Dr Barry Snow

Neurologist

Auckland District Health Board

A Modern View of Parkinsons Disease and Dystonia - Concurrent Workshop Repeated

Saturday, 22 June 2013	Start 11:00am	Duration: 55mins	Works
	Start 12:05pm	Duration: 55mins	Works

Dystonia and Parkinson's disease

Barry Snow

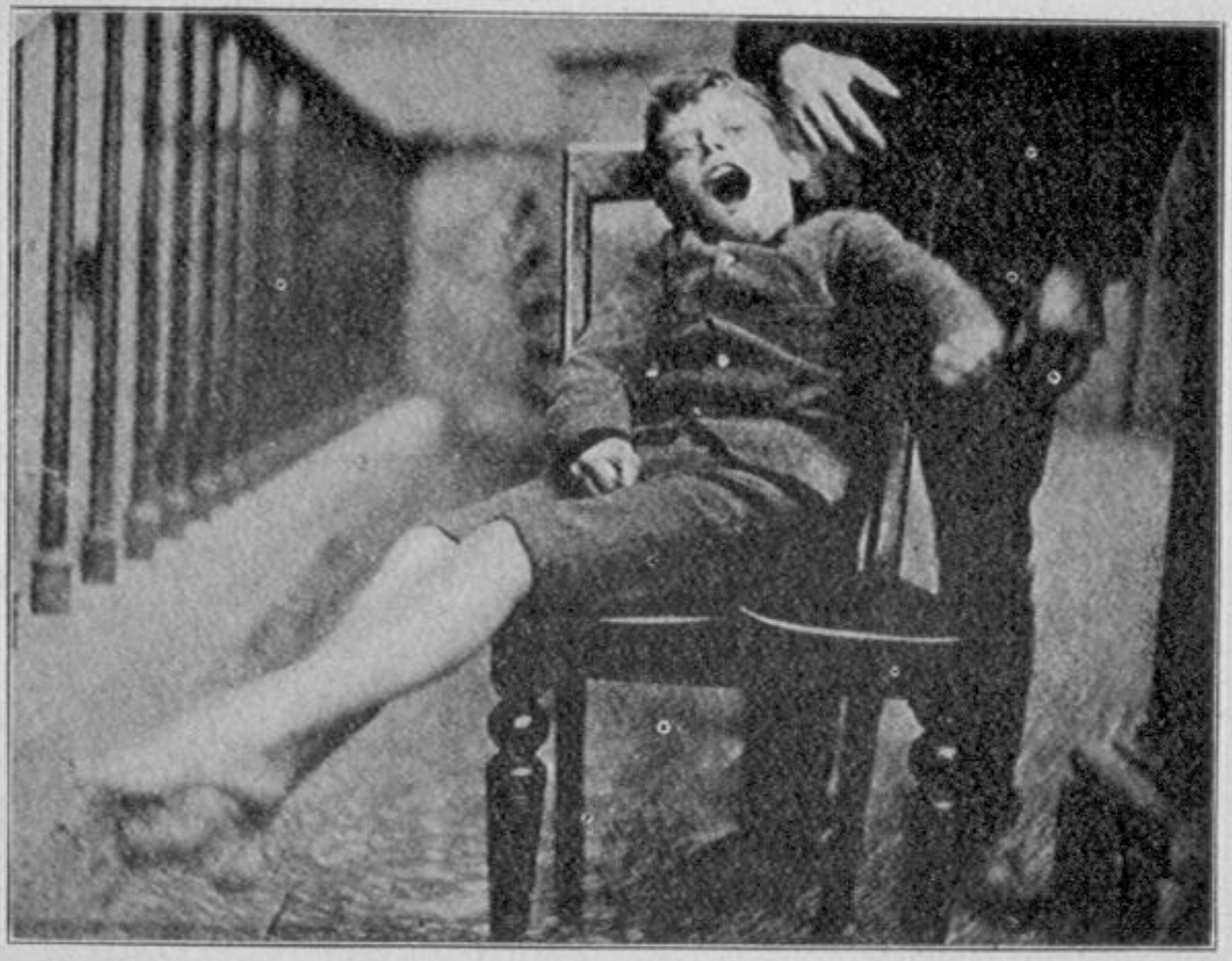


FIG. 2.—S. M. (Gowers.) Note the apparent indifference of the patient to the fact that is mouth is widely open. From the original in the notes at the National Hospital.

Gowers 1888: Tetanoid chorea

Dystonia

a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.

Dystonia is a:

– Clinical description

– Diagnosis

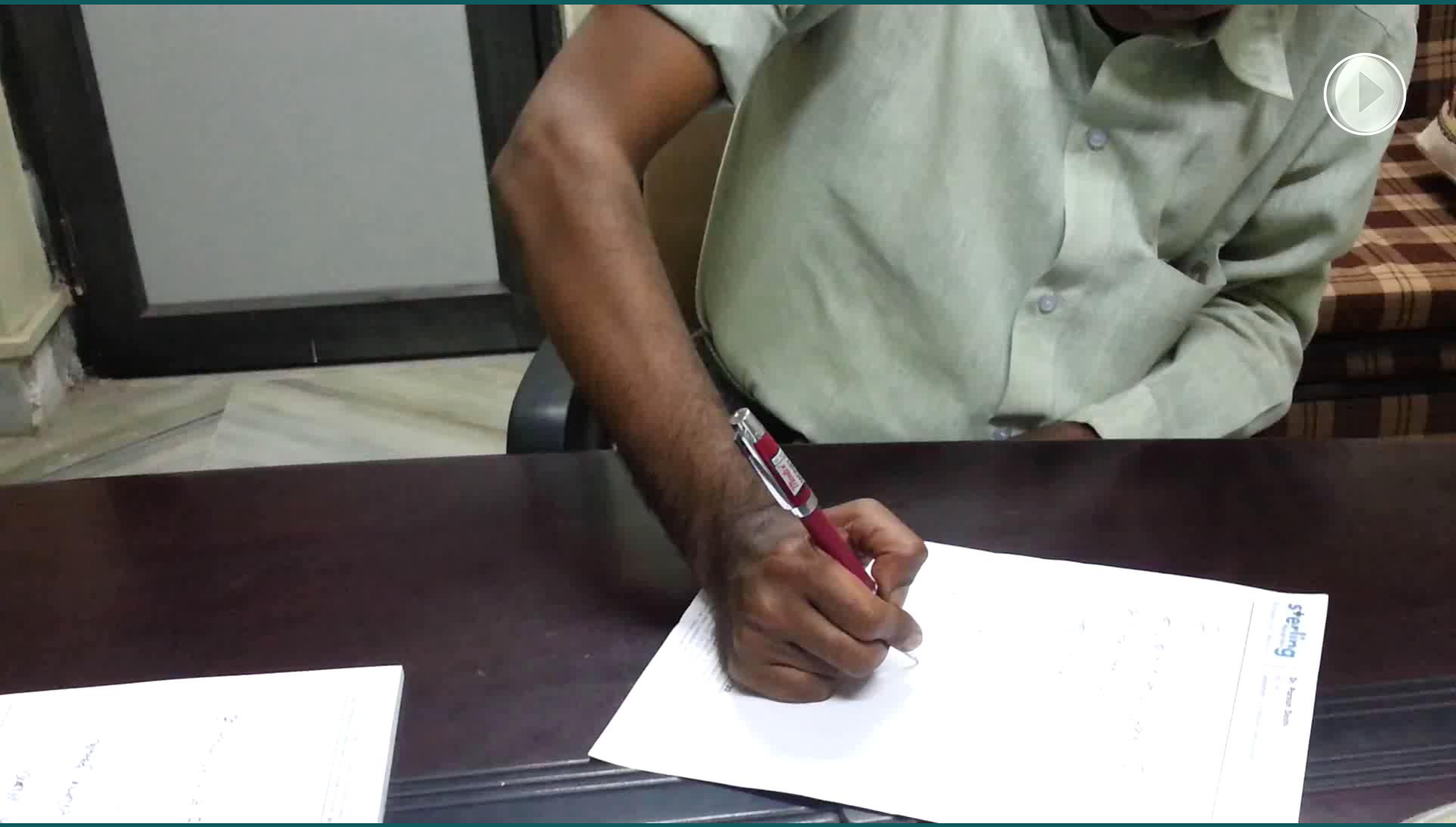
WARNING

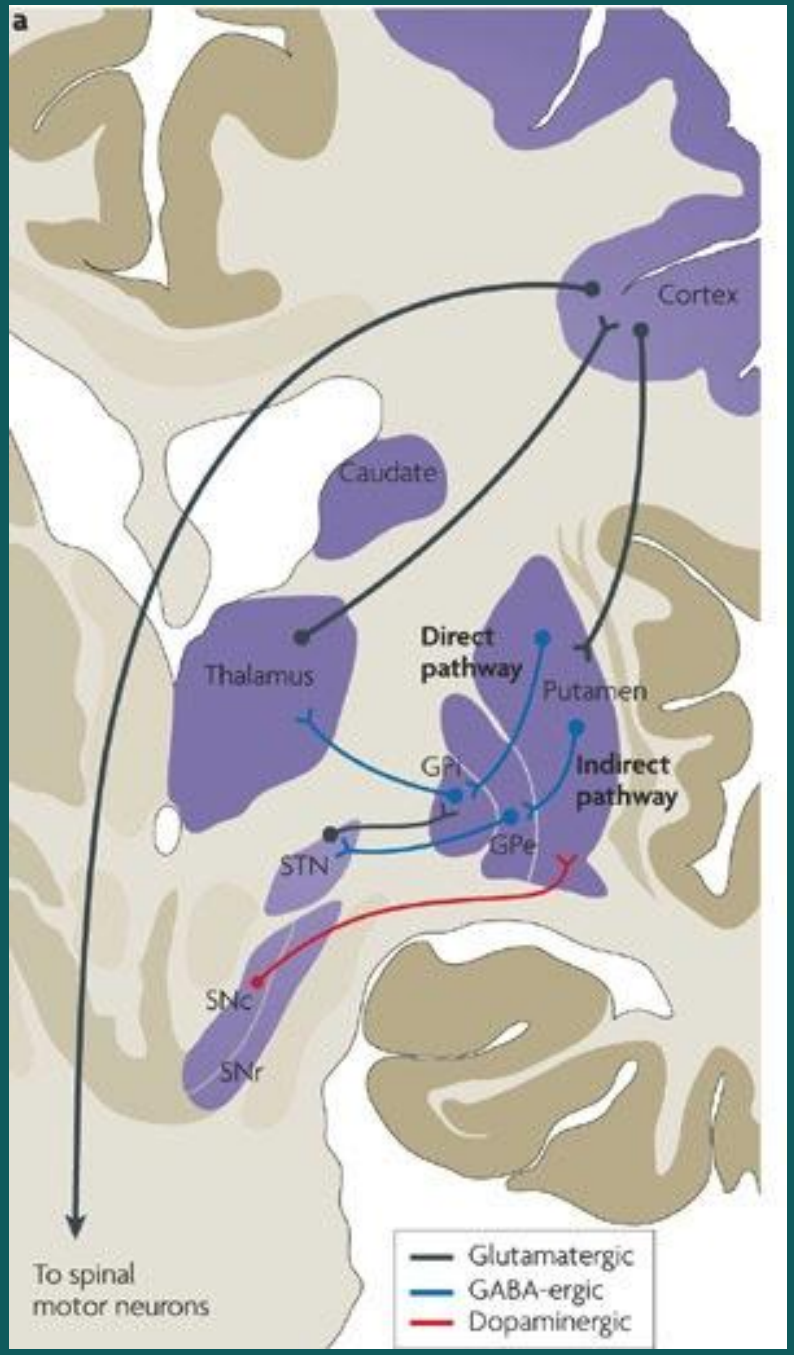
The following video is confidential
and contains patient information

BMW2964
??/11/2008

Phenomenology

- Involuntary
- Sustained
- Patterned
- Often repetitive
- Twisting movements
- Abnormal postures
  - Rapid movements
  - Tremor
    - Head tremor
    - Postural tremor of hands
    - 25% of cervical dystonia
- Overflow


sterling


a
Cortex
Caudate
Thalamus
Direct pathway
Putamen
GPi
Indirect pathway
GPe
STN
SNc
SNr
To spinal motor neurons
Glutamatergic
GABA-ergic
Dopaminergic

Pathophysiology

- Sensory disturbance
  - Abnormal spatial discrimination
  - Abnormal cortical representation of dystonic structure
  - “fusion of representational zones”
- Aberrant or maladaptive brain plasticity

Classification of Dystonia

Distribution

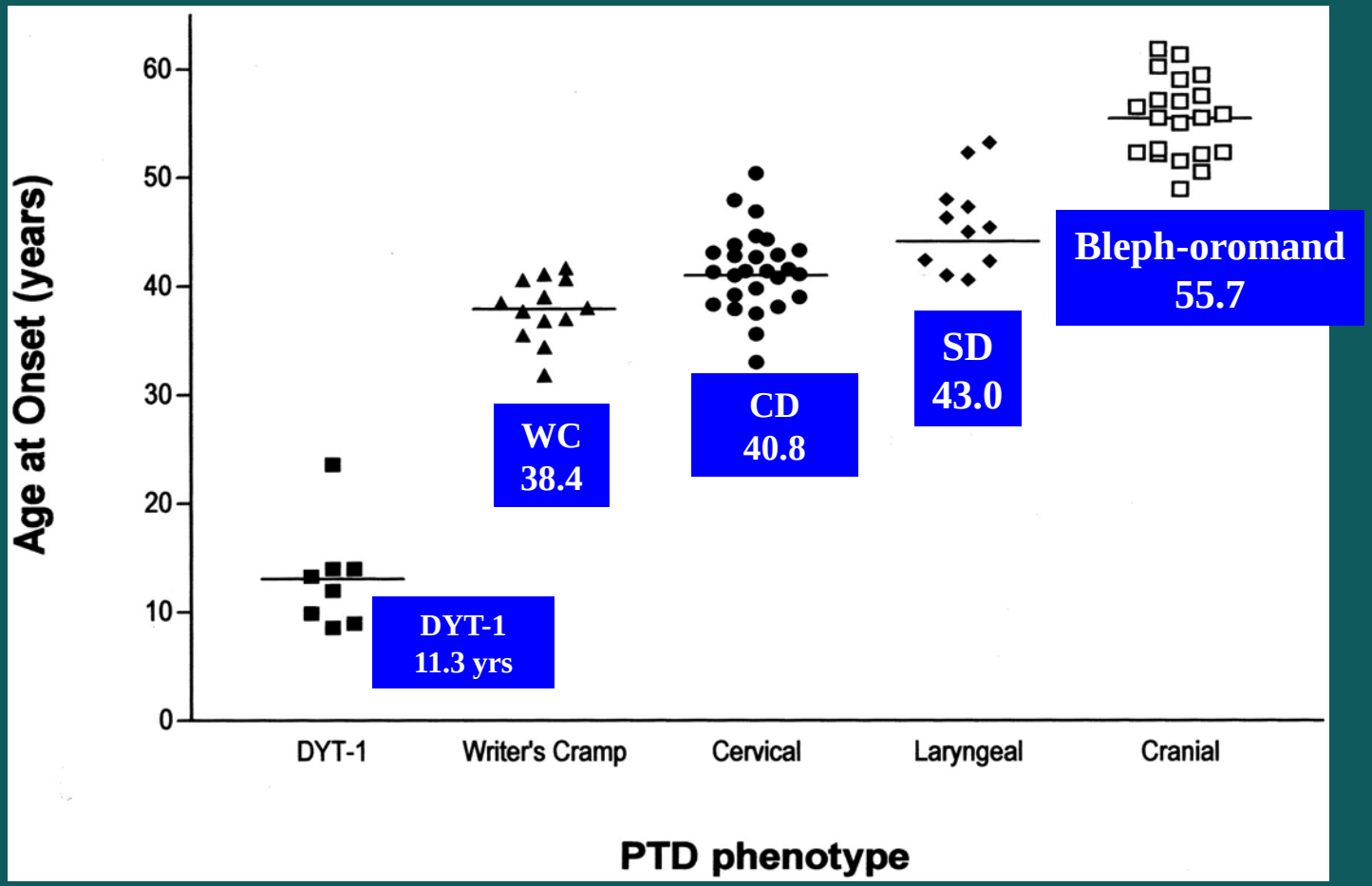
- Focal
  - cervical dystonia, blepharospasm, spasmodic dysphonia, oromandibular dystonia, brachial dystonia
- Segmental
  - For example, Meige syndrome, craniocervical dystonia, bibrachial dystonia
- Multifocal
- Hemidystonia
- Generalised

Age of onset

- Early-onset (≤26 years)
- Late-onset (>26 years)

