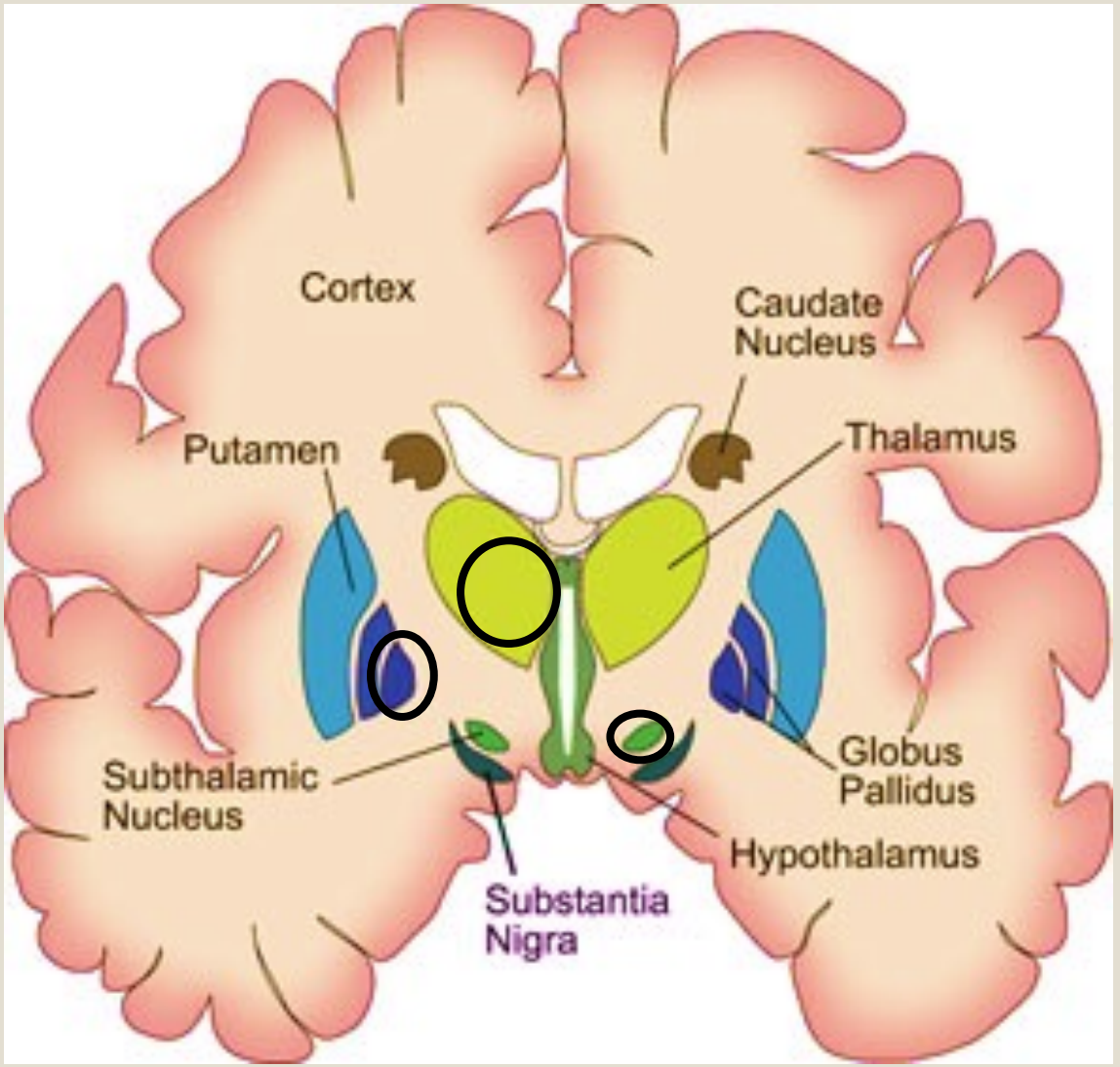


Where to operate?

