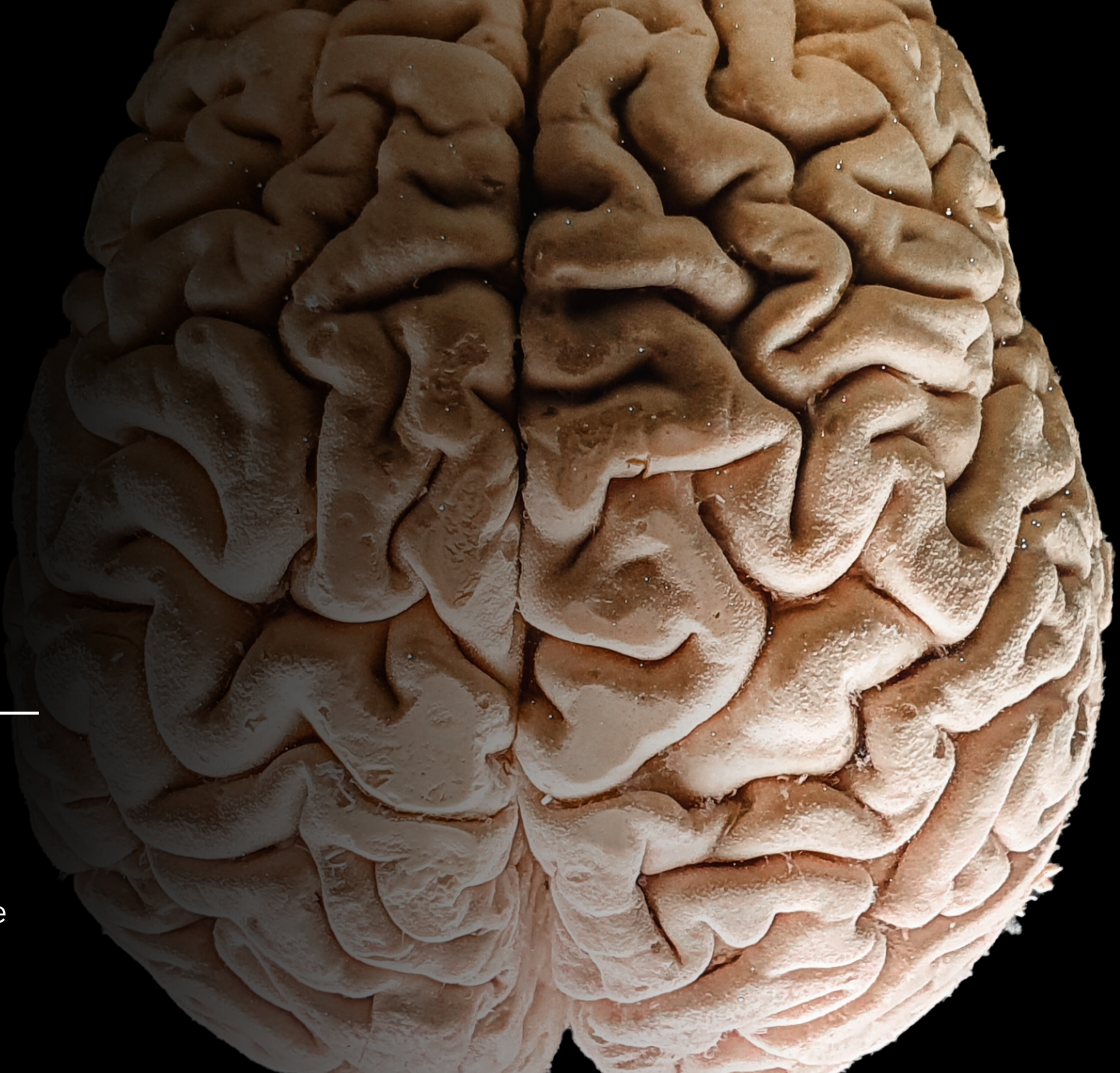
Ziekte van Parkinson



Dr. Vincent Van Iseghem

Neuroloog

vincent.vaniseghem@azgroeninge.be

Objectieven

Diagnose

Behandeling

Wat brengt de toekomst ?

Praktische tips

Diagnose

AN

ESSAY

ON THE

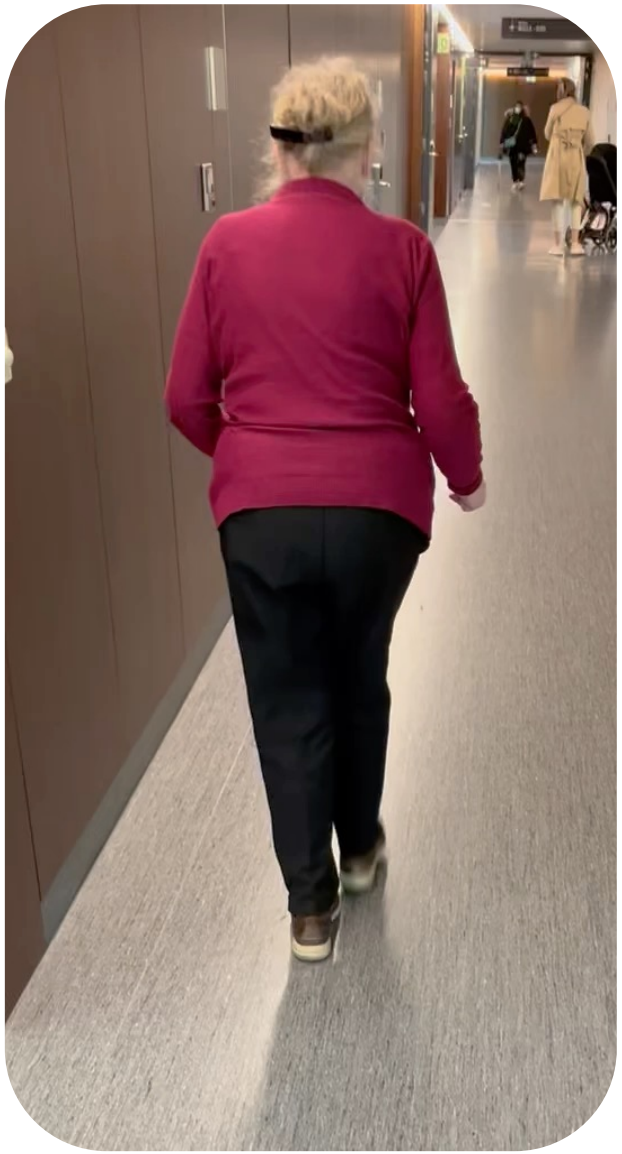
SHAKING PALSY.