Focal dystonia: age of onset

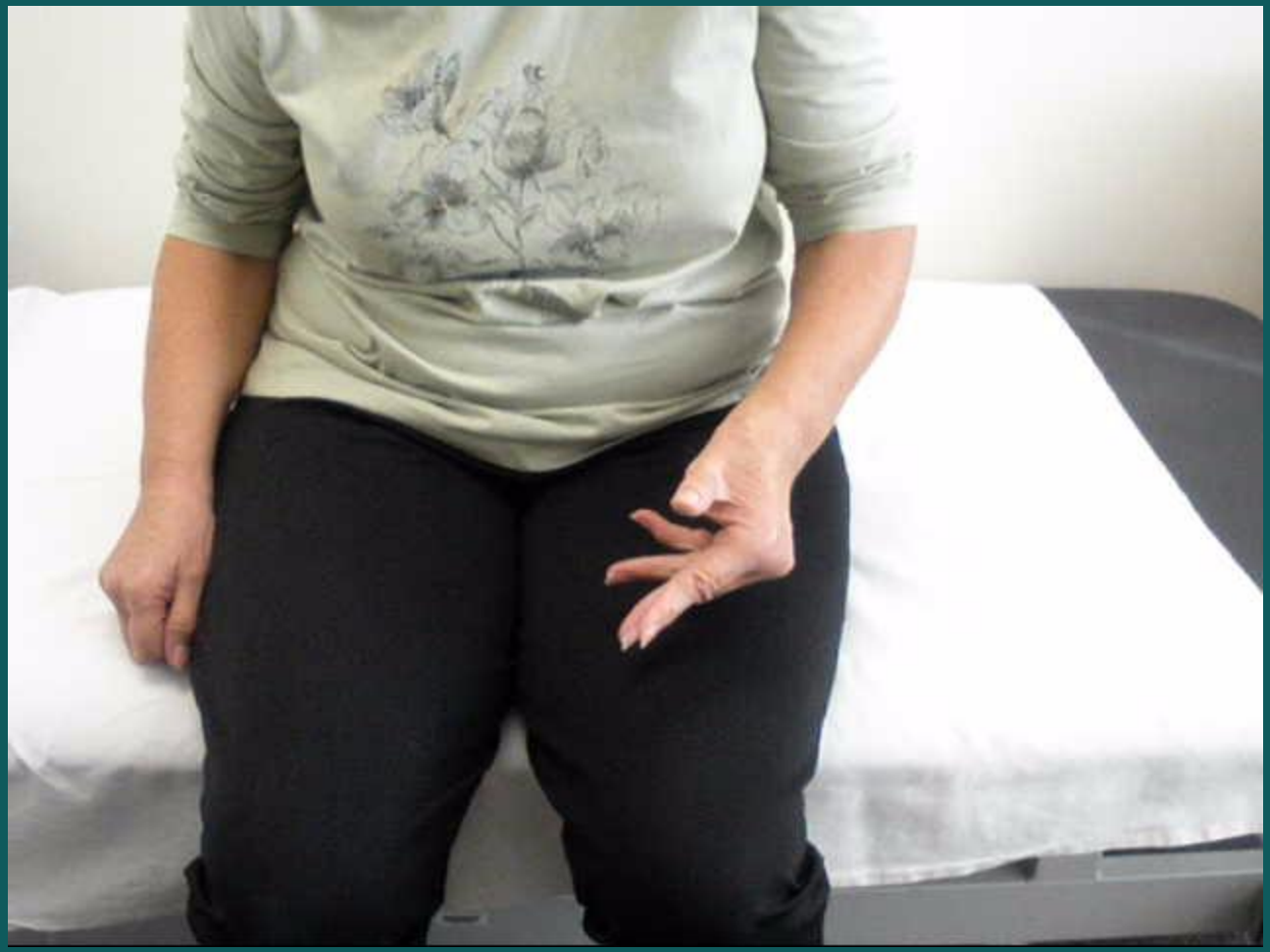
O' Riordan S, Raymond D, Lynch T et al. Neurology 2004;63:1423-6.

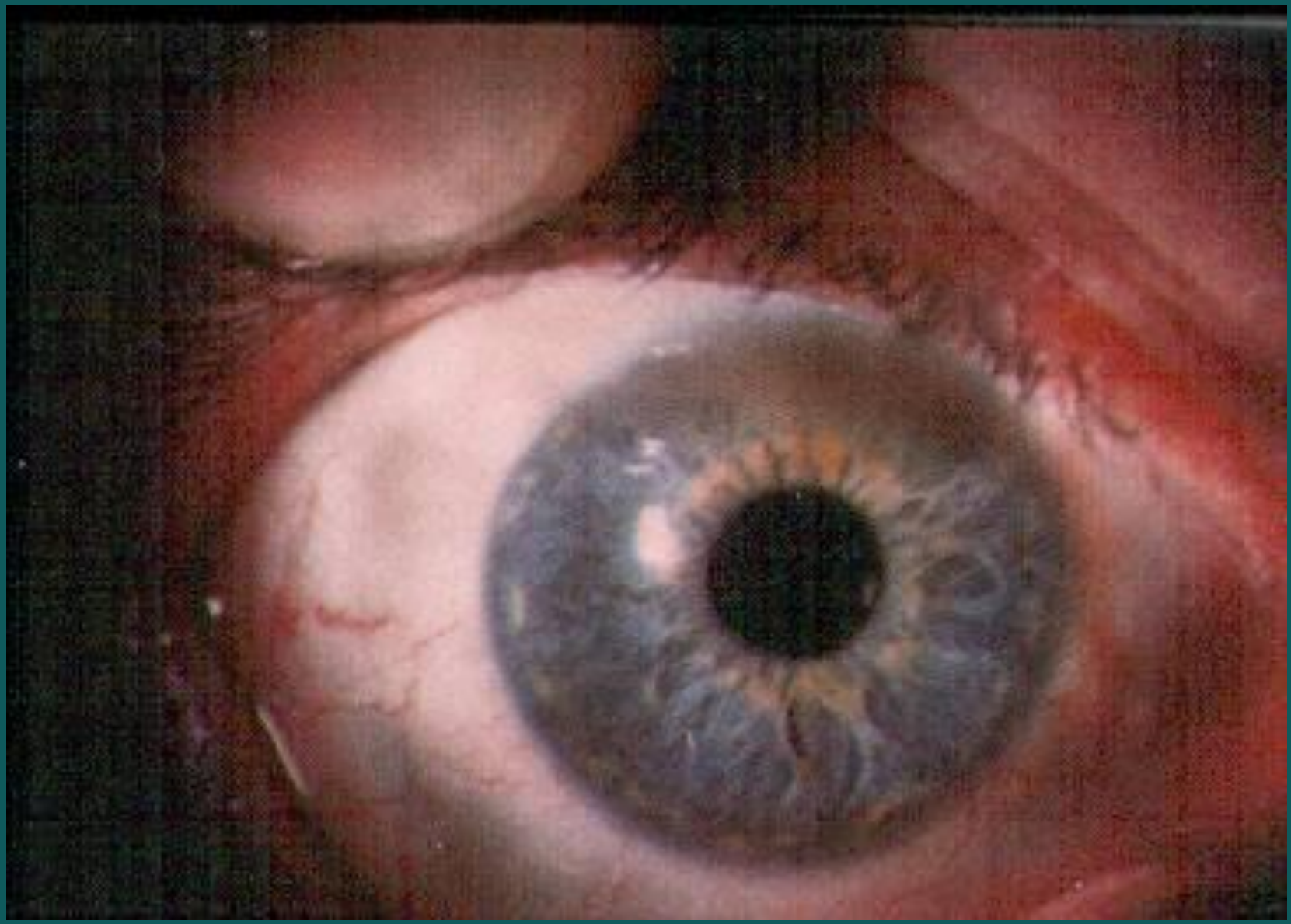


Classification of Dystonia

Cause

- Primary (idiopathic) dystonia
- Secondary dystonia
  - Associated with inherited neurological disorders
  - Dystonia-plus syndromes
  - Degenerative diseases
  - Symptomatic of an exogenous or environmental cause
  - Associated with Parkinson's disease and other parkinsonian disorders
  - Dystonic phenomenology in another movement disorder





Dystonia

- Abnormal posturing
- Often with extra movements
- Responds to treatment
  - Sometimes medications
  - Botulinum toxin
  - DBS
- Needs a neurologist!

AN

ESSAY

ON THE

SHAKING PALSY.

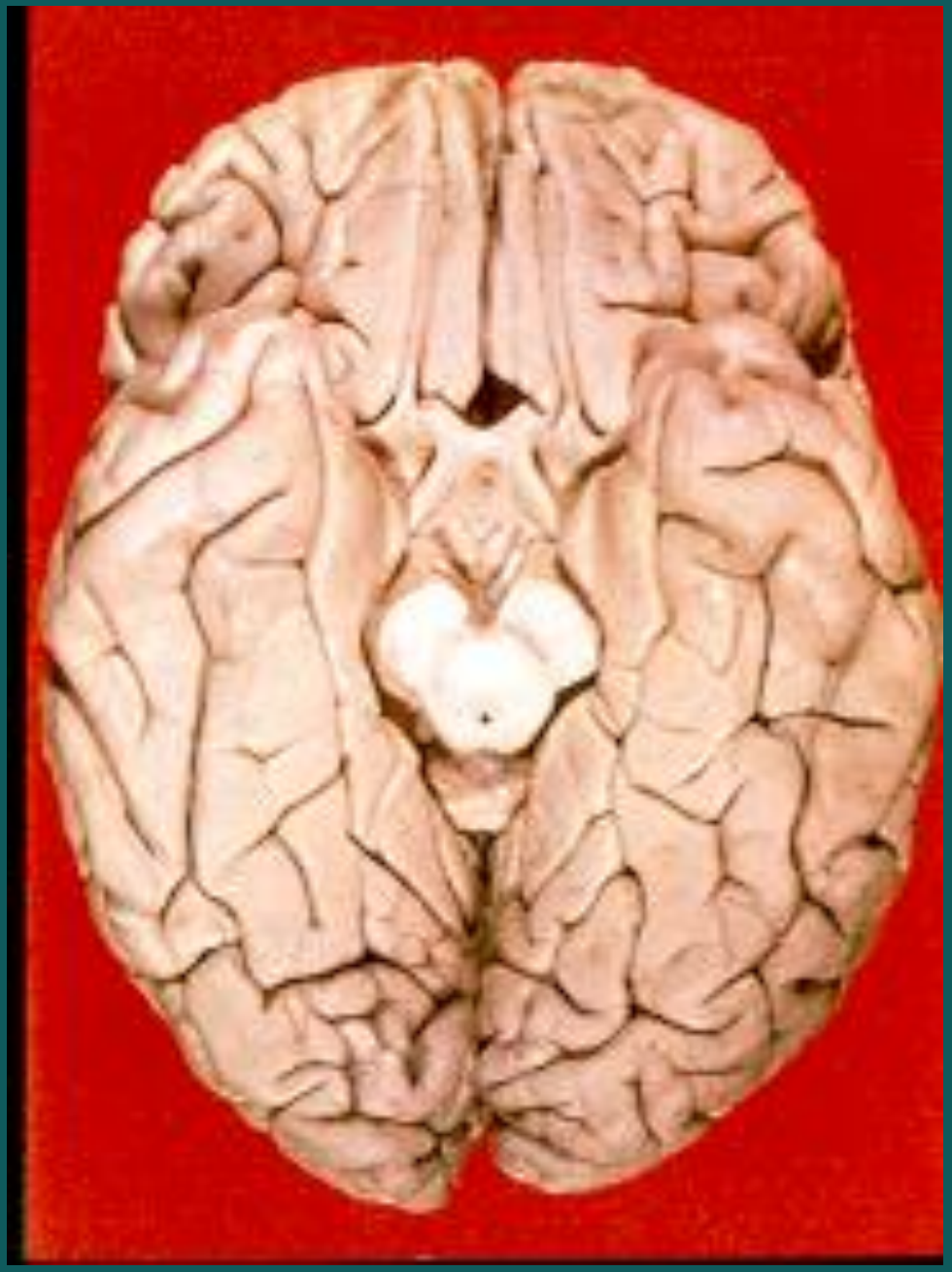
BY

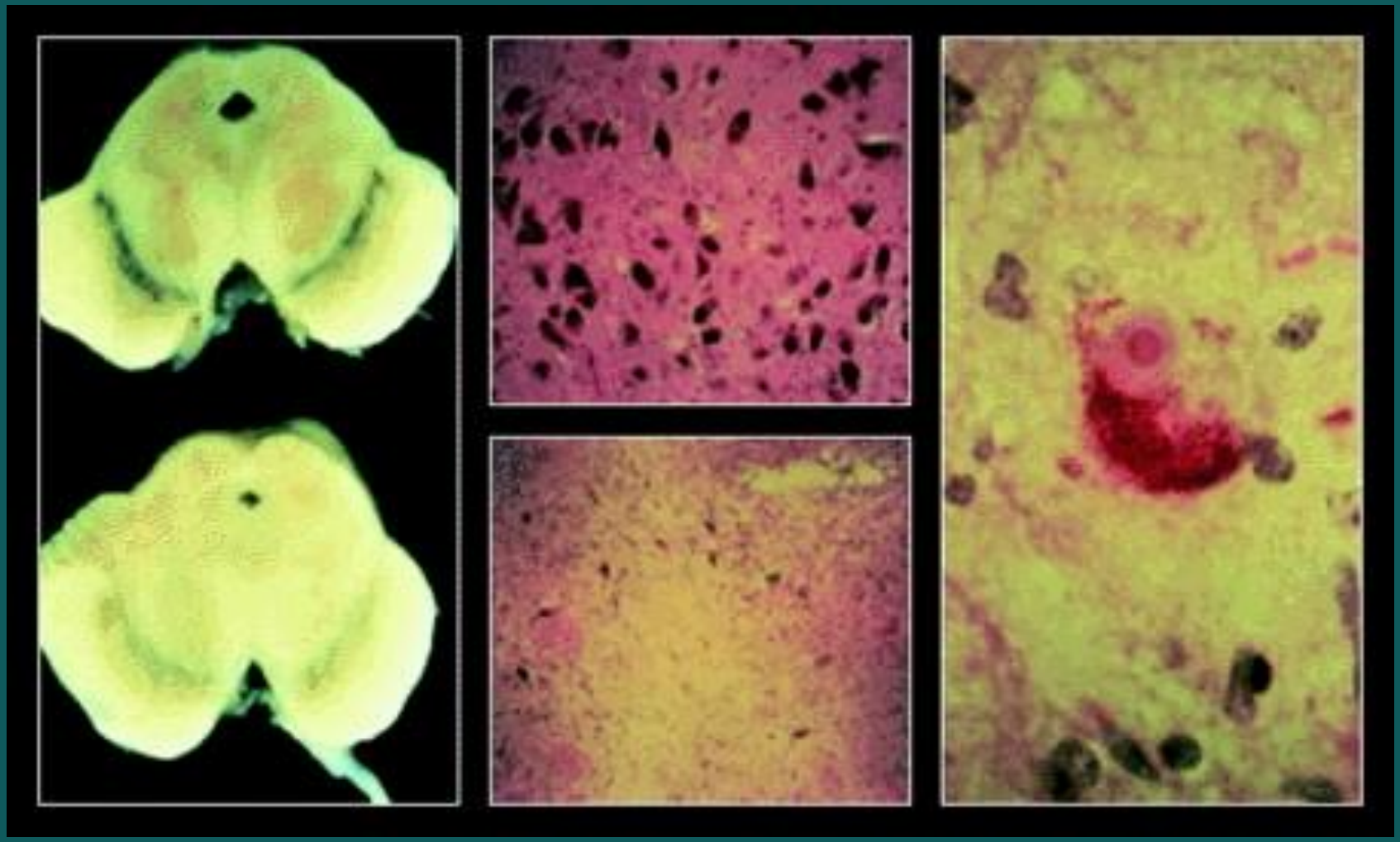
JAMES PARKINSON,
MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:
PRINTED BY WHITTINGHAM AND ROWLAND,
Caxton Street,
FOR SHERWOOD, NEELY, AND JONES,
PATERNOSTER ROW.
1817.