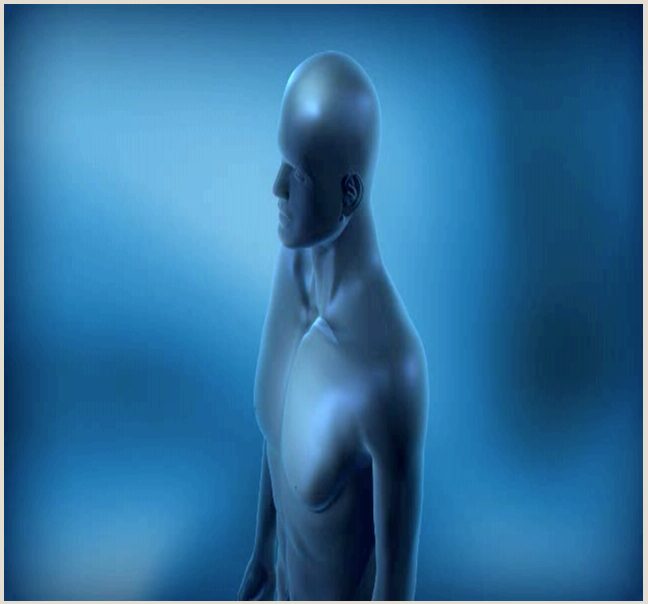
Tremor

Dyskinesia
Slowness
Rigidity

Tremor
Slowness
Rigidity
Reduce drugs
Dyskinesia

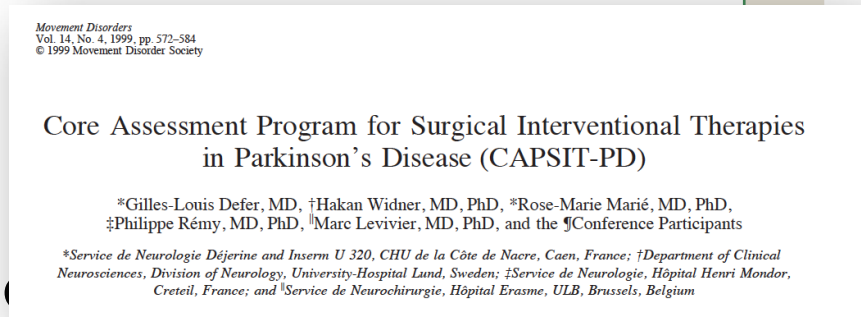


Deep Brain Stimulation



Who are the ideal candidates for DBS?

- ✓Diagnosis of Parkinson's disease
- ✓Symptoms not optimally controlled with meds
- ✓Off periods > 25% diurnal time
- ✓Bothersome dyskinesia
- ✓Age preferably < 70
- ✓Disease duration > 4-5
- ✓Good response to levodop
- ✓Good cognition
- ✓No severe gait/balance problems



Movement Disorders
Vol. 14, No. 4, 1999, pp. 572–584

Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease (CAPSIT-PD)

*Gilles-Louis Defer, MD, †Hakan Widner, MD, PhD, *Rose-Marie Marié, MD, PhD, ‡Philippe Rémy, MD, PhD, ‖Marc Levivier, MD, PhD, and the ¶Conference Participants

**Service de Neurologie Déjerine and Inserm U 320, CHU de la Côte de Nacre, Caen, France; †Department of Clinical Neurosciences, Division of Neurology, University-Hospital Lund, Sweden; ‡Service de Neurologie, Hôpital Henri Mondor, Creteil, France; and ‖Service de Neurochirurgie, Hôpital Erasme, ULB, Brussels, Belgium*

Selection of patients

Disease aspects

Diagnosis of PD

Predominant symptoms

Patient aspects:

Age

Expectations

Brain MRI

DBS

Cognitive assessment aspects

Psychiatric evaluation

Response to levodopa challenge

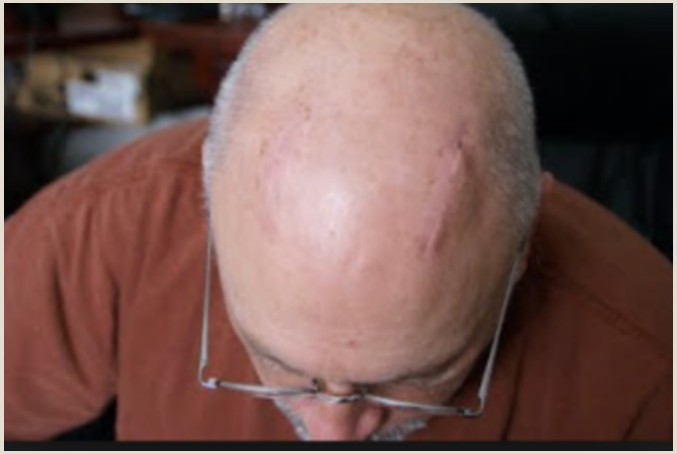
Are there risks?

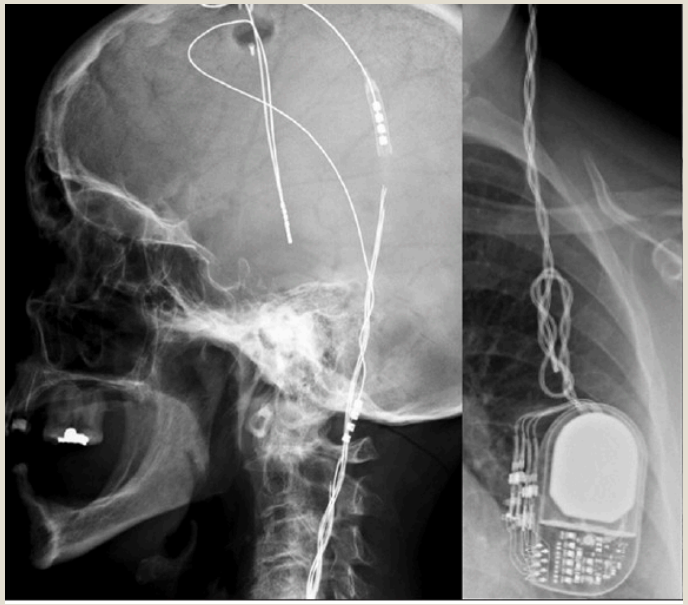
- Infection (skin, neck, pulse generator, skull) can occur in 1 to 10% of patients.

- Intra cerebral bleeding:

  1 to 5 %

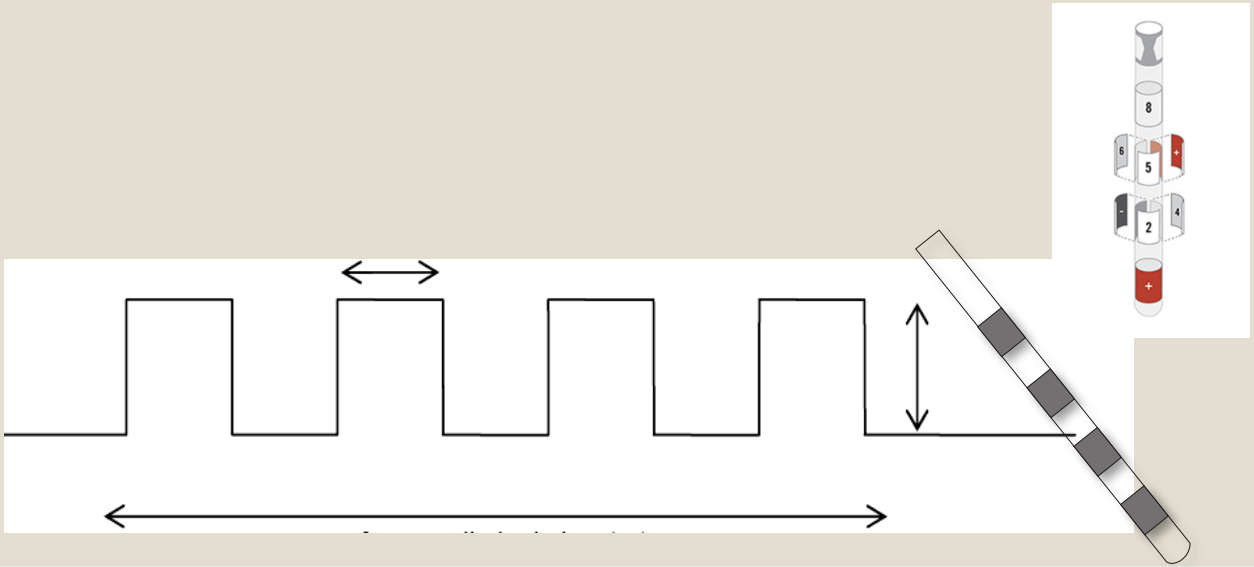
- Problems with the device, battery replacements.