BY

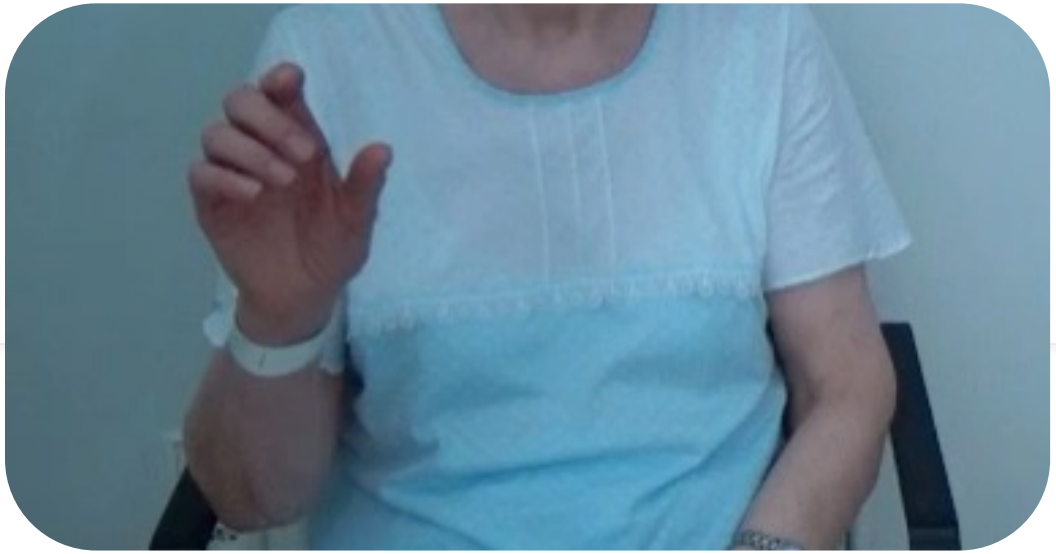
JAMES PARKINSON,
MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

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

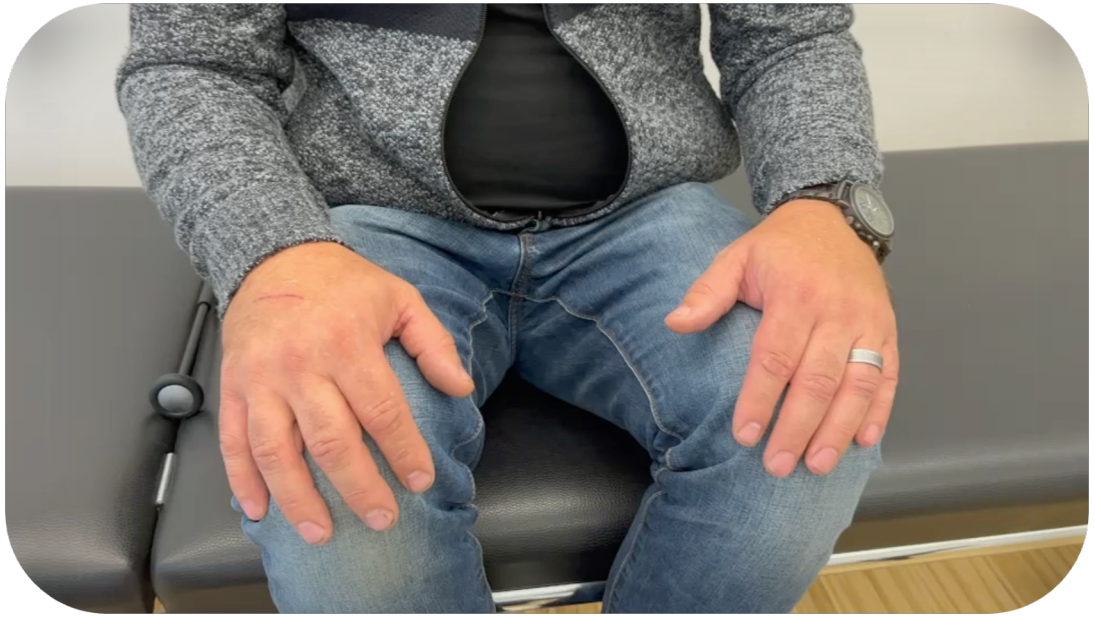
1817.