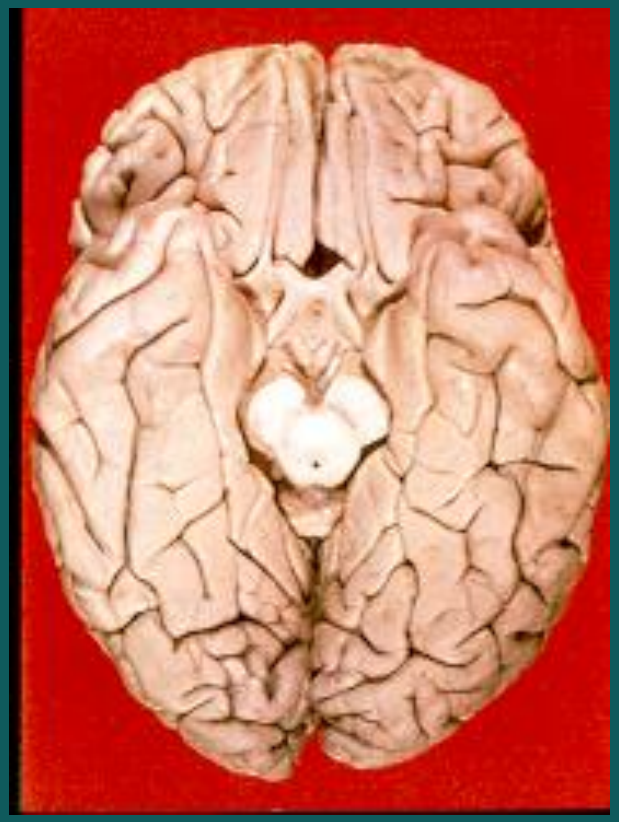
Parkinsonism

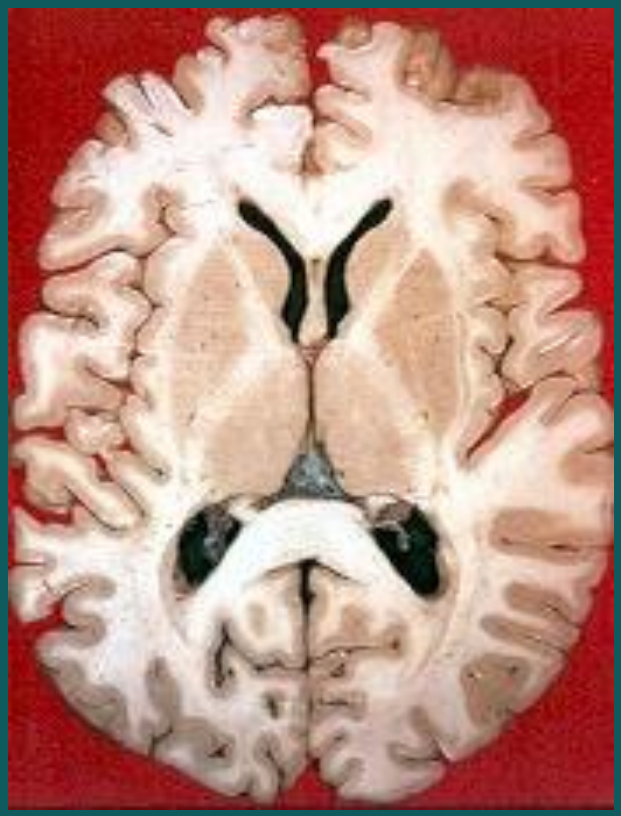
- Tremor
  - resting
- Slowness
  - bradykinesia
- Stiffness
  - rigidity
- Loss of balance

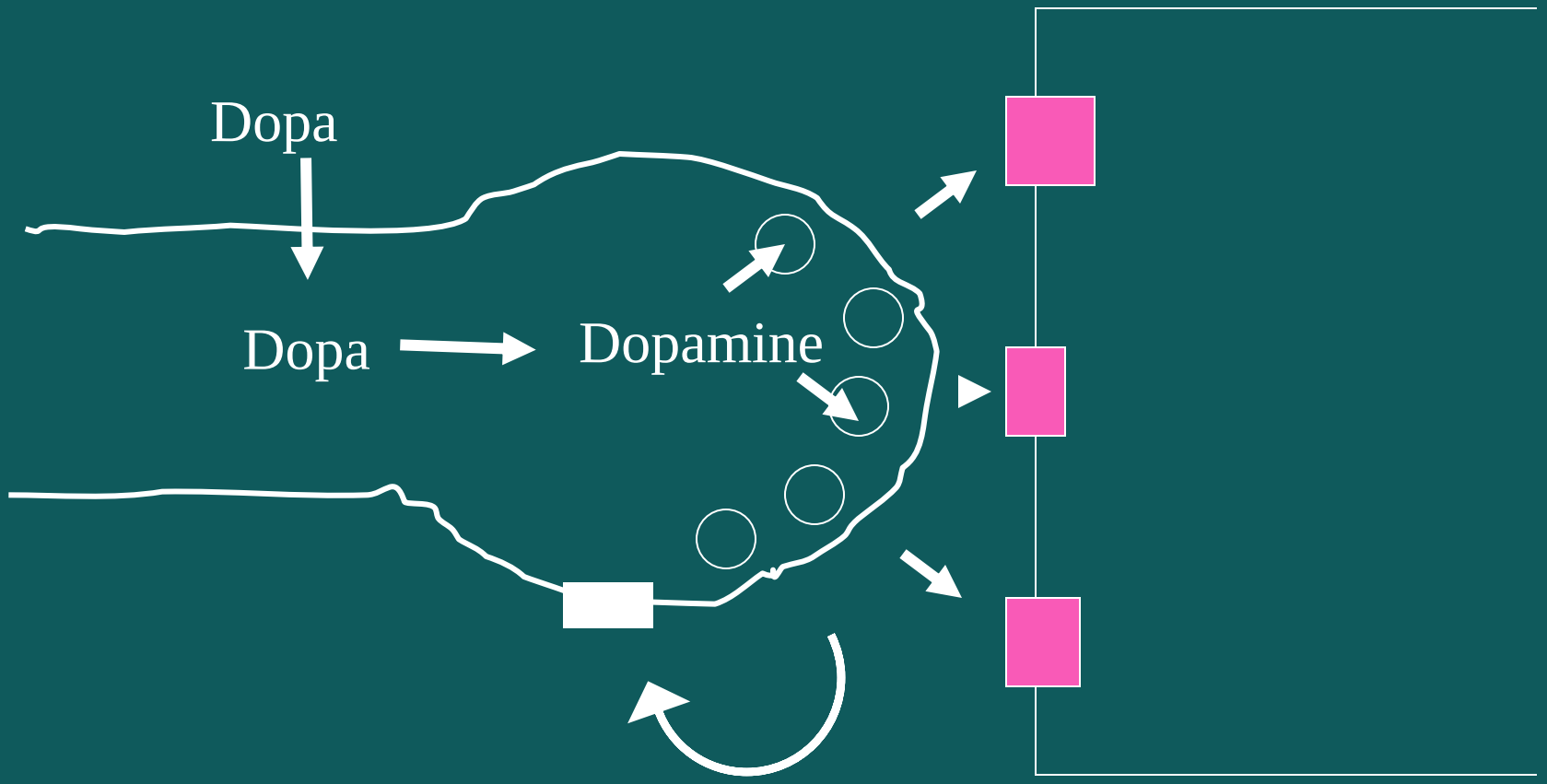


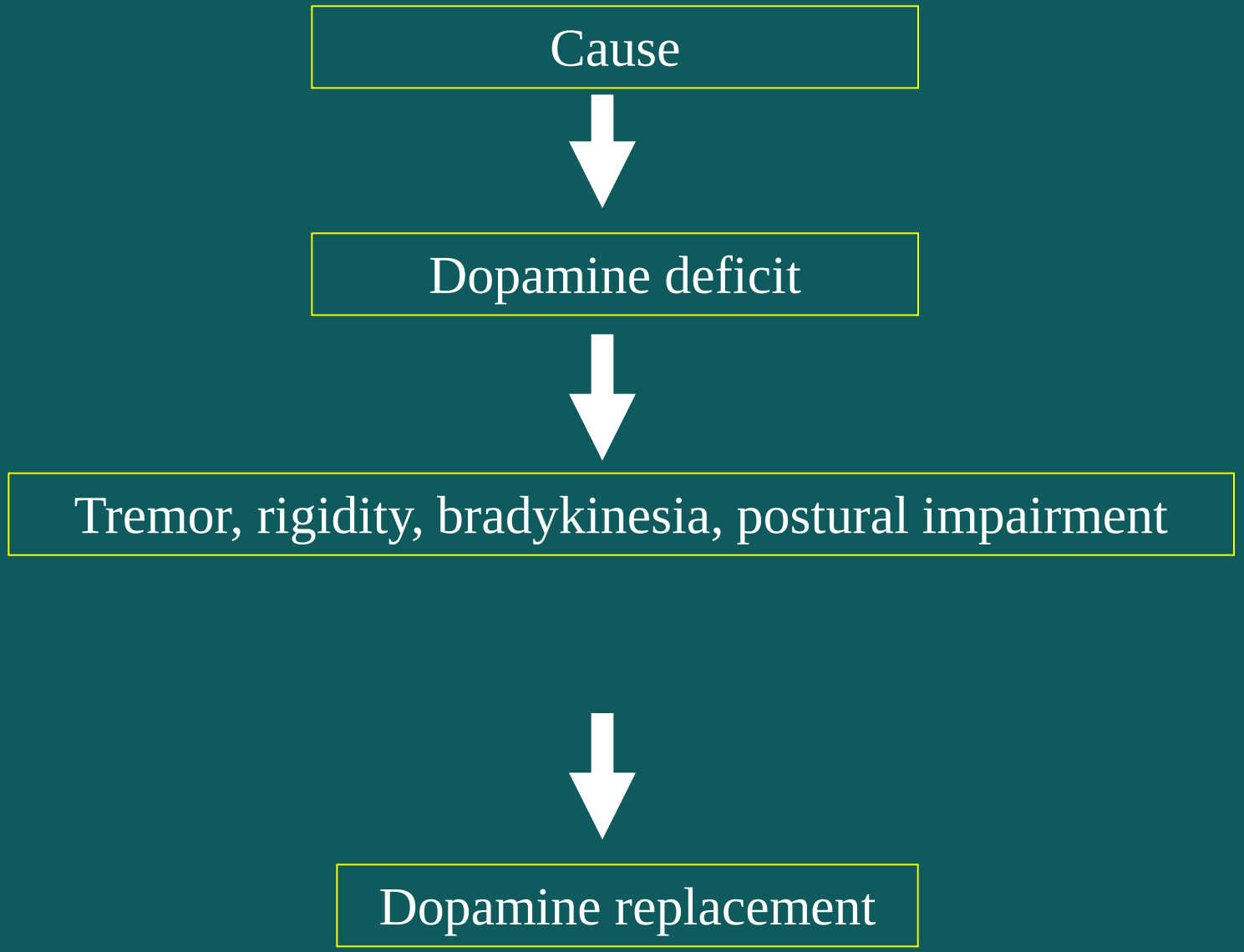


Olanow. Neurology 2009






Dopa
Dopa
Dopamine


Cause
Dopamine deficit
Tremor, rigidity, bradykinesia, postural impairment
Dopamine replacement

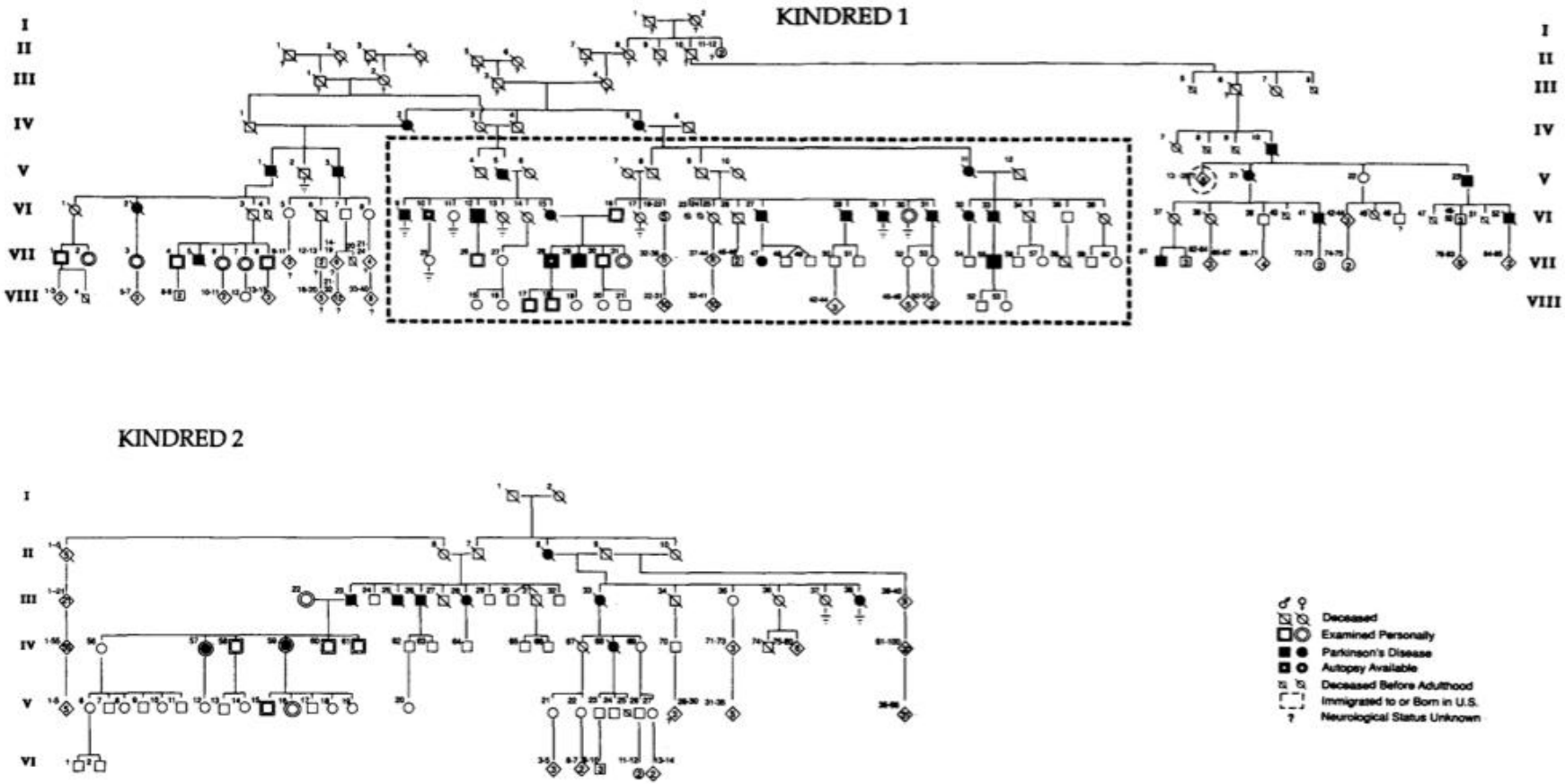
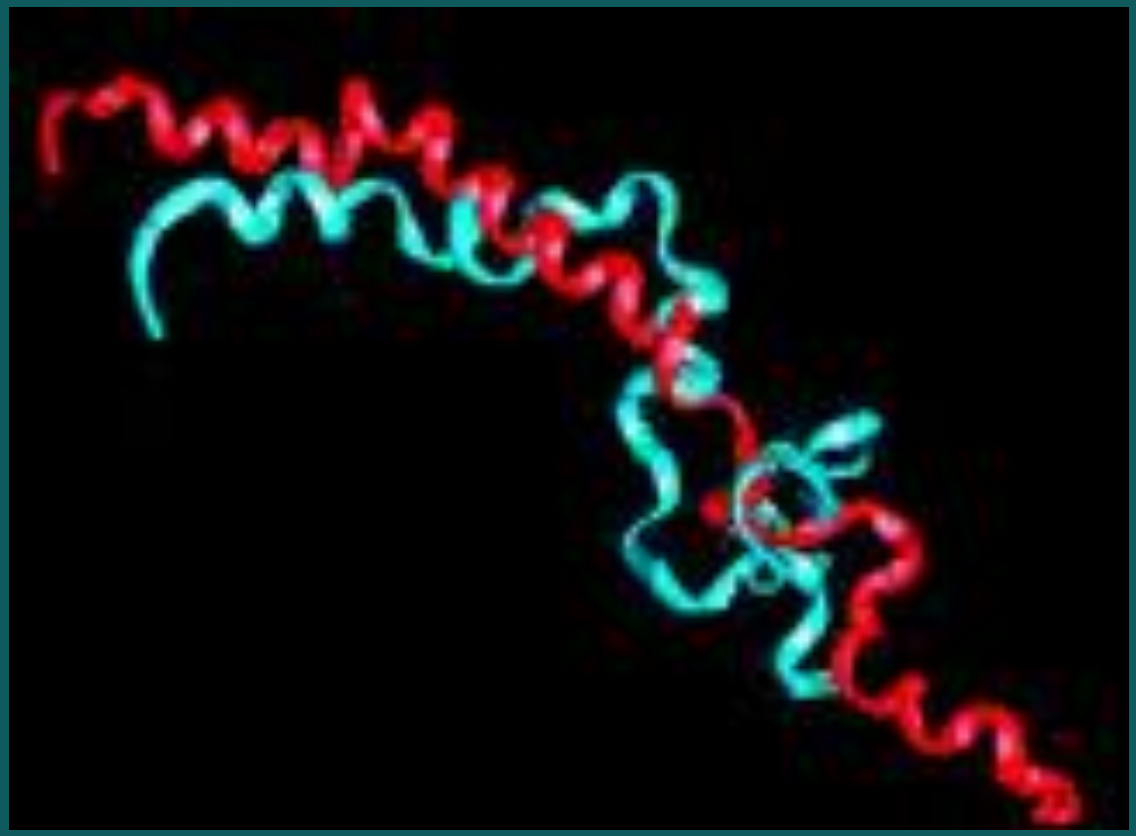
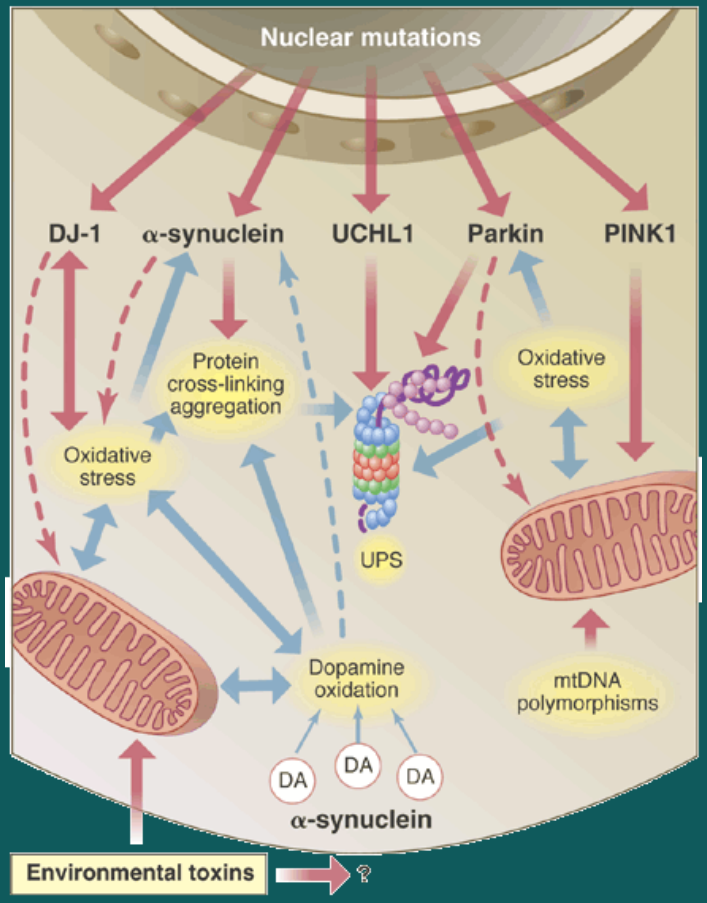


Fig 1. Pedigrees. K2: II-8 is the only known affected member of K2 whose disease course occurred in Italy, so the dashed line was not included in the chart for K2. K1: VII–VIII and K2: IV–VI include individuals still at risk. We assume that the two kindreds are related because of similarity of parkinsonian phenotype and because both originated in Contursi.