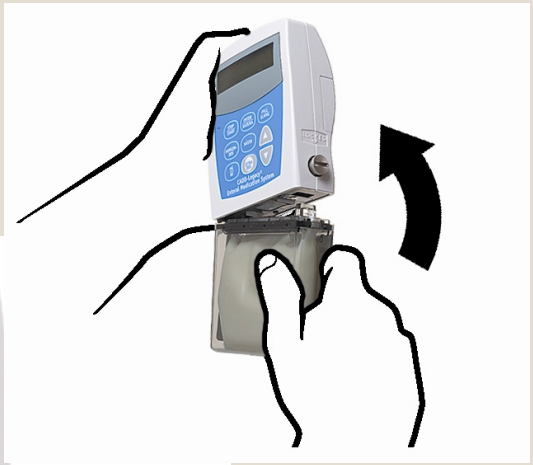


After surgery

- Acute effect - microlesional
- Gradual increase of stimulation (usually after 4 weeks)
- In parallel, reduction of medications
- Final settings in 1 to 3 months



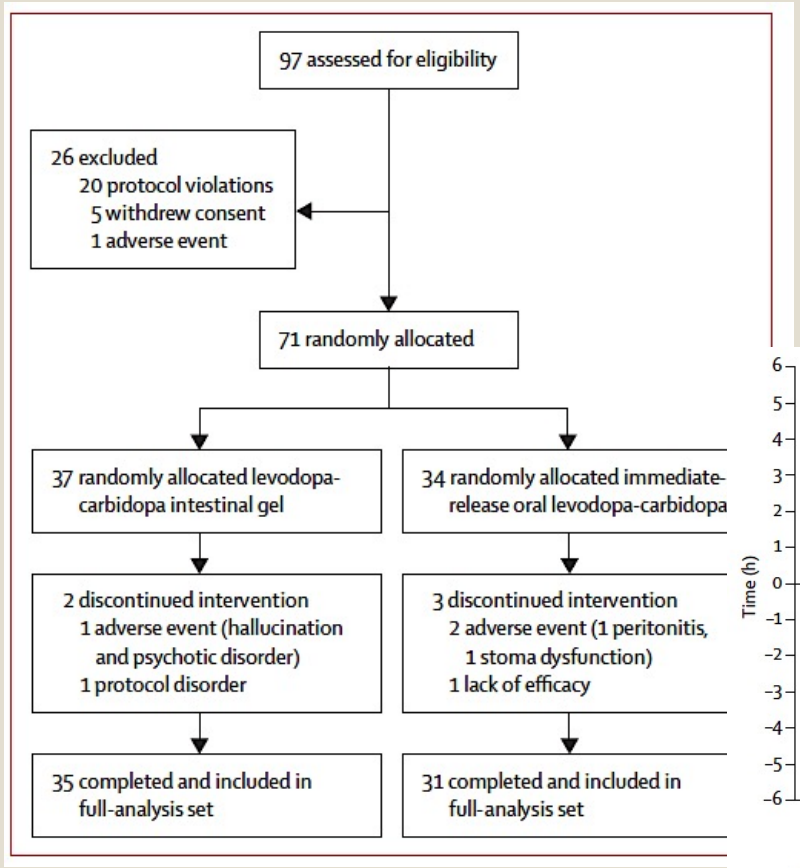
DUOPA®

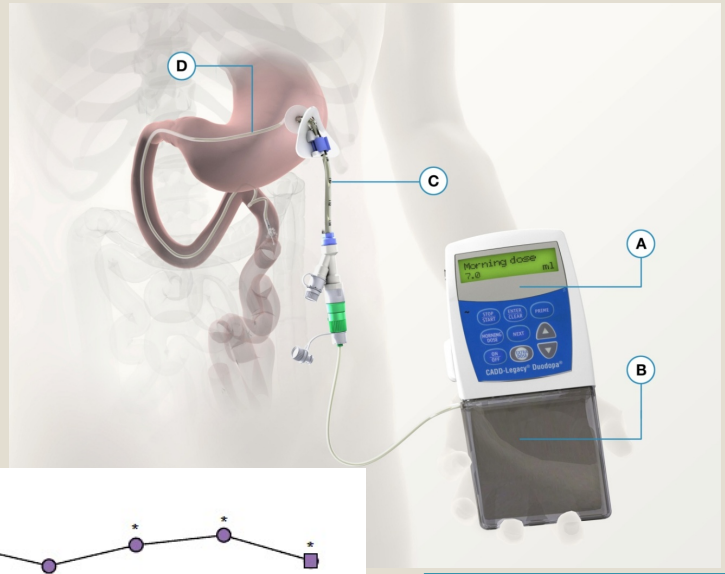


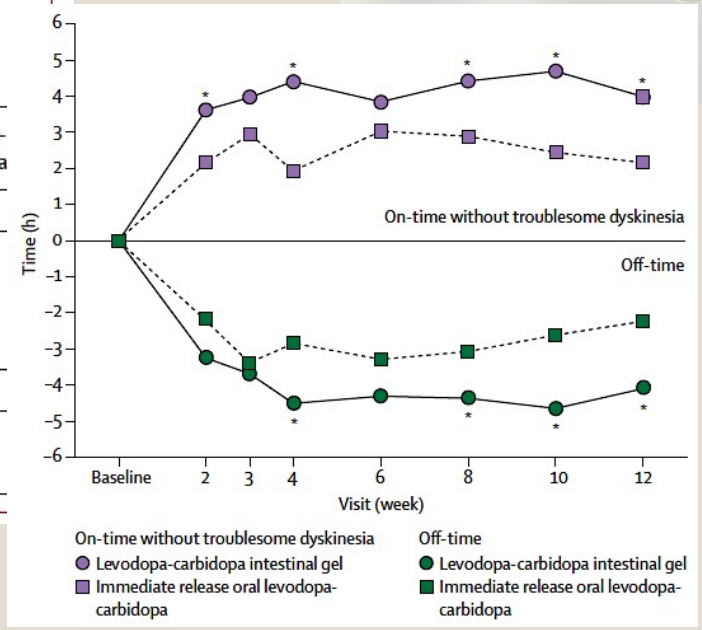
- **Intestinal Gel**
  - Concentrated suspension of levodopa/carbidopa (2g / 0.5g for 100 ml)
  - **Same ratio 4:1** as common oral formulations
  - **Cassette of 100ml**
    - Levodopa 20 mg/ml
    - Carbidopa 5 mg/m
- **Portable pump**
  - **Specially designed**
  - Programmable to allow **individualized dose regimen** infusion
  - **Security features** available :
    - Controlled programming