Parkinsonsime



- **Bradykinesie**
  - = traagheid EN decrement in amplitude of snelheid



- EN/OF
  - Rigiditeit
  - Rusttremor

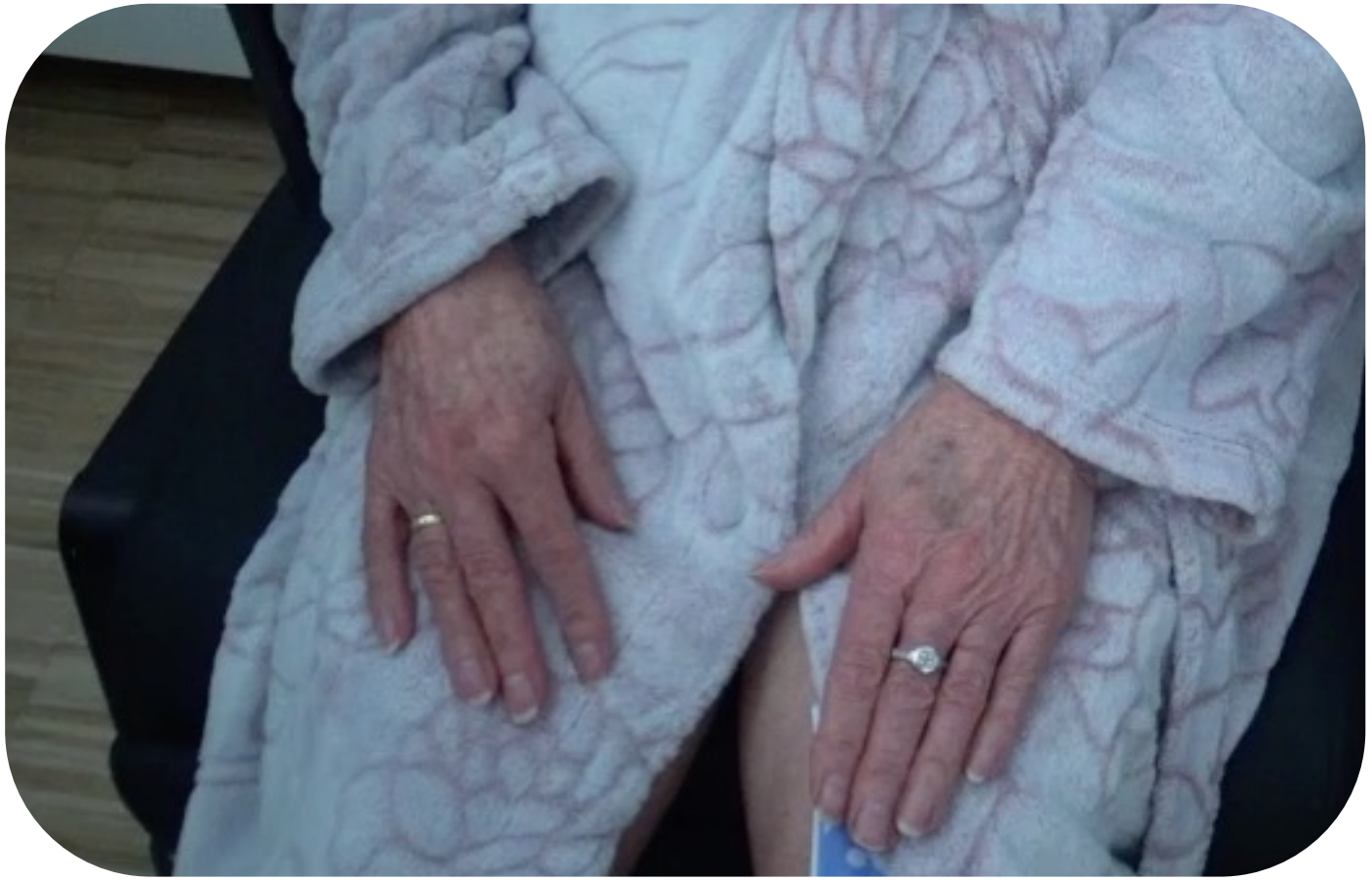
Parkinsonisme

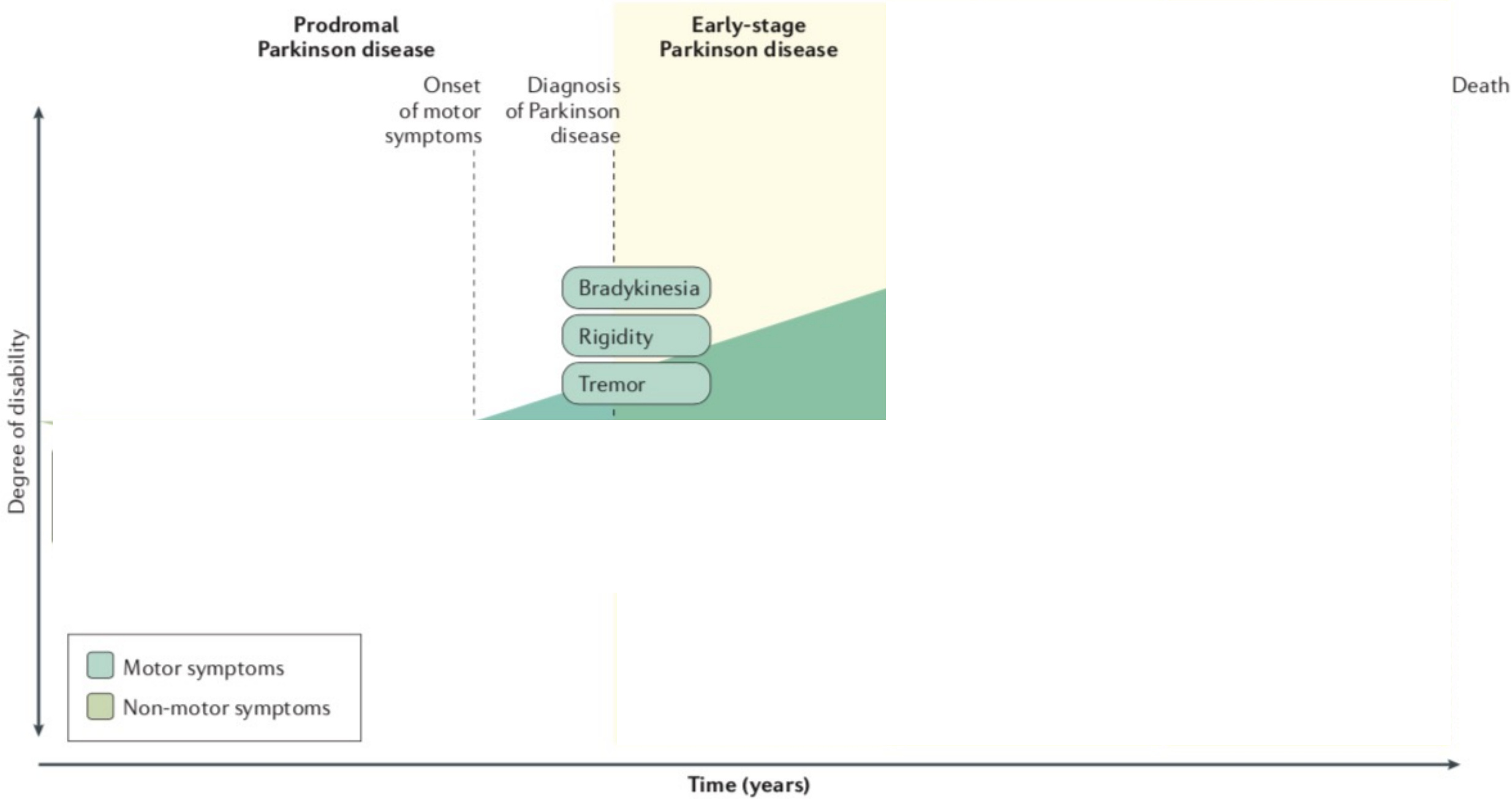
- Rigiditeit
  - ‘tandrad’
  - ‘loden pijp’

  - bij passieve mobilisatie
  - Onafhankelijk van snelheid
  - <-> spasticiteit

Parkinsonisme

- **Rust**tremor
  - 4-6Hz
  - ‘Re-emergent’




Prodromal Parkinson disease
Early-stage Parkinson disease
Onset of motor symptoms
Diagnosis of Parkinson disease
Death
Bradykinesia
Rigidity
Tremor
Degree of disability
Motor symptoms
Non-motor symptoms
Time (years)

Diagnostische criteria Ziekte van Parksinon

- **<u>Parkinsonisme</u>**
  - BRADYKINESIE
    - Rigiditeit en/of Tremor
- Exclusie van **andere oorzaken**
- Supportieve criteria
  - Goed effect op Levodopa
  - Levodopa geïnduceerde dyskinesieën
  - Klassieke rusttremor
  - Hyposmie
  - Cardiale sympathische denervatie op MIBG scintigrafie
- Geen **rode vlaggen** (snelle progressie, valpartrijen vroeg in de ziekte ed.)