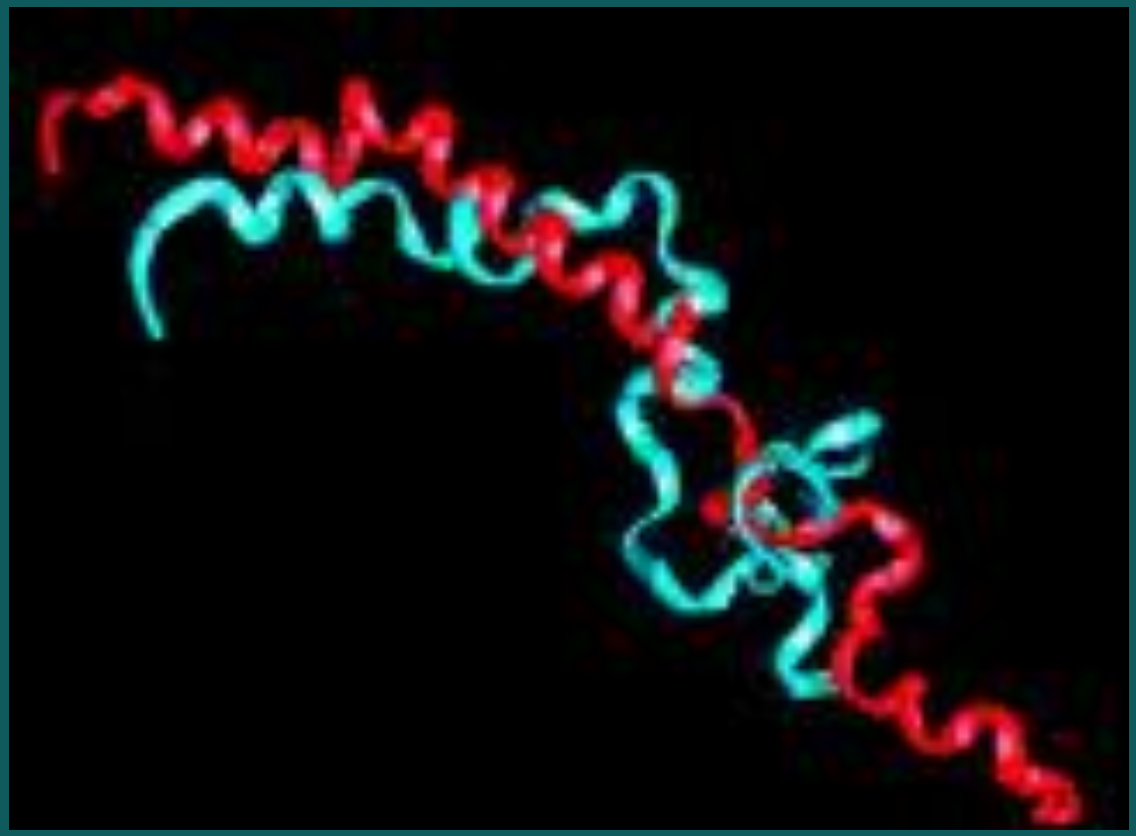
Golbe 1990

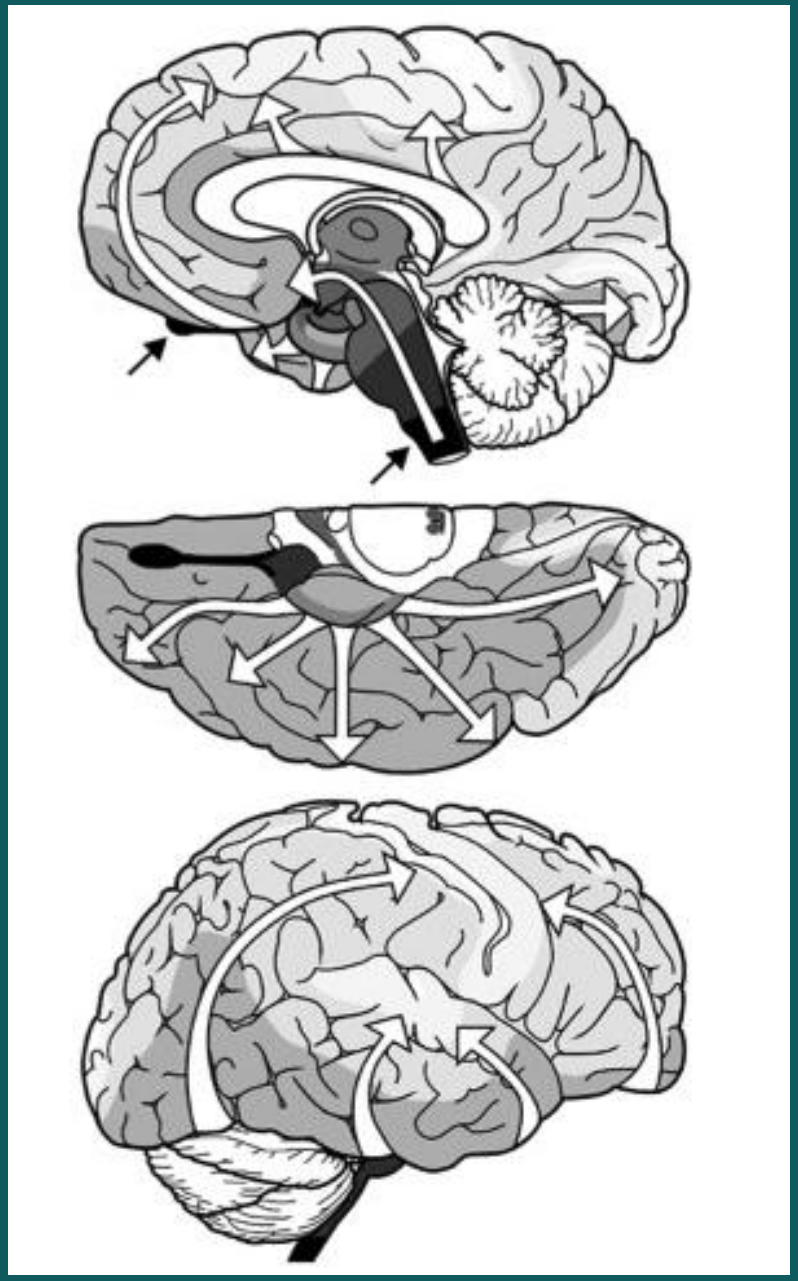


Parkinson's – divergent causes, convergent mechanisms (Science 21 May 04)

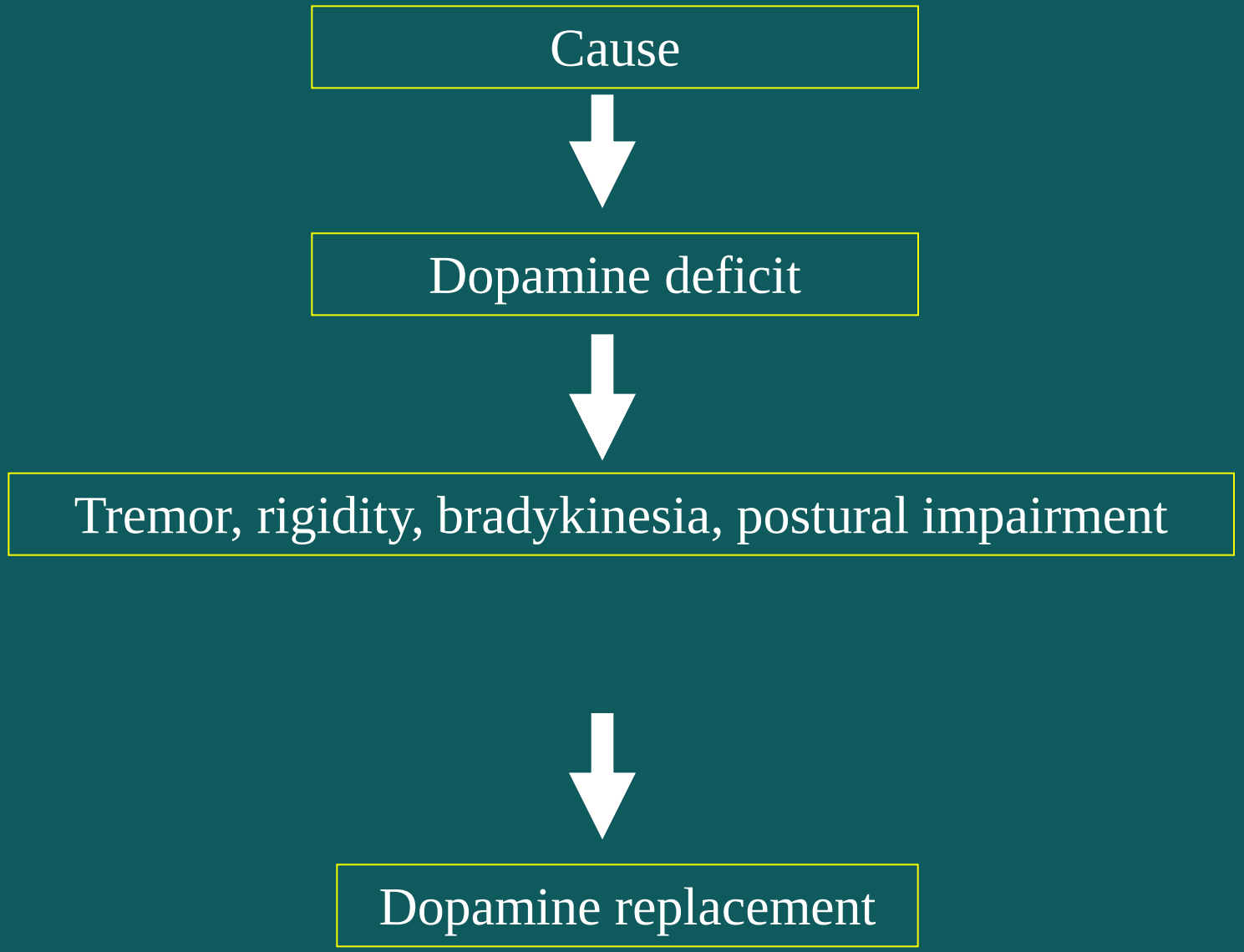


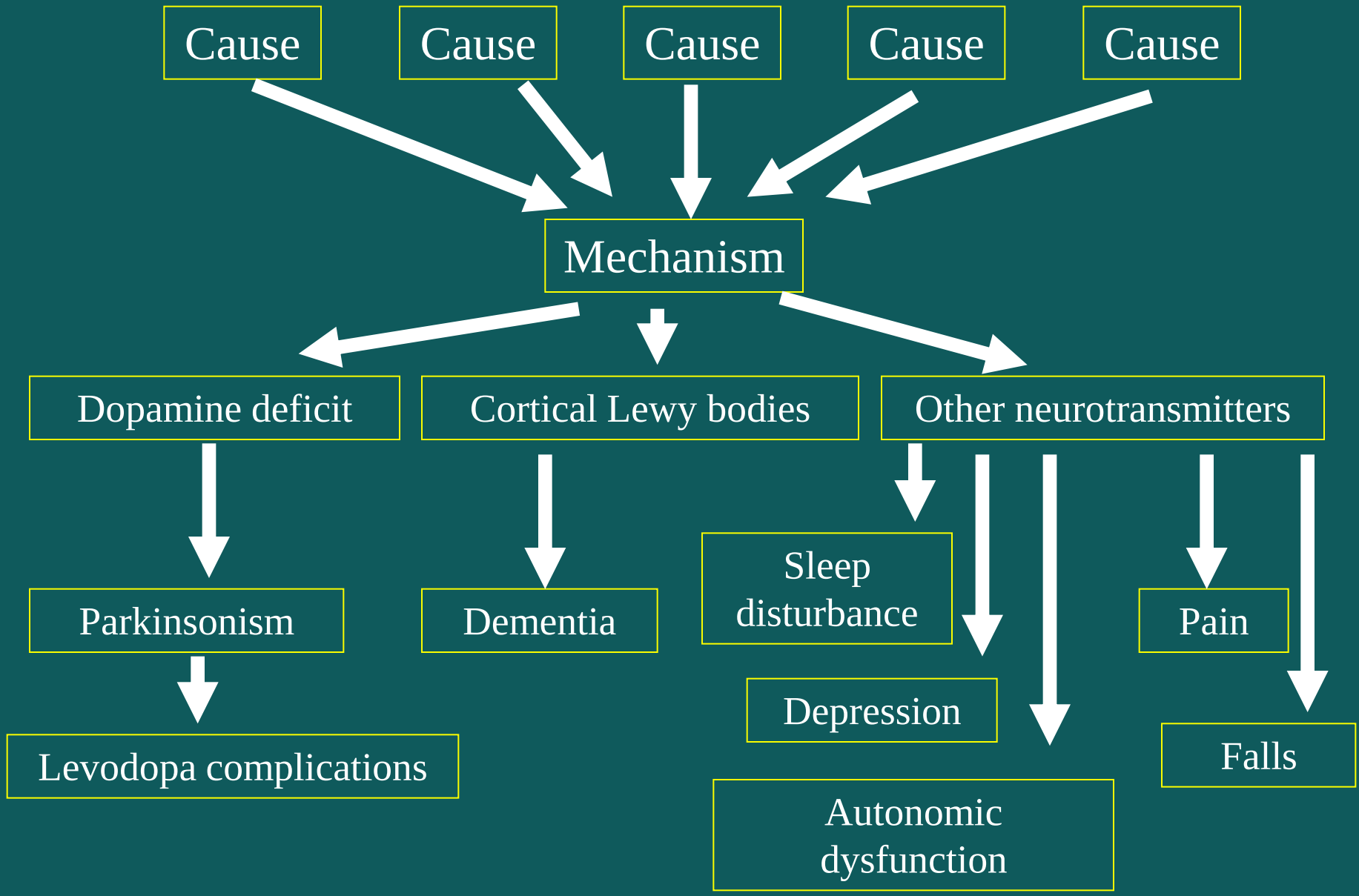
There seem to be multiple, divergent causes of PD, yet the pathogenesis of this disease appears to be converging on common mechanisms—mitochondrial impairment, oxidative stress, and protein mishandling, all of which are tightly linked.