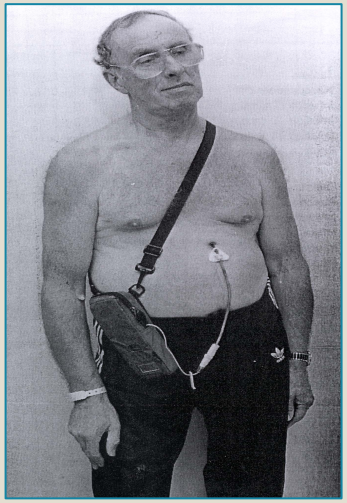
Lancet Neurol 2014; 141-49

Levodopa/carbidopa intestinal gel - Duopa®









Lancet Neurol 2014; 141-49

Levodopa/carbidopa intestinal gel - Duopa®

	Levodopa-carbidopa intestinal gel (n=35)	Immediate-release oral levodopa-carbidopa (n=31)	Treatment difference (95% CI)	p value
Primary efficacy outcome				
Off-time, h per day	−4·04 (0·65)	−2·14 (0·66)	−1·91 (−3·05 to −0·76)	0·0015
Secondary efficacy outcomes				
PDQ-39 summary index	−10·9 (3·3)	−3·9 (3·2)	−7·0 (−12·6 to −1·4)	0·0155
Mean CGI-I score at final assessment‡	2·3 (0·4)	3·0 (0·4)	−0·7 (−1·4 to −0·1)	0·0258
UPDRS part II§	−1·8 (1·3)	1·3 (1·3)	−3·0 (−5·3 to −0·8)	0·0086