Box 1 | **MDS diagnostic criteria for Parkinson disease**

Step 1: diagnosis of parkinsonism (core feature)

- Presence of bradykinesia as a slowness of movement and a decrement in amplitude or speed (or progressive hesitations or halts) as movements are continued
- In combination with at least one of: rigidity and/or rest tremor

Step 2: determining Parkinson disease as the cause of parkinsonism with two levels of diagnostic certainty

Diagnosis of clinically established Parkinson disease requires all three of the below parameters:

- Absence of absolute exclusion criteria. These criteria include clinical or imaging evidence for alternate diagnoses of parkinsonism, such as atypical parkinsonism, drug-induced parkinsonism or essential tremor.
- Two or more supportive criteria. These include L-DOPA responsiveness, the presence of classic rest tremor, the presence of L-DOPA-induced dyskinesias, the presence of either olfactory loss or cardiac sympathetic denervation on metaiodobenzylguanidine (MIBG) scintigraphy.
- No red flags. This refers to features that are unusual but not absolutely exclusionary for Parkinson disease, for example, the rapid progression of gait impairment that requires wheelchair use or the development of severe autonomic failure within 5 years after onset.

Diagnosis of clinically probable Parkinson disease requires:

- Absence of absolute exclusion criteria (mentioned above)
- Presence of red flags (mentioned above) that are counterbalanced by supportive criteria

For a full listing of absolute exclusion criteria, red flags and supportive criteria see REF. 118.

MDS, International Parkinson and Movement Disorder Society.

Rode vlaggen

- Snelle progressie van gangmoeilijkheden ;
  - **rolstoel < 5 jaar**
  - **Recurrente valpartijen < 3 jaar**
- Geen progressie > 5 jaar

Rode vlaggen 

- Klinische tekenen van ’andere’ etiologie
  - ataxie
  - **oogbewegingsstoornissen**
  - apraxie, afasie
- **Geen effect van hoge dosis levodopa**
- Behandeling met neuroleptica (en tijdsrelatie met °symptomen)
- Afwijkende structurele beeldvorming
- Normale DaT-scan

Differentiaaldiagnose

Essentiële tremor

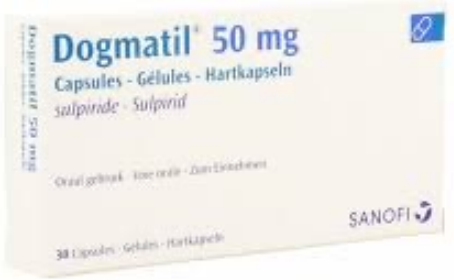
- Actietremor
- Bilateraal
- > 3 jaar
- Familiale voorgeschiedenis
- Hoofd- en stemtremor
- Geen micrografie

Alty et al. A practical guide to the differential diagnosis of tremor. (2011).