Braak 2005


Cause
Dopamine deficit
Tremor, rigidity, bradykinesia, postural impairment
Dopamine replacement


Cause
Cause
Cause
Cause
Cause
Mechanism
Dopamine deficit
Cortical Lewy bodies
Other neurotransmitters
Parkinsonism
Dementia
Sleep disturbance
Pain
Depression
Falls
Levodopa complications
Autonomic dysfunction

Dopaminergic

Parkinsonism

Motor fluctuations
and dyskinesia

anosmia
RBD

anxiety
depression

pain

Falls
autonomic failure
dementia

Non-Dopaminergic

Dopaminergic

Parkinsonism

Motor fluctuations
and dyskinesia

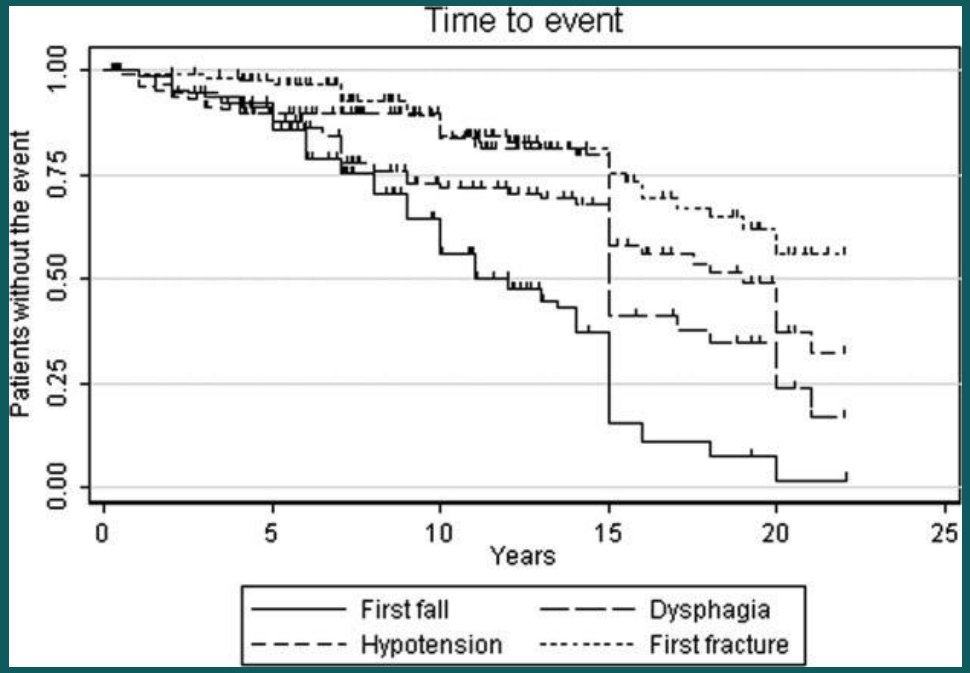
anosmia
RBD

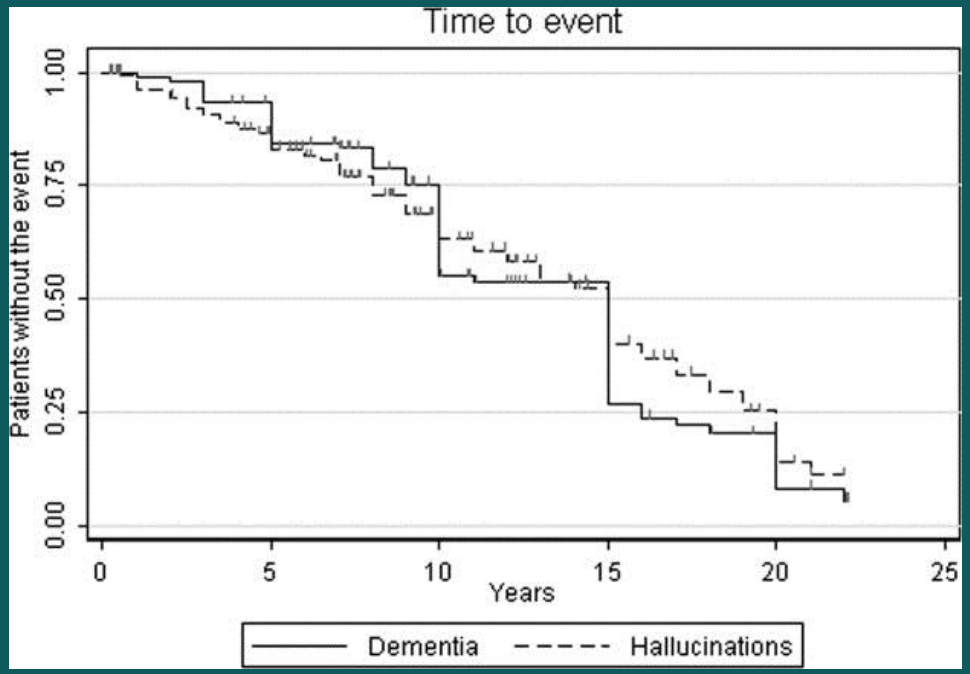
anxiety
depression

pain

Falls
autonomic failure
dementia

Non-Dopaminergic


Time to event
Patients without the event
1.00
0.75
0.50
0.25
0.00
0
5
10
15
20
25
Years
First fall
Dysphagia
Hypotension
First fracture


Time to event
Patients without the event
1.00
0.75
0.50
0.25
0.00
0
5
10
15
20
25
Years
Dementia
Hallucinations

Hely 2008

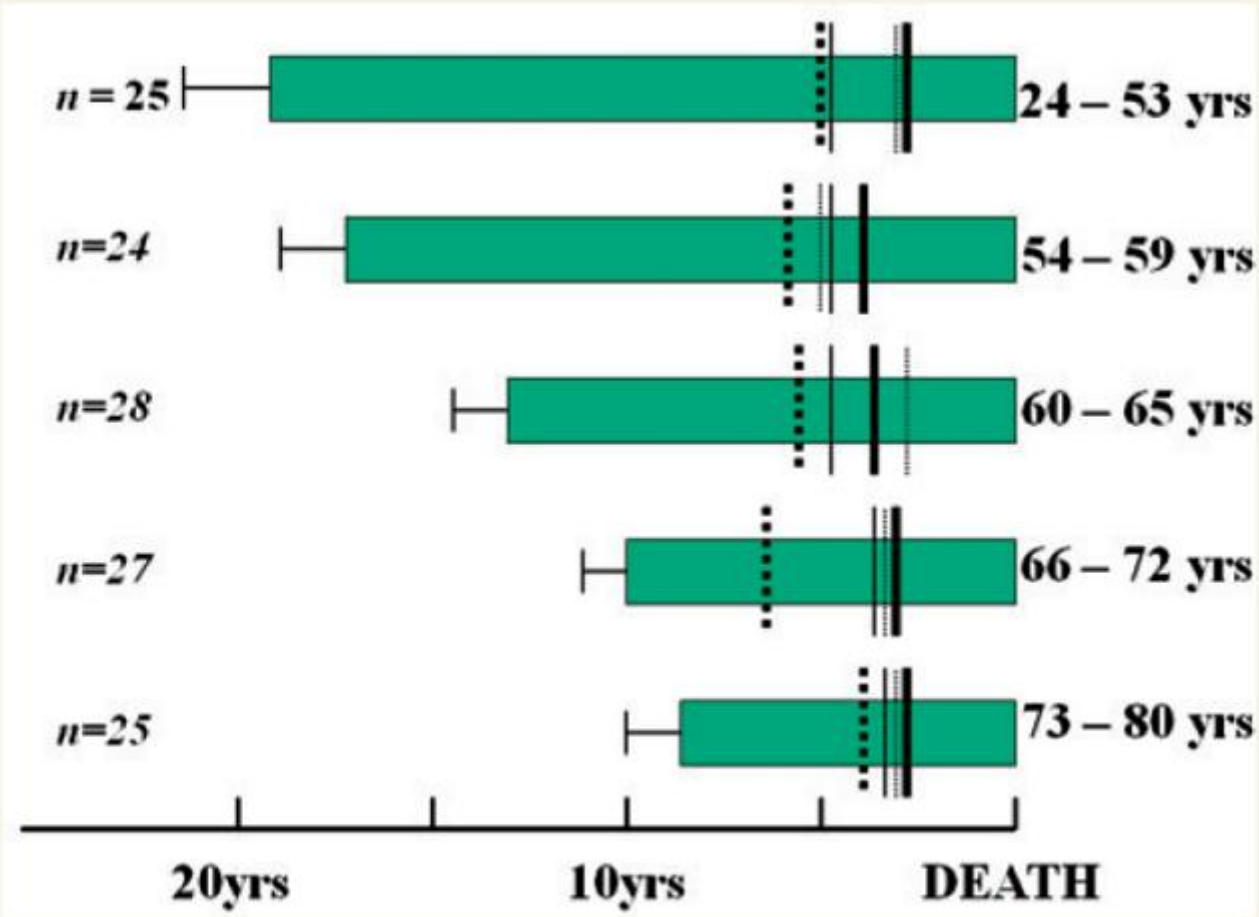
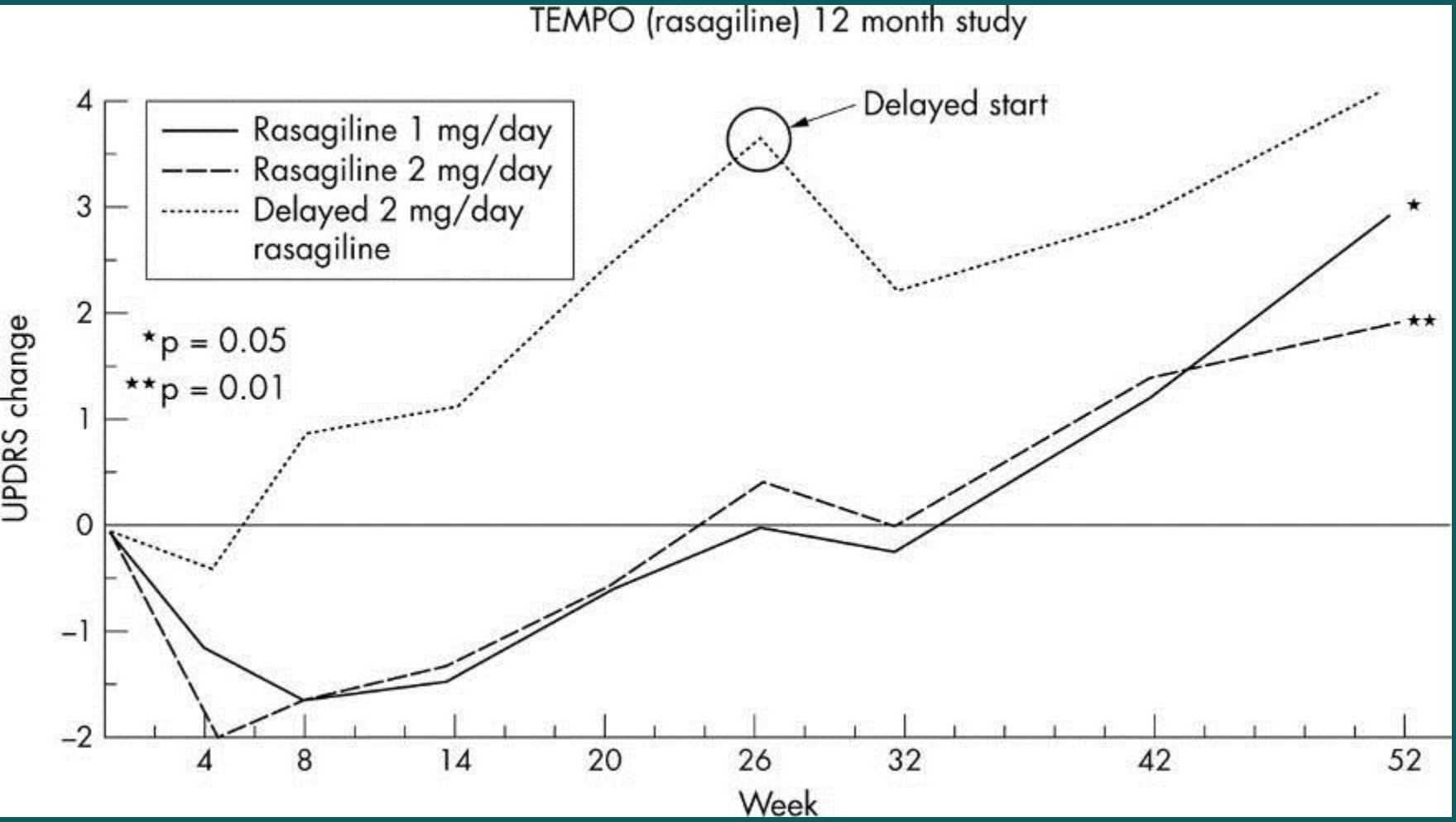
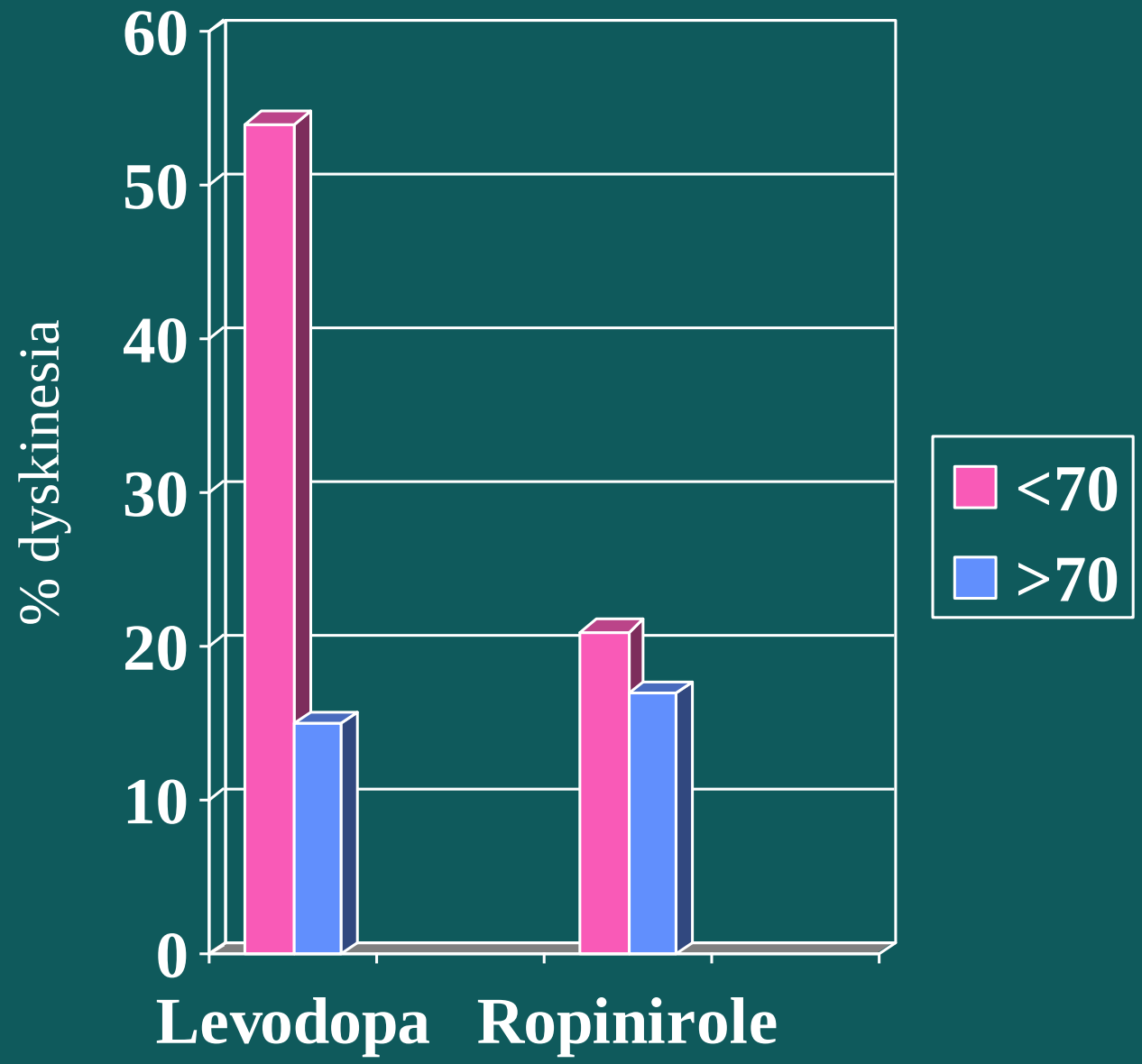


Figure 2 Disease course and disability milestones for five age-at-onset groups. Disease courses aligned for time of death. Same milestone legend as Fig. 1. Error bars show the standard error of the mean disease duration.

Kempster Brain 2010

Does early treatment lead to better later PD status?





Adapted from Rascol 054 Study

Initial treatment

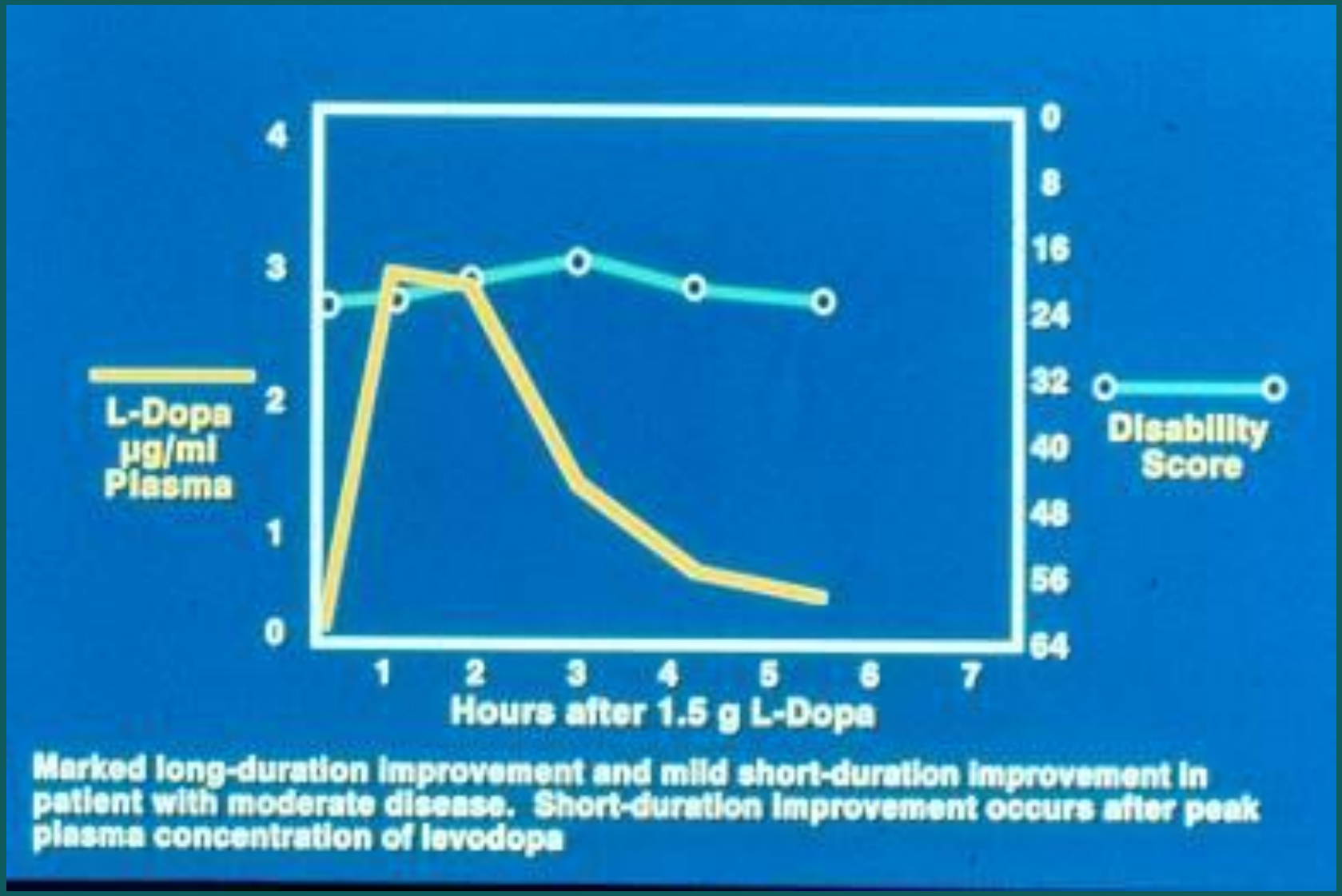
- Young patients: dyskinesia
  - Dopamine agonists (ropinirole 3 mg tds)
- Old patients: dementia
  - Levodopa (100 mg tds)