Levodopa levels in plasma

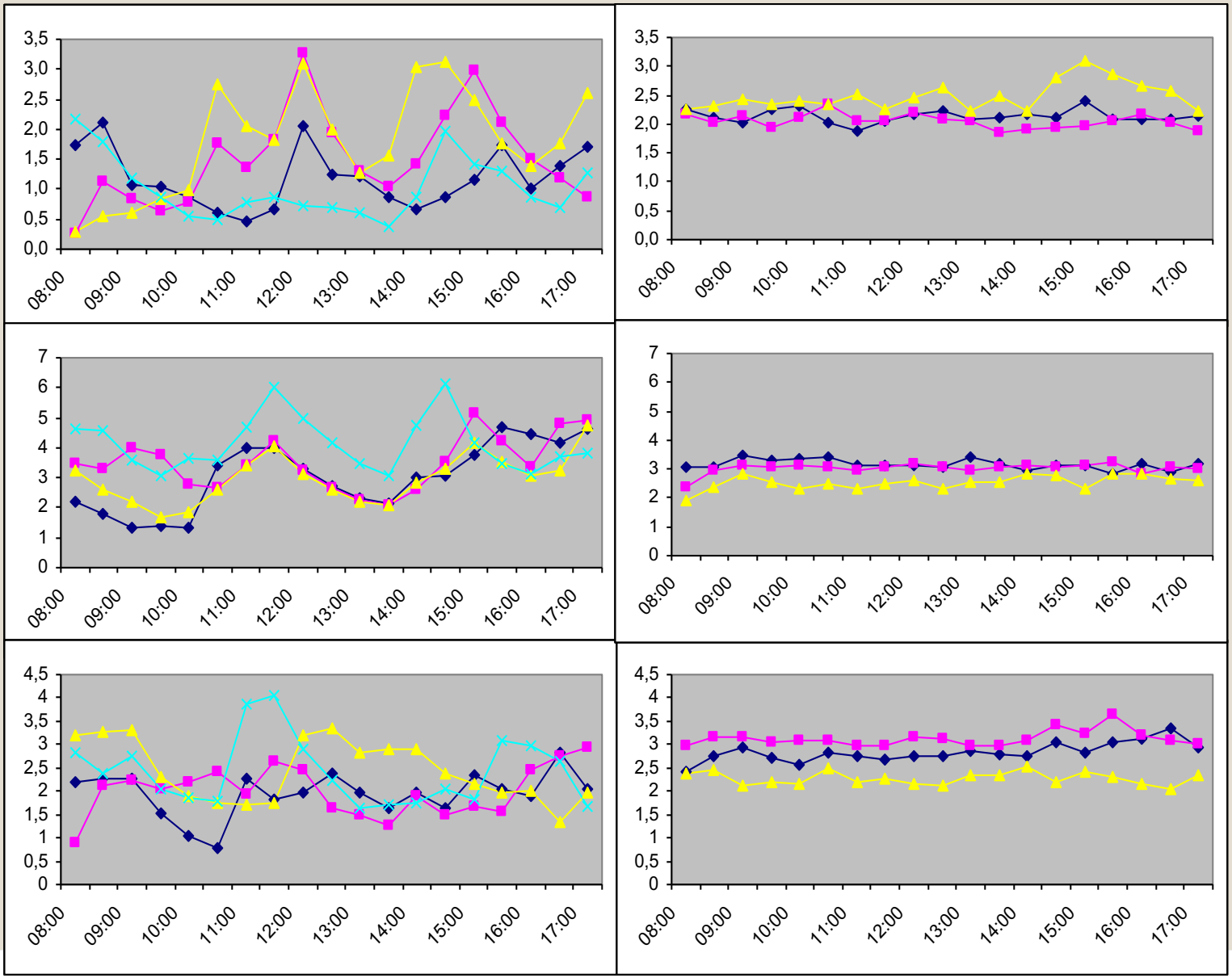
Sinemet

Duopa®

Patient 7

Patient 14

Patient 16

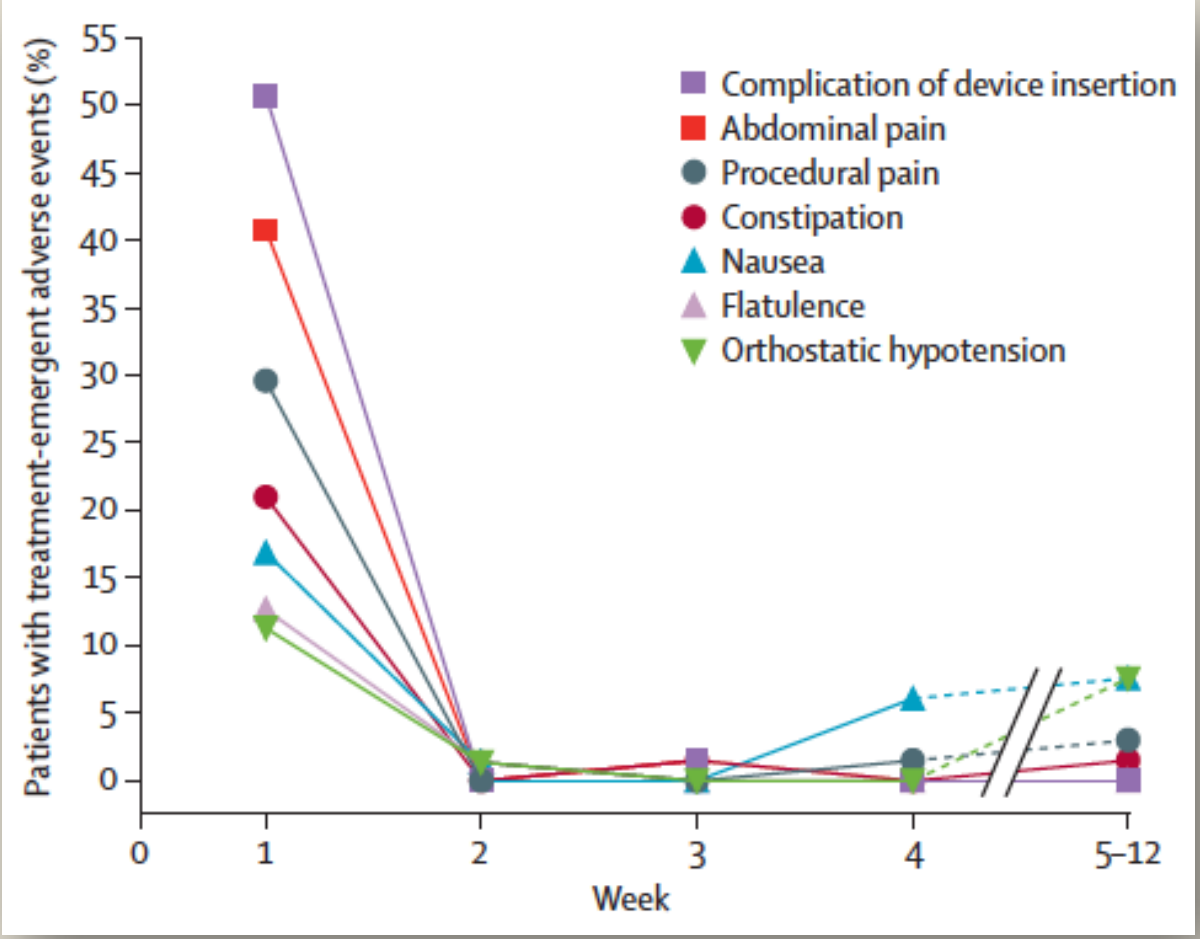


DUOPA® Patient profile

How to select patients:

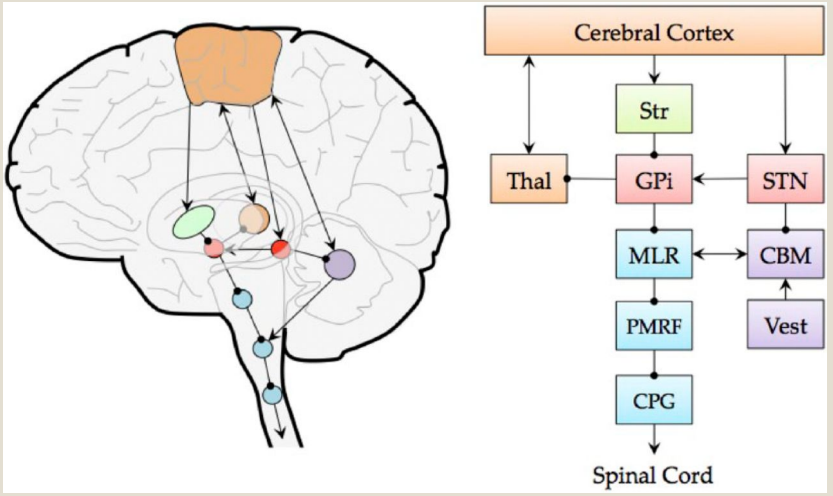
- Severe motor fluctuations
  - Tried different oral drug combinations
  - Clear response to levodopa
    ► good "ON" period
  - Preferably no dementia
  - Preferably no severe depression
  - No age limit restrictions

Duopa adverse events



Freezing of gait and balance problems

- Are complex, and probably involves several distinct circuits: attention, cognition, brainstem degeneration, cholinergic systems.
- It may be a particular problem in patients receiving DBS.



Trials on freezing of gait and balance

- Amantadine
- Donepezil
- Methylphenidate
- Droxidopa
- Atomoxetine
- Memantine
- DBS of the Pedunculopontine Nucleus
- Spinal Cord Stimulation

- **Controversial results, waiting for more definite answers.**

Conclusions

- The better understanding of the mechanism of PD symptoms contributes research and development of new treatments.
- Several ongoing studies might give us more options.
- Despite of limitations, DBS and Duopa are effective therapies motor complications.
- Hopefully future disease modifying therapies will overcome the limitations of symptomatic therapies.

Questions?

Vitoria, ES - Brazil