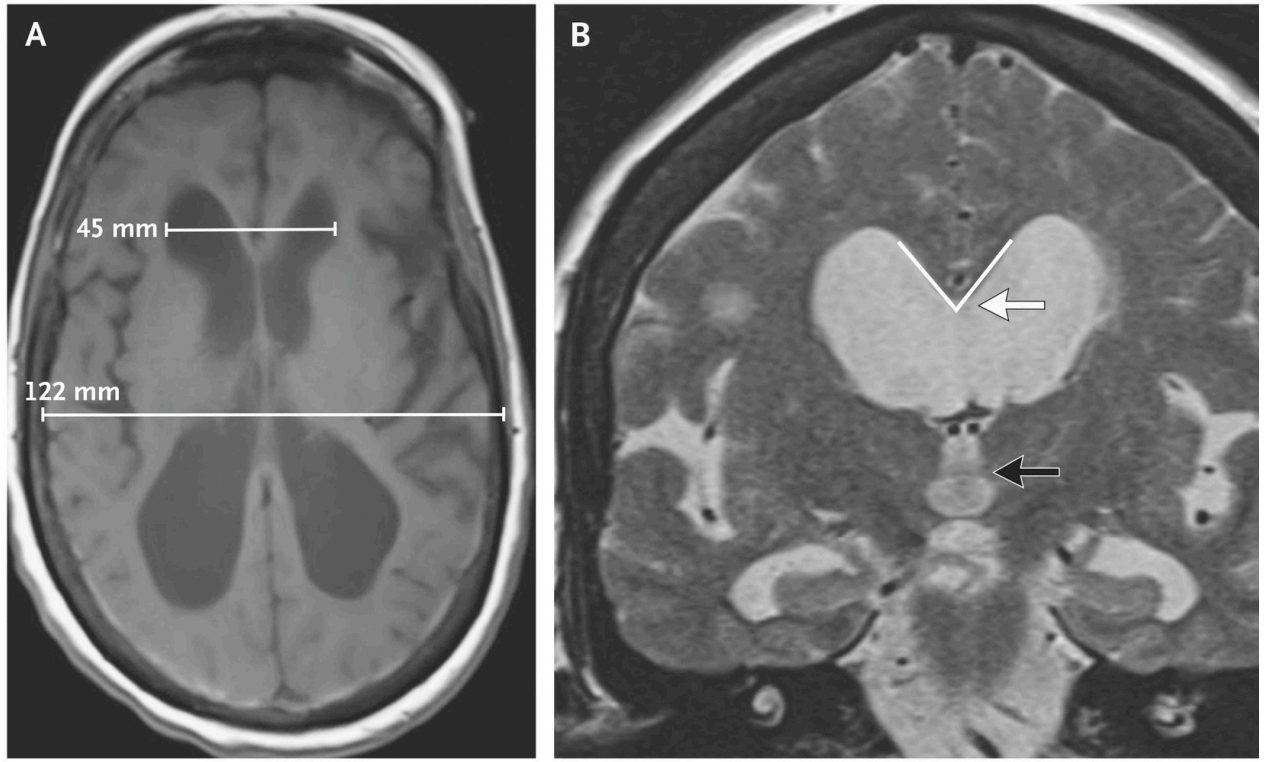
Medicatie geïnduceerd

- Neuroleptica
- Antihistaminica

- Vaak symmetrisch + tremor
- ‘Wear-out’ kan tot 1 jaar duren



NPH – normale druk hydrocephalie

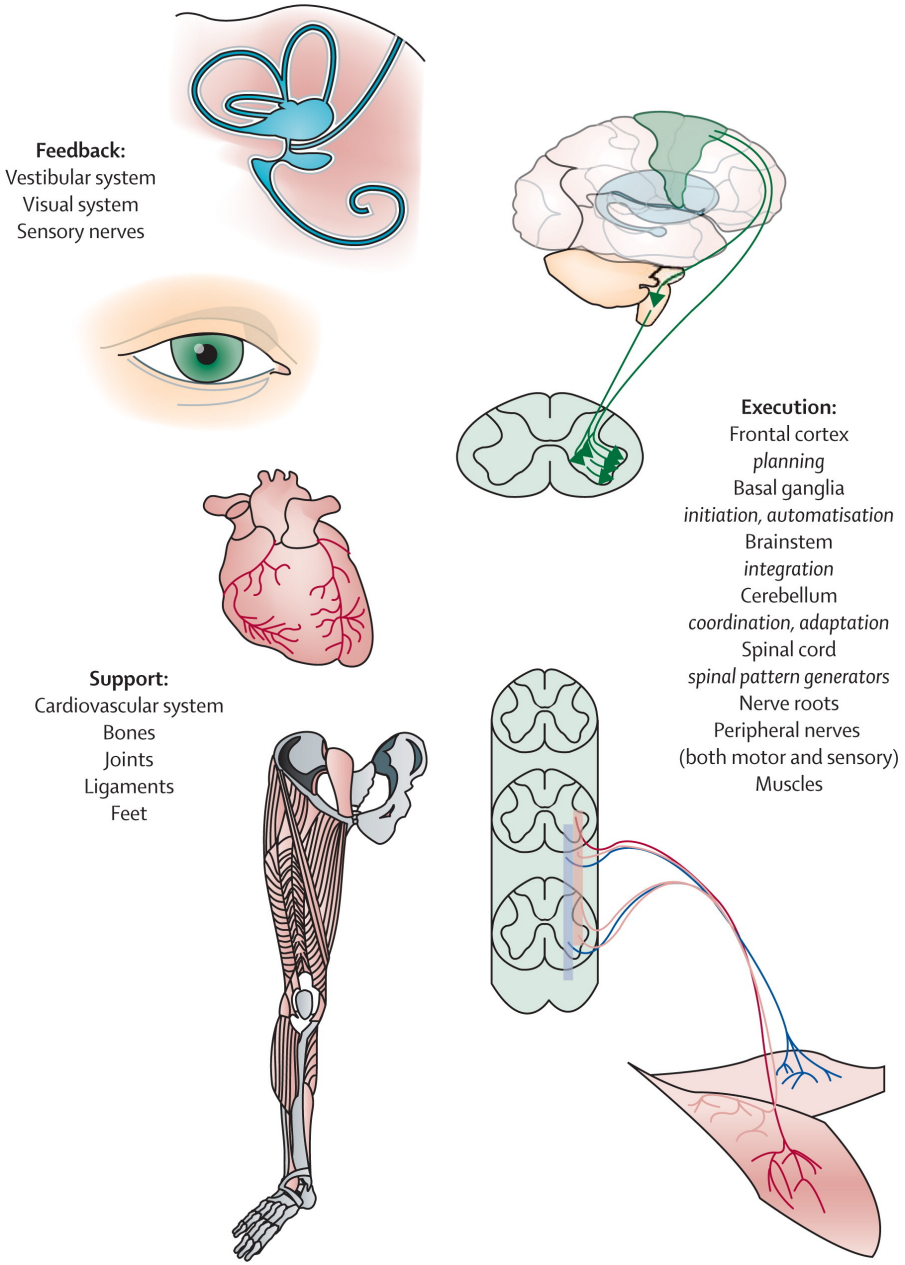


- Triade :
  1. Gang- en evenwichtsproblemen
  2. Cognitieve dysfunctie
  3. OAB
- Weinig betrokkenheid BL
- Ventriculomegalie
- R/ Evacuerende punctie – ventriculoperitoneale drainage

NPH

Andere gangstoornissen

- ‘Vasculair parkinsonisme’
  - Wittestoflijden cerebraal
  - ‘Lower body parkinsonisme’
  - NPH beeld
- Sensorische gangataxie
  - Neuropathie
  - Romberg ++ (↑ ogen gesloten)
- ‘Higher level gait disorder’



Snijders et al. Neurological gait disorders in elderly people: clinical approach and classification. Lancet Neurol. 2007 Jan;6(1):63-74.

Andere gangstoornissen

- ‘Vasculair parkinsonisme’
  - Wittestoflijden cerebraal
  - ‘Lower body parkinsonisme’
  - NPH beeld
- Sensorische gangataxie
  - Neuropathie
  - Romberg ++ (↑ ogen gesloten)
- ‘Higher level gait disorder’

Parkinson-plus syndromen

	Multiple Systeem Atrofie (MSA) (MSA – C en MSA – P)	**Progressieve Supranucleaire Parese (PSP)**	**Corticobasale Degeneratie Syndroom (CBS)**
Onset	57	63	63
Symmetrie	Asymmetrisch	Symmetrisch	Symmetrisch
Dementie	- (+)	+++ (frontaal)	++
Tremor	++	-	+ (schokkerig)
Autonoom falen	+++	-+	-+
Andere	Stridor	Supranucleaire blikparese	Apraxie

Essentiele tremor

Bilateraal
> 3 jaar
Familiale voorgeschiedenis
Hoofd- en stemtremor
Geen micrografie

Medicamenteus

Symmetrisch
Polyfarmacie
(oa. Neuroleptica, Primperan, Lithium, Antihistaminica …)

Vasculair Parkinsonisme

Normale Druk Hydrocephalie

Afwijkende CT/MR hersenen
‘ Lower Body ‘ parkinsonisme
Magnetische gang

Parkinson – plus syndromen

MSA – multiple systeematrofie
PSP – progressieve supranucleaire parese
CBS – corticobasaal syndroom

Snel ziekteverloop
Weinig tot geen respons op medicatie

Vals negatieven

Journal of Neurology, Neurosurgery, and Psychiatry 1989;**52**:63–66

Frozen shoulder and other shoulder disturbances in Parkinson's disease

D RILEY, A E LANG, R D G BLAIR, A BIRNBAUM, B REID

From the Movement Disorders Clinic, Toronto Western Hospital, Toronto, Canada

SUMMARY The frequency of shoulder disturbances, particularly frozen shoulder, has not been assessed previously in Parkinson's disease. In a survey of 150 patients compared with 60 matched control subjects a significantly higher incidence of both a history of shoulder complaints (43% vs. 23%) and frozen shoulder (12·7% vs. 1·7%) was found in the Parkinson's disease population. Those developing a frozen shoulder had initial disease symptoms indicative of akinesia twice as frequently as tremor while the ratio was reversed in those without frozen shoulder. In at least 8% of the patients frozen shoulder was the first symptom of disease, occurring 0–2 years prior to the onset of more commonly recognised features. Parkinson's disease should be added to the list of causes of frozen shoulder, and clinicians must be aware that the latter is often the presenting symptom of Parkinson's disease.

Vals negatieven

- Young-onset Parkinson (YOP)
  - Parkinson : +- 5-10 % < 50 jaar
  - Genetisch ?
  - Ander ziekteverloop

Behandeling

Behandeling

Levensstijl

Lichaamsbeweging

Dieet?