Ropinirole
Adverse Events (compared to levodopa)

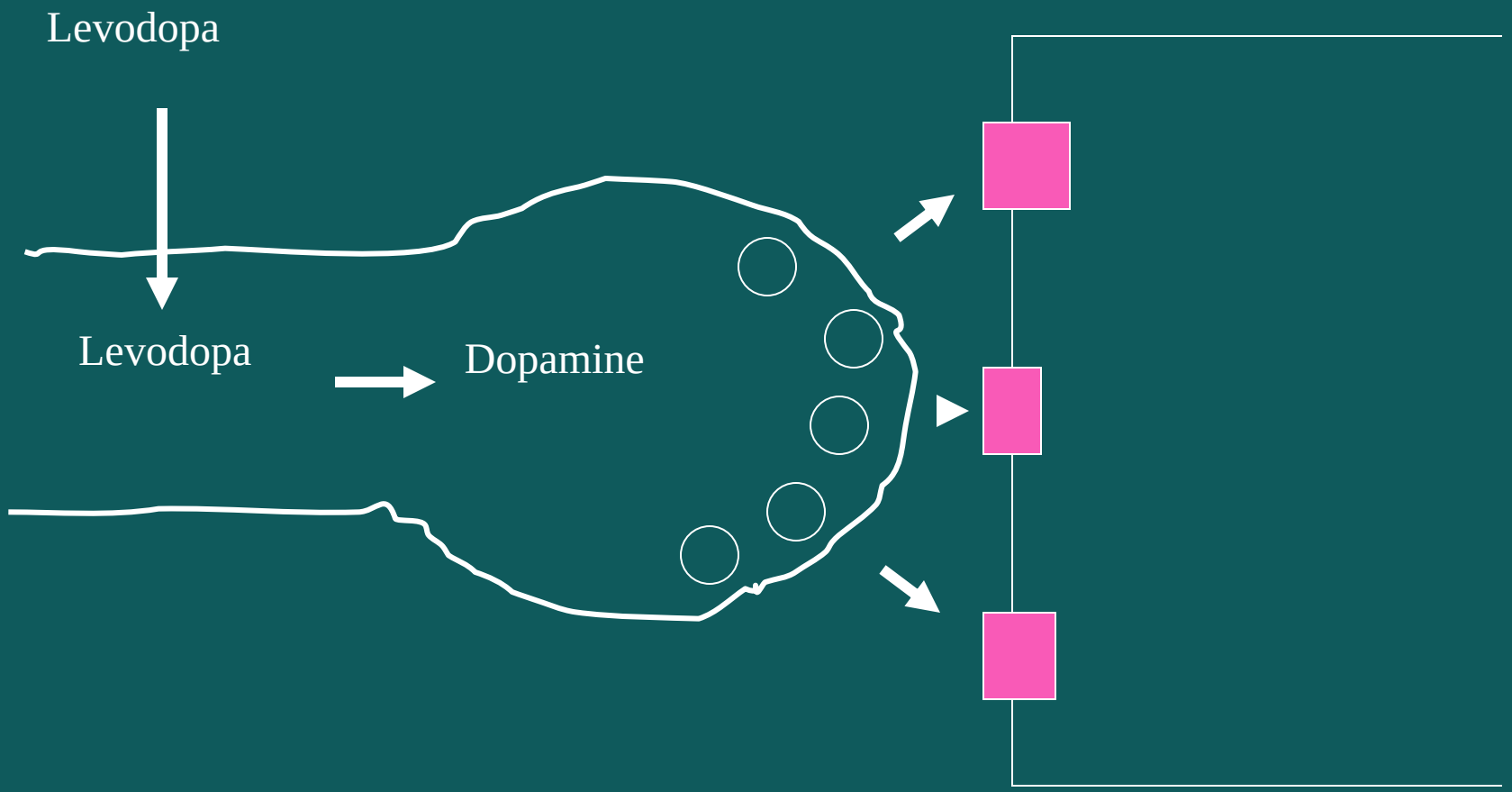
	Ropinirole	Levodopa
Nausea	48.6%	36.7%
Somnolence	27.4	17.3
Hallucination	**17.3**	**3.3**
Edema	**14.0**	**4.0**

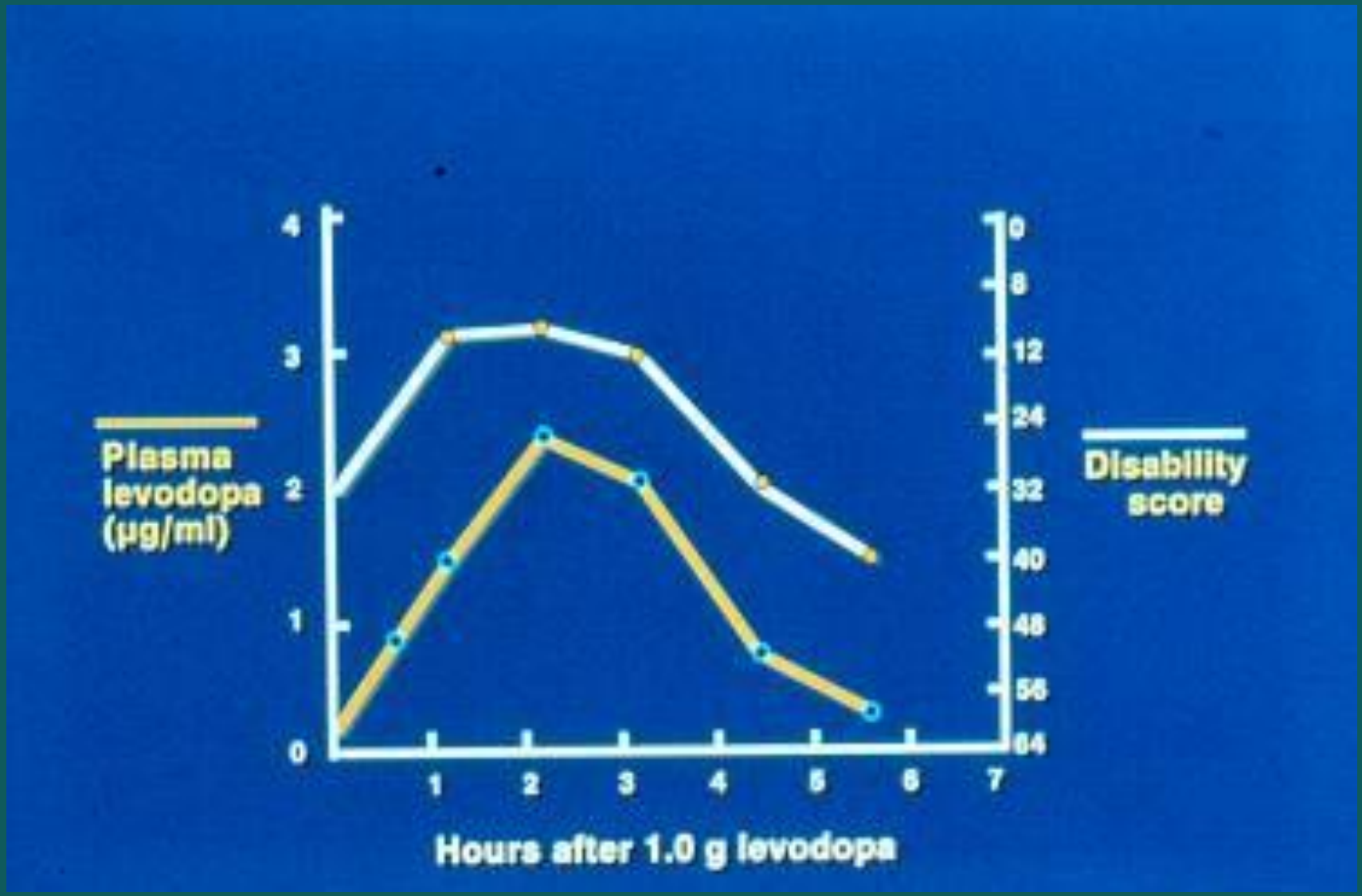
Agonists and disinhibition

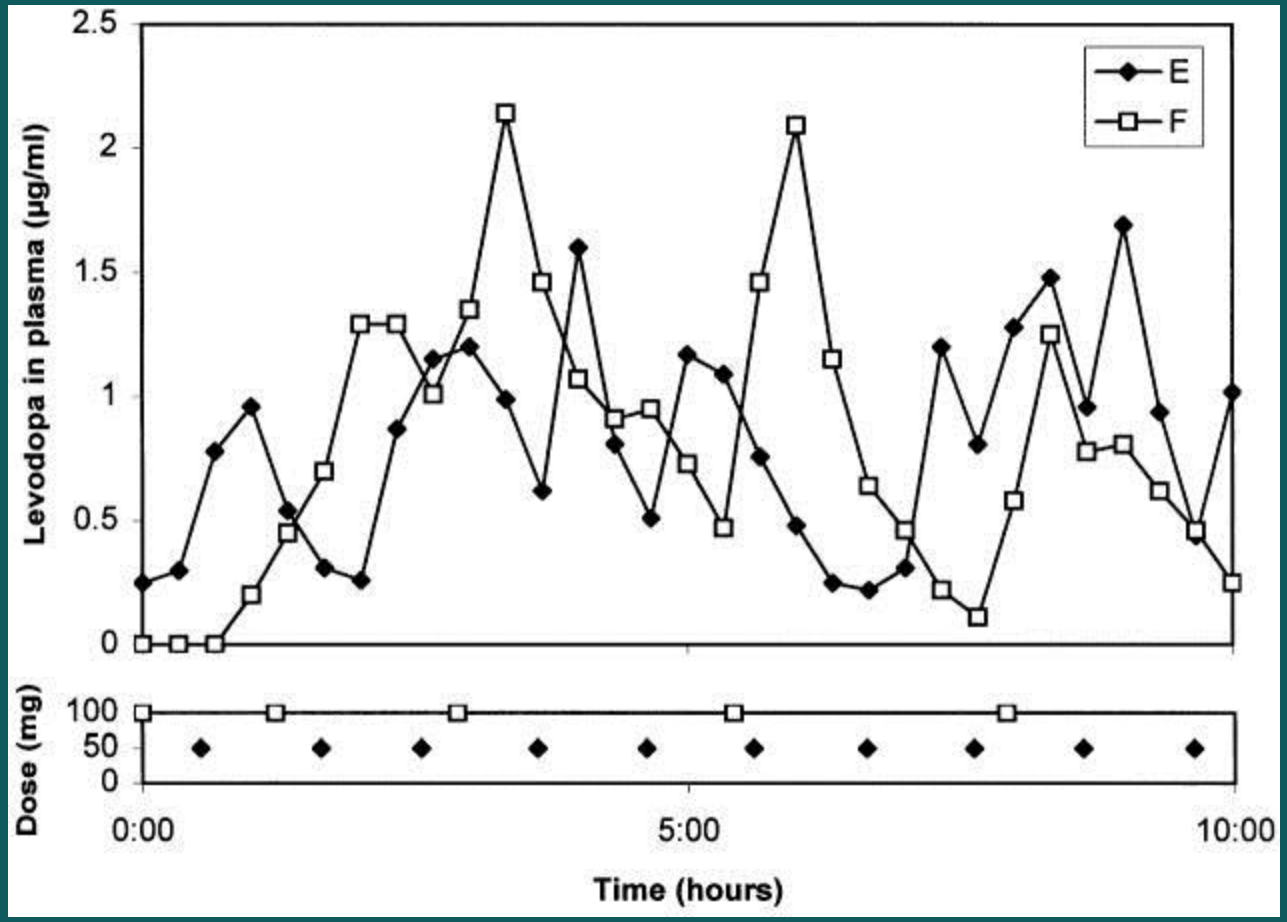
- Gambling
- Impulsive sexual behaviour
- Shopping
- Eating
- Punding



Marked long-duration improvement and mild short-duration improvement in patient with moderate disease. Short-duration improvement occurs after peak plasma concentration of levodopa

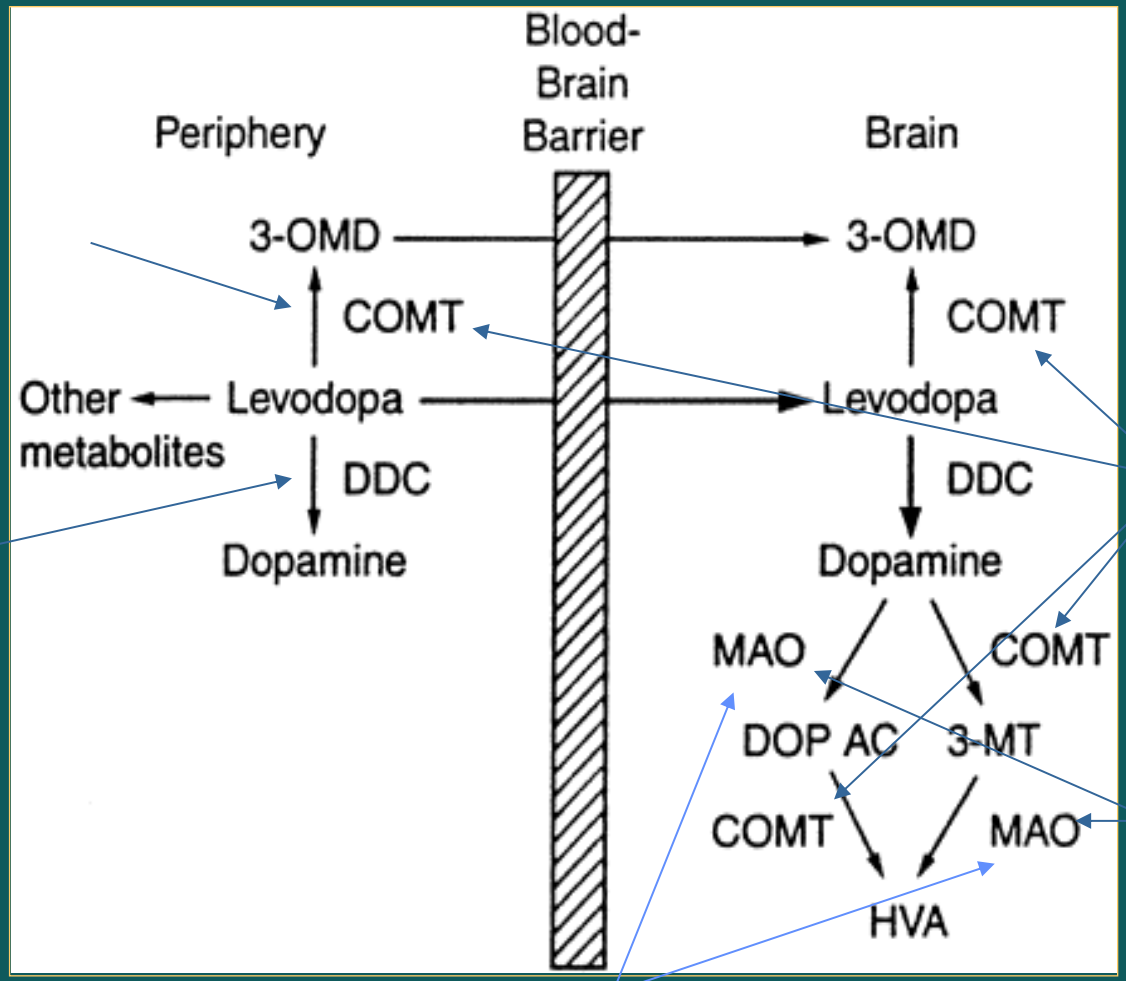

Levodopa
Levodopa
Dopamine


Plasma levodopa (μg/ml)
4
3
2
1
0
0
8
12
24
32
40
48
56
64
Disability score
1
2
3
4
5
6
7
Hours after 1.0 g levodopa