(Para)Medisch

Kinesitherapie

Logopedie

Gespecialiseerd verpleegkundige

…

Medicatie

Symptomatisch

“Wait and see” ook mogelijk

'Device-aided'

DBS

Pomptherapie

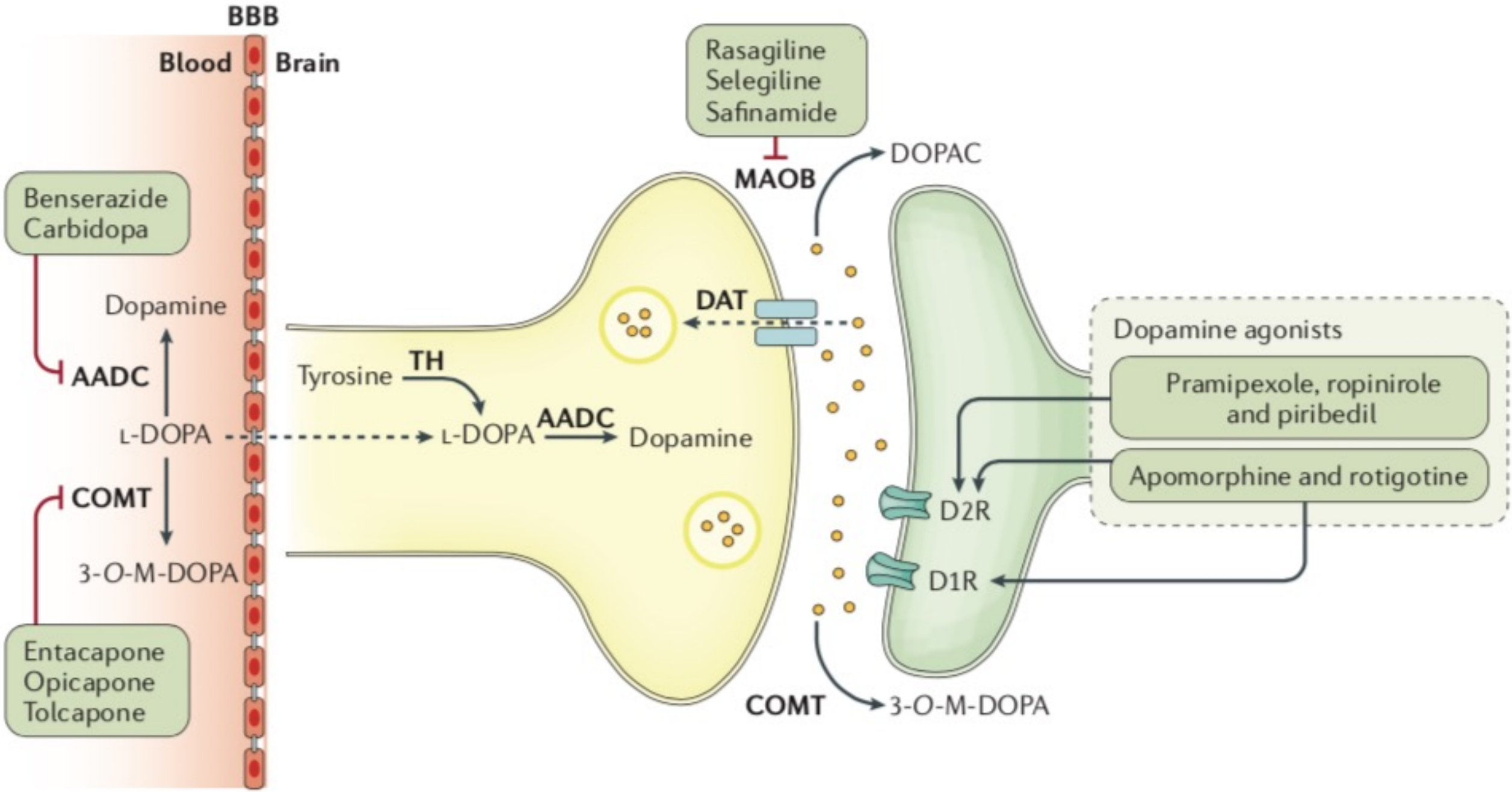
Medicatie

- Niet-motore symptomen
  - Orthostatisme
  - Constipatie
  - Insomnie
  - …

- Motore symptomen

Medicatie

Monotherapie	Levodopa (Prolopa, Sinemet, Isicom) Dopamine-agonisten (Pramipexole/Mirapexin, Ropinirole/Requip)
Add-on	MAO-B inhibitoren (Rasagiline/Azilect, Safinamide/Xadago) COMT inhibitoren (Entecapone/Comtan/Stalevo, Tolcapone/Tasmar) Amantadine Anticholinergica (Artane, Akineton)
Andere …	Ikv niet-motorische symptomen Device-aided therapies (DAT) ; Apo-Morfine (Apo-Go), Levodopa-carbidopa intestinale gel (Duodopa/Lecigimon)


BBB
Blood
Brain
Benserazide
Carbidopa
Dopamine
AADC
L-DOPA
COMT
3-O-M-DOPA
Entacapone
Opicapone
Tolcapone
Rasagiline
Selegiline
Safinamide
MAOB
DOPAC
DAT
Tyrosine
TH
L-DOPA
AADC
Dopamine
Dopamine agonists
Pramipexole, ropinirole and piribedil
Apomorphine and rotigotine
D2R
D1R
COMT
3-O-M-DOPA

Algemene principes

- Wanneer?
  - Bij functionele last
- ‘Symptomatisch’

- Wat?
  - Initiatie
    - Levodopa : Bv. Prolopa 250 ; 3x1/4 (= 3x50mg) tot 3x1/2 tot max. 3x1 tabl
    - Dopamine Agonisten

Dopamine-agonisten

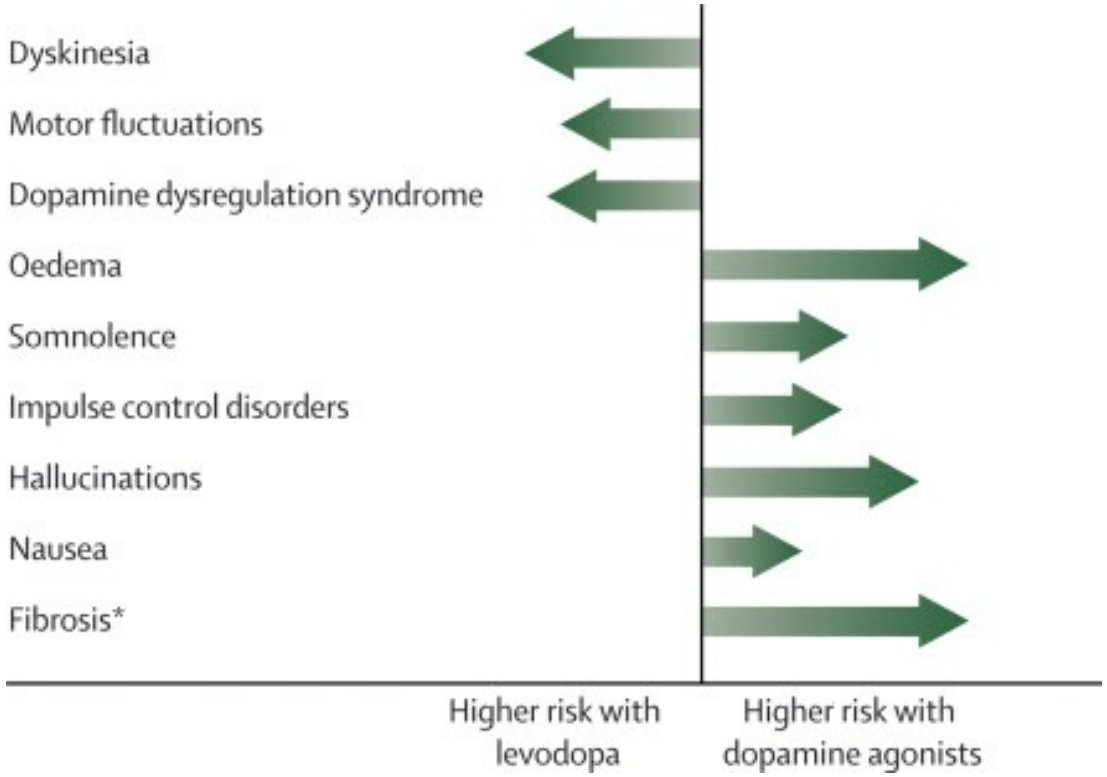
- Ergot derivaten (bv. bromocriptine, pergolide) vs non-ergot derivaten (bv. pramipexole, ropinirole)
- Monotherapie of add-on bij L-dopa
- Andere Dopamine-Receptor affiniteit

👍 Langere $T^{1/2}$

👍 Minder kans op motor complicaties

👎 Minder effectief

👎 Bijwerkingen



Antonini A, Tolosa E, Mizuno Y, Yamamoto M, Poewe WH. A reassessment of risks and benefits of dopamine agonists in Parkinson's disease. Lancet Neurol. 2009 Oct;8(10):929-37. doi: 10.1016/S1474-4422(09)70225-X. Epub 2009 Aug 24. PMID: 19709931.

Levodopa

" Before the 1960s, the clinical features and basic neuropathology of the disorder had been established, anticholinergic drugs and stereotaxic surgery were popular, but the illness progressed relentlessly and was a cause of miserable disability.. The discovery of selective striatal dopamine deficiency in the parkinsonian brain in the early 1960s changed everything."

C.D. Marsden (Lancet 1990)

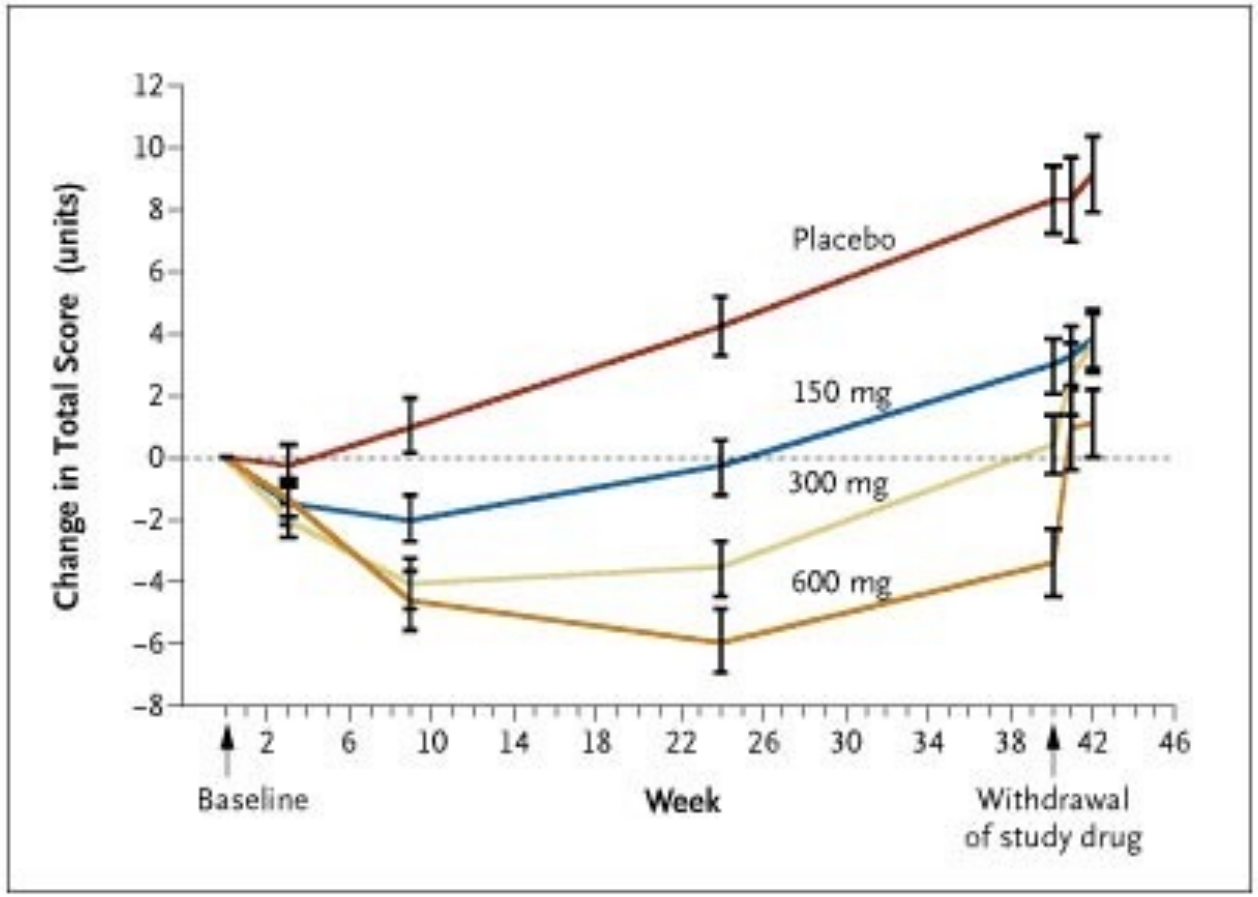
- 1959 : A. Carlsson*
- 1961 : Hornykiewicz – Birkmayer
- 1970 : FDA approved

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Levodopa and the Progression of Parkinson's Disease