Nyholm. Clinical Neuropharmacology 2002;25:89

Levodopa Enzyme Inhibition



entacapone

carbidopa

tolcapone

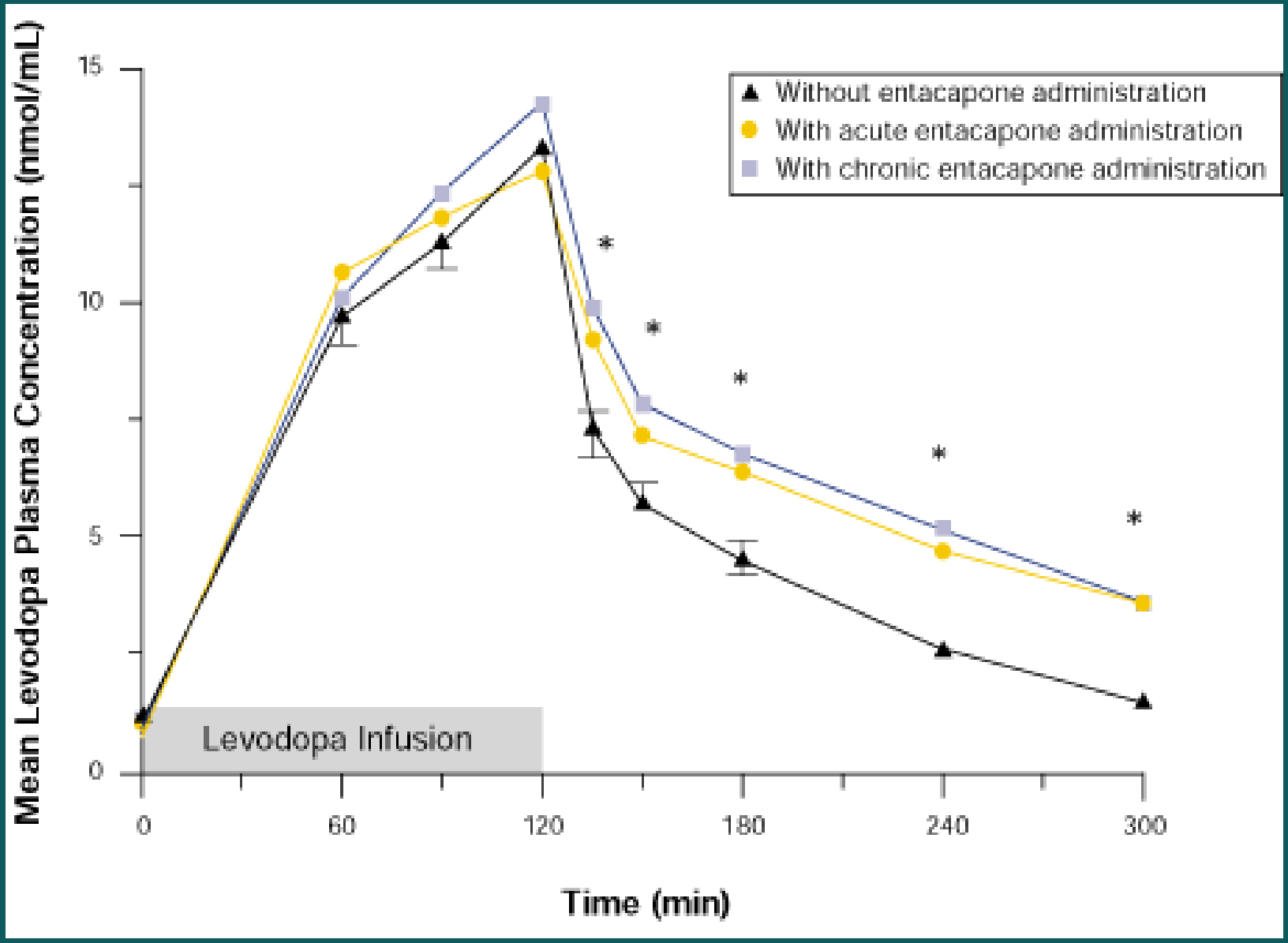
selegiline

rasagiline

modified from Olanow et al. Neurology 2001;56(11 Suppl 5) S1-88)

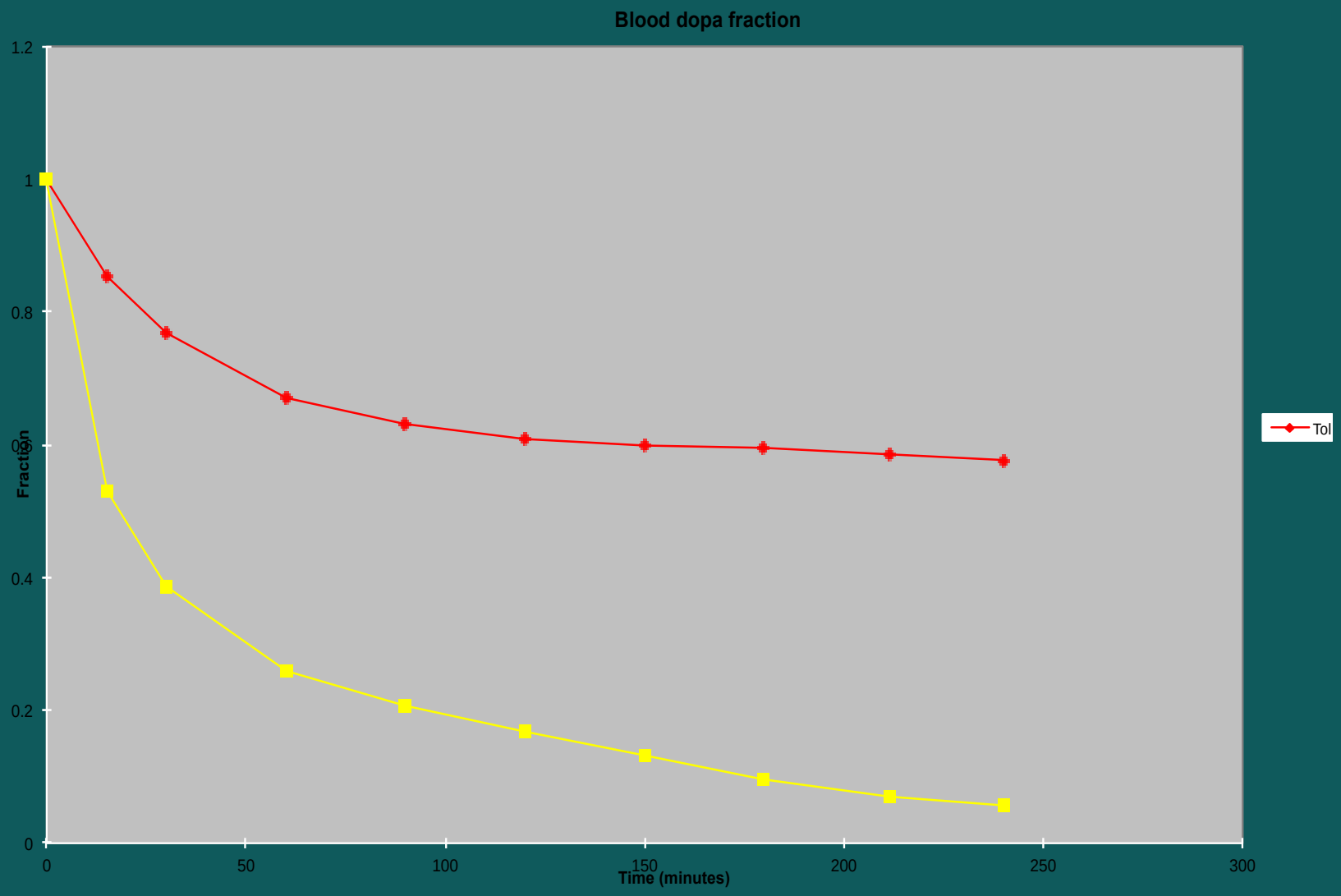
COMT inhibition: Entacapone

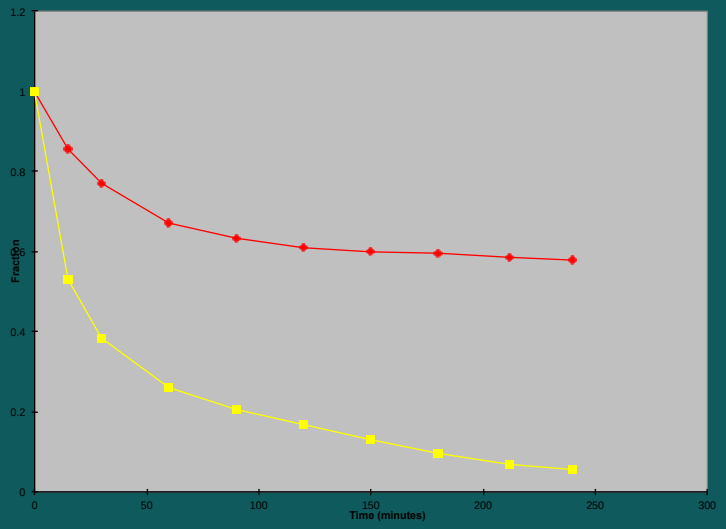
- 200mg with each dose of levodopa
- Easy to use
- Minimal diarrhoea 2.5%
- Not as powerful as tolcapone

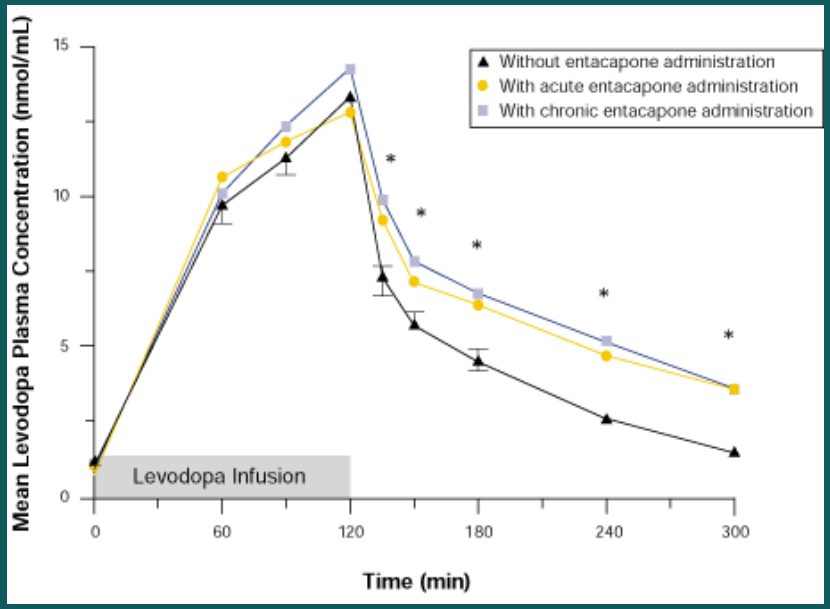

Mean Levodopa Plasma Concentration (nmol/mL)
15
10
5
0
Without entacapone administration
With acute entacapone administration
With chronic entacapone administration
*
*
*
*
*
Levodopa Infusion
0
60
120
180
240
300
Time (min)

COMT inhibition: Tolcapone

- 100-200 mg tds
  - do not adjust the dose
- Powerful
- More levodopa side effects
- More diarrhoea - 12%
- Need to monitor liver function


Blood dopa fraction
1.2
1
0.8
0.6
0.4
0.2
0
Fraction
0
50
100
150
200
250
300
Time (minutes)
Tol

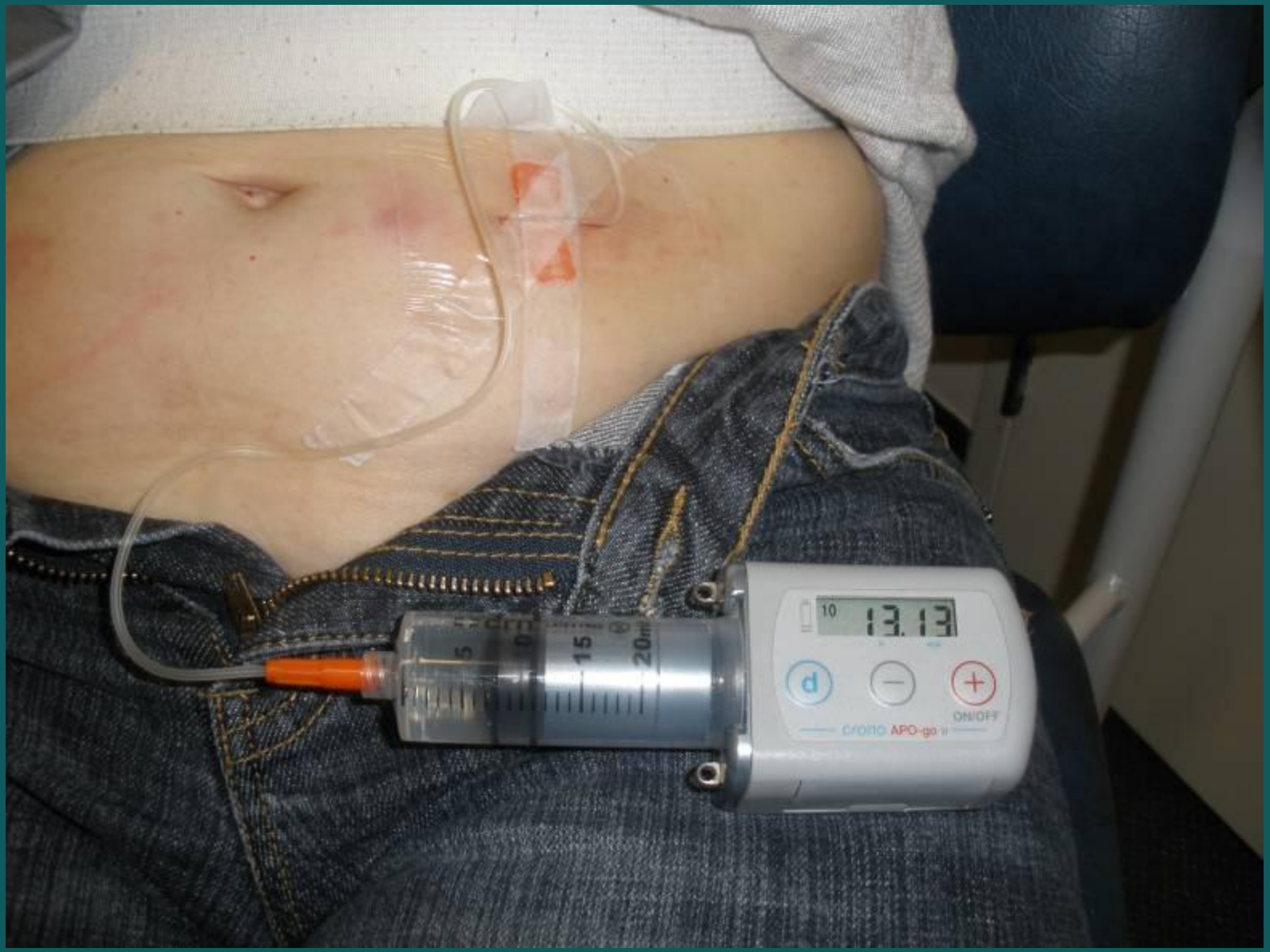

1.2
1
0.8
0.6
0.4
0.2
0
Fraction
0
50
100
150
200
250
300
Time (minutes)

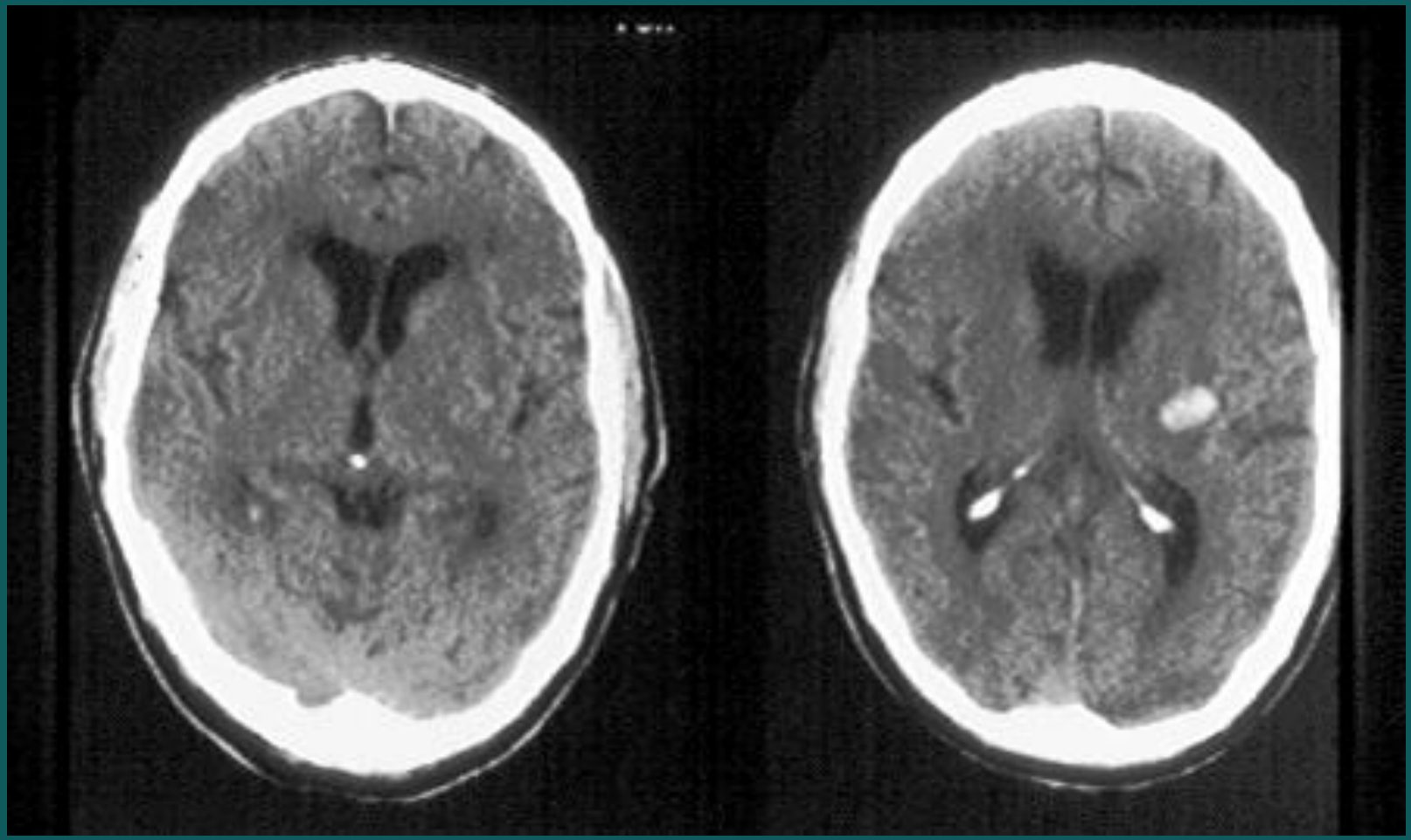

Mean Levodopa Plasma Concentration (nmol/mL)
15
10
5
0
Without entacapone administration
With acute entacapone administration
With chronic entacapone administration
*
*
*
*
*
Levodopa Infusion
0
60
120
180
240
300
Time (min)