The Parkinson Study Group*



- Elldopa-studie
  - Versnelde progressie?
  - → Neuroprotectief effect?
  - → Verlengd effect Ldopa

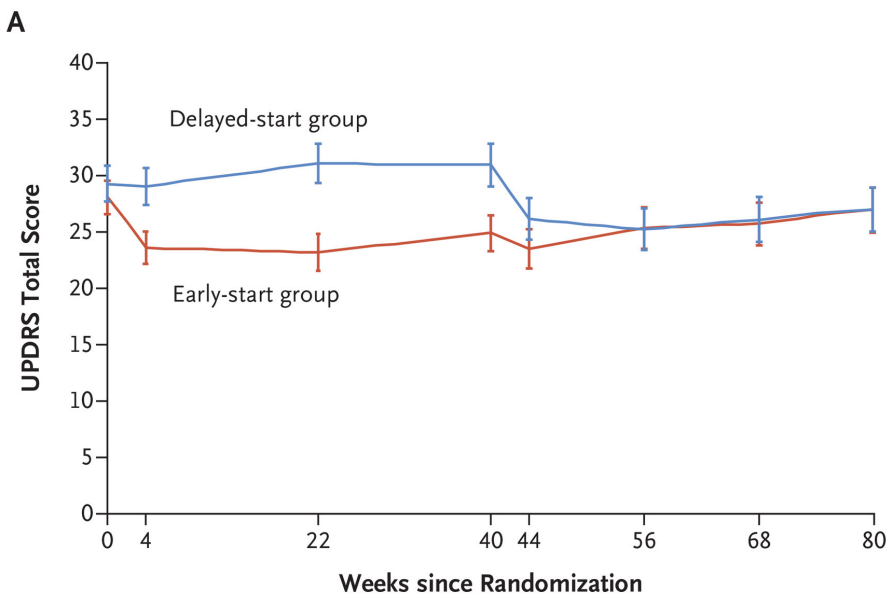
N Engl J Med 2004; 351:2498-2508

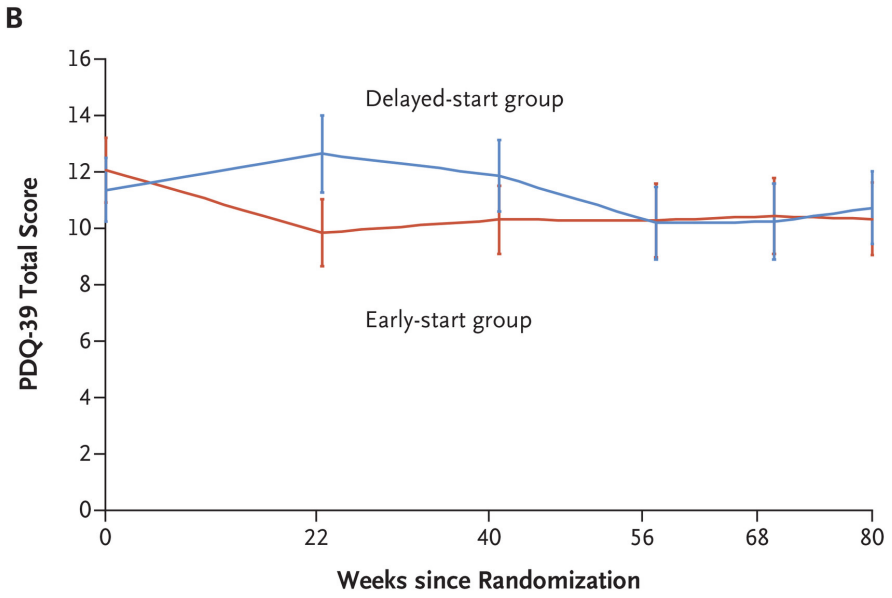
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 24, 2019 VOL. 380 NO. 4

Randomized Delayed-Start Trial of Levodopa in Parkinson's Disease

C.V.M. Verschuur, S.R. Suwijn, J.A. Boel, B. Post, B.R. Bloem, J.J. van Hilten, T. van Laar, G. Tissingh, A.G. Munts, G. Deuschl, A.E. Lang, M.G.W. Dijkgraaf, R.J. de Haan, and R.M.A. de Bie, for the LEAP Study Group*





Casus 1

M.V., 78j. (vrouw)

VG : heupprothese, schouderpijn, endogene depressie, VKF

Reden consultatie : Algemene achteruitgang

Medicatie: Bisoprolol 2,5mg, Eliquis 2x5mg, Zaldiar SOS

Klinisch:

- Rusttremor in rechterhand
- Bradykinesie bij alternerende bewegingen
- Verminderde armzwaai rechts

Technisch: CT hersenen: geen bijzonderheden

Therapie ?

Bv. Prolopa 250 : + ¼ tabl. Tot 3 x ¼ (¼– ¼ - ¼)

Casus 2

P.D., 68j. (man)

VG : Angststoornis, COPD, lumbalgie, Chronische nierinsufficiëntie, Ethylisme

Medicatie: Sipralexa 10mg, Bisoprolol 2,5mg, Coversyl 5mg, Paracetamol 1g, Deanxit, Befact Forte

Klinisch:

- Gang met kleine passen
- Bilateraal verminderde armzwaai
- Bilateraal rusttremor

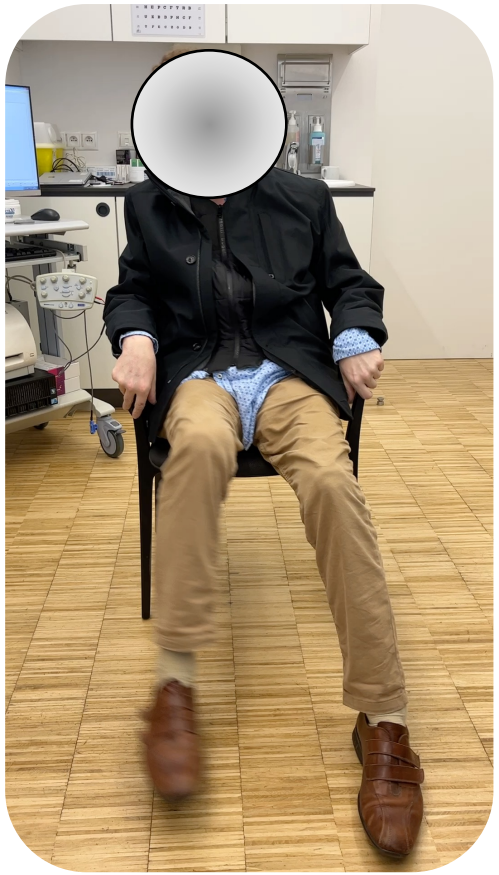
Technisch: CT hersenen toont milde globale atrofie.

Therapie ?