Apomorphine

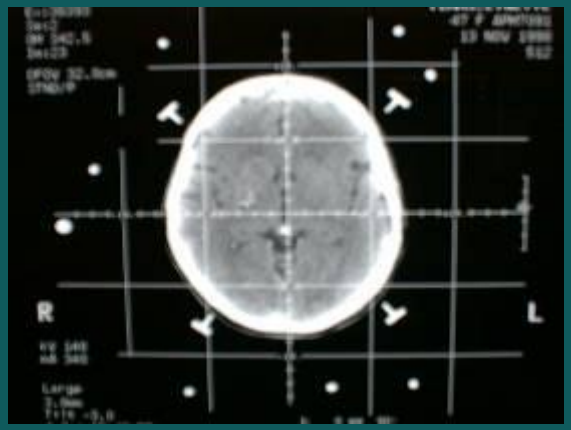
- Morphine decomposition product by boiling with concentrated acid
- Occasionally used to enhance erectile function
- Non-selective dopamine agonist
- Suitable for parenteral use

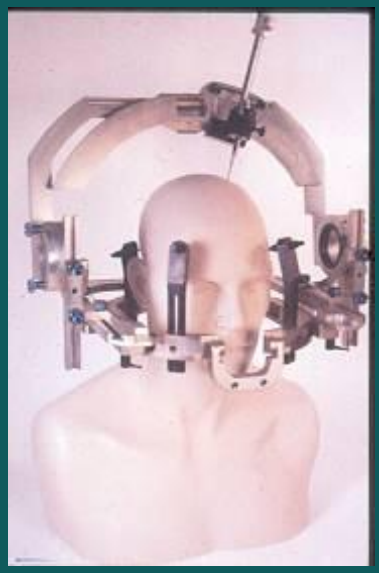
Apomorphine

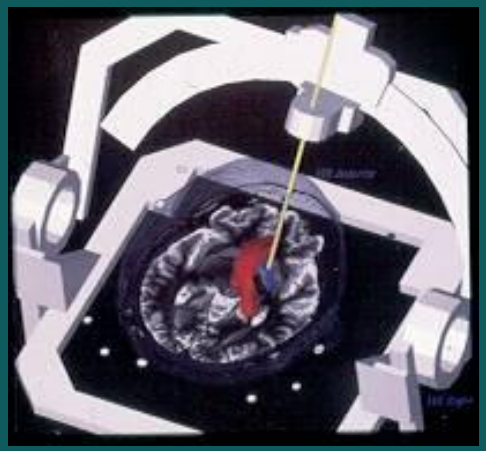

10
13.13
d
ON/OFF
crono APO-go

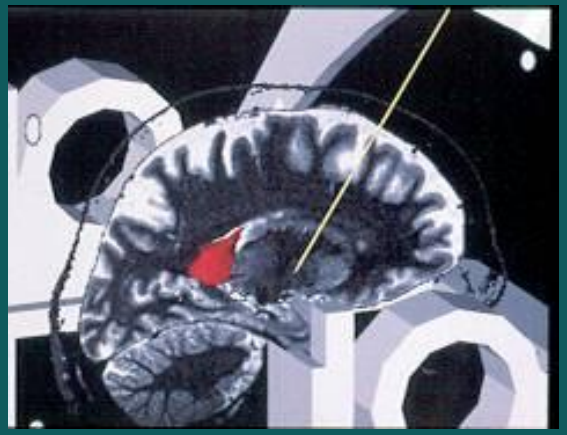


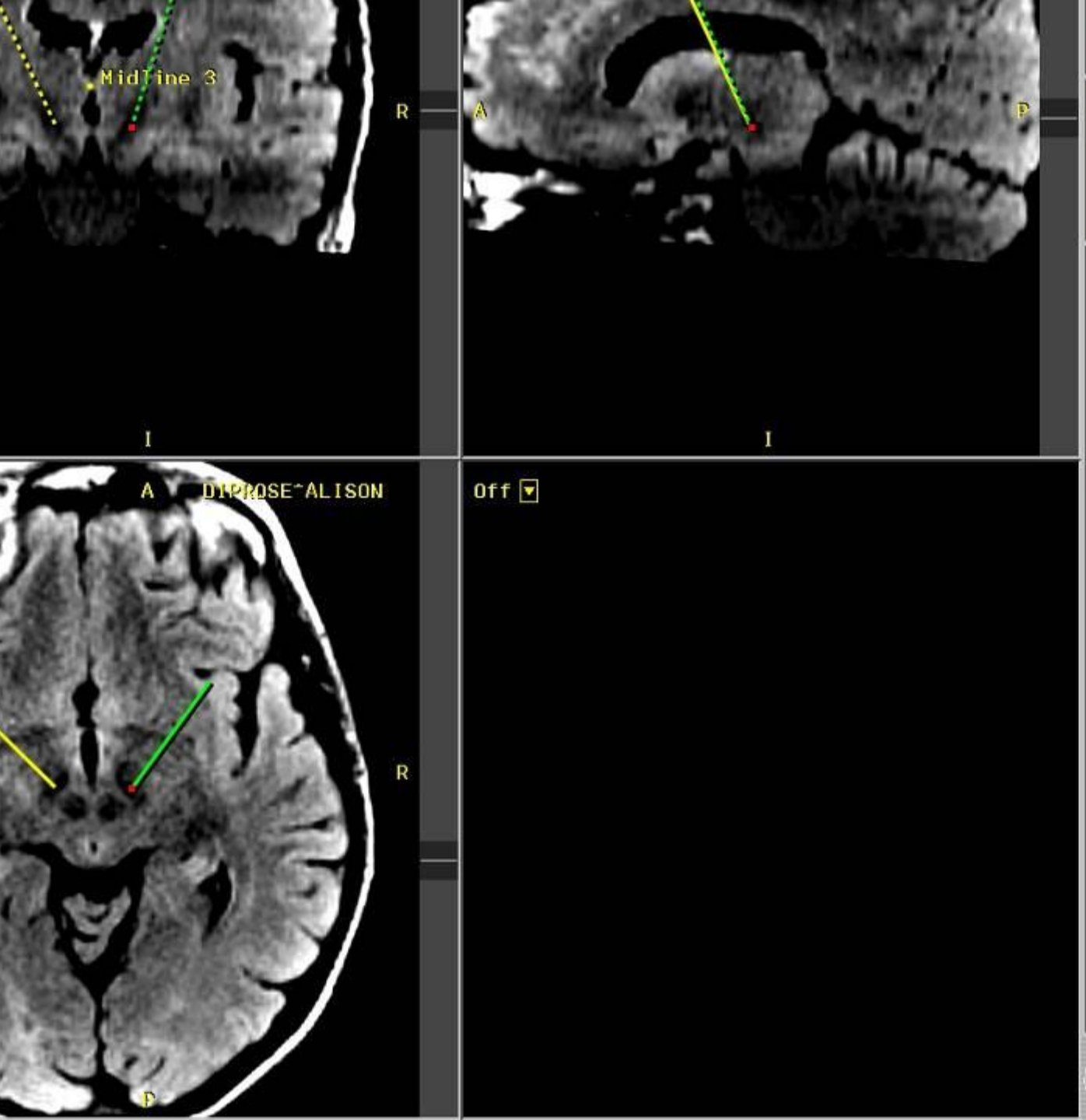
Deep Brain Stimulation











Planning

Frame Settings

Select a plan and read the frame settings.

STN_right_

Edit...

76.0

Set Entry

Length 76.0 mm

Set Target

0.0 mm past target
0.0 mm off plan

Frame Settings

Lat (x):	+5.5	+/-(x)	
A-P (y):	+0.5	+/-(y)	
Vert (z):	-19.5		
Ring:	74.1		
Arc:	19.0		

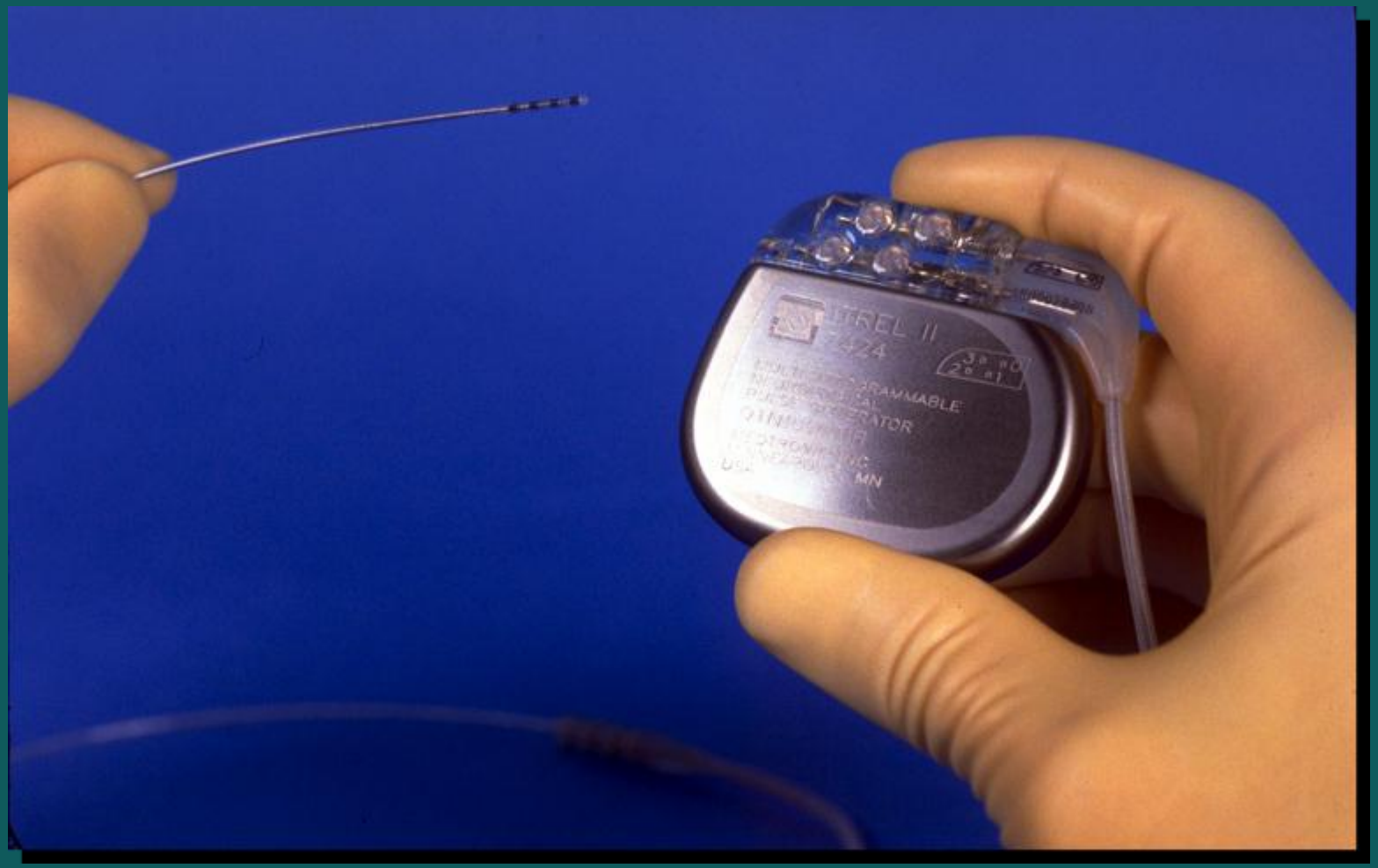
New Track

Current Frame Coordinate

Lat: +5.5 A-P: +0.5 Vert: -19.5

Back

Next



3387S-4X Electrodes 1.5mm apart; over 10.5mm
3389S-4X Electrodes 0.5mm apart; over 7.5mm
Body of Leads are 1.27mm diam.

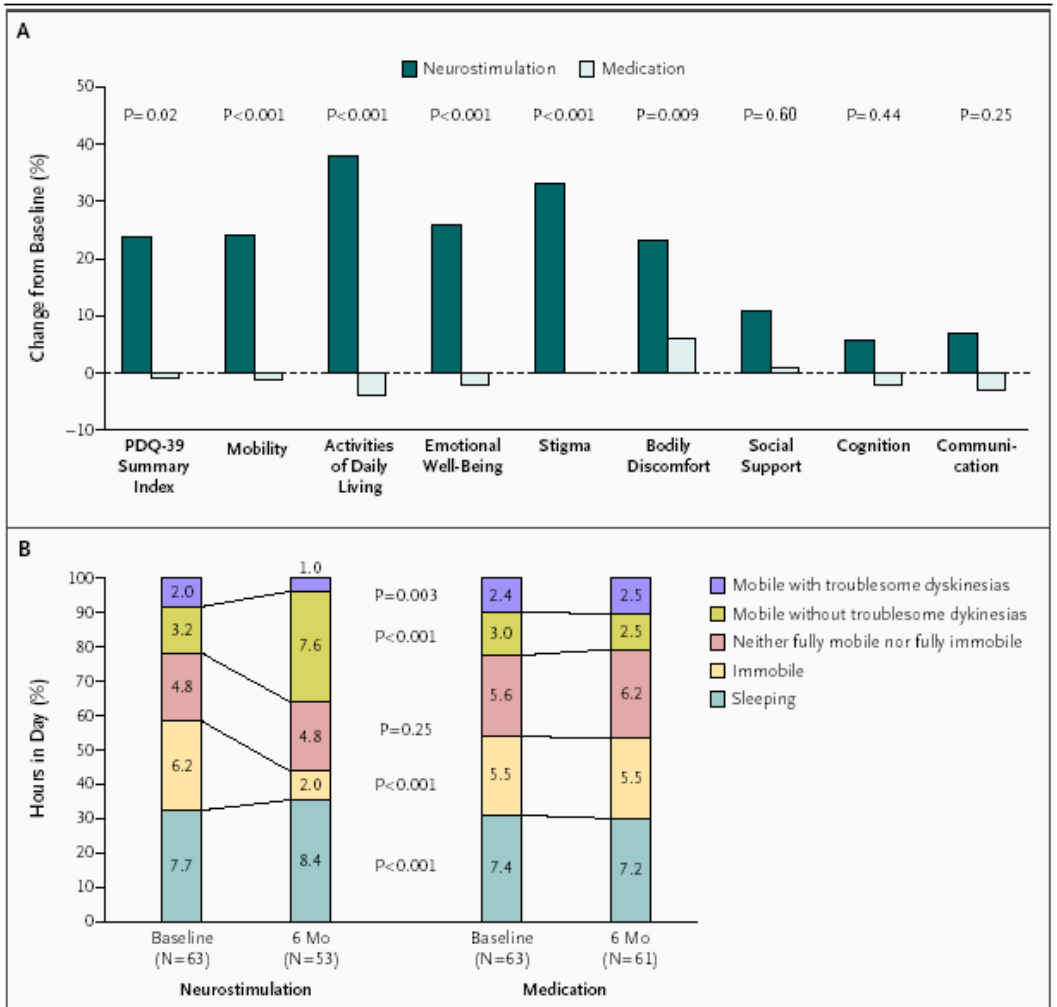


Figure 2. Changes in PDQ-39 Subscores (Panel A) and Patients' Diaries (Panel B) from Baseline to Six Months in the Neurostimulation and Medication Groups.

Panel A shows changes in the PDQ-39 subscores (percentage of baseline values) for the two groups. The subscores evaluate various domains of quality of life. Significant changes occurred only in the neurostimulation group. The greatest improvements occurred in activities of daily living, stigma of the disease, and emotional well-being. The subscores for mobility and bodily discomfort were improved to the same extent as the summary index. There was no significant improvement in social support, cognition, or communication. Panel B shows the results of the diaries kept by the patients. For each 30-minute interval throughout the day, the patients recorded whether they were mobile with troublesome dyskinesias, mobile without troublesome dyskinesias, neither fully mobile nor fully immobile,

Deuschl NEJM 2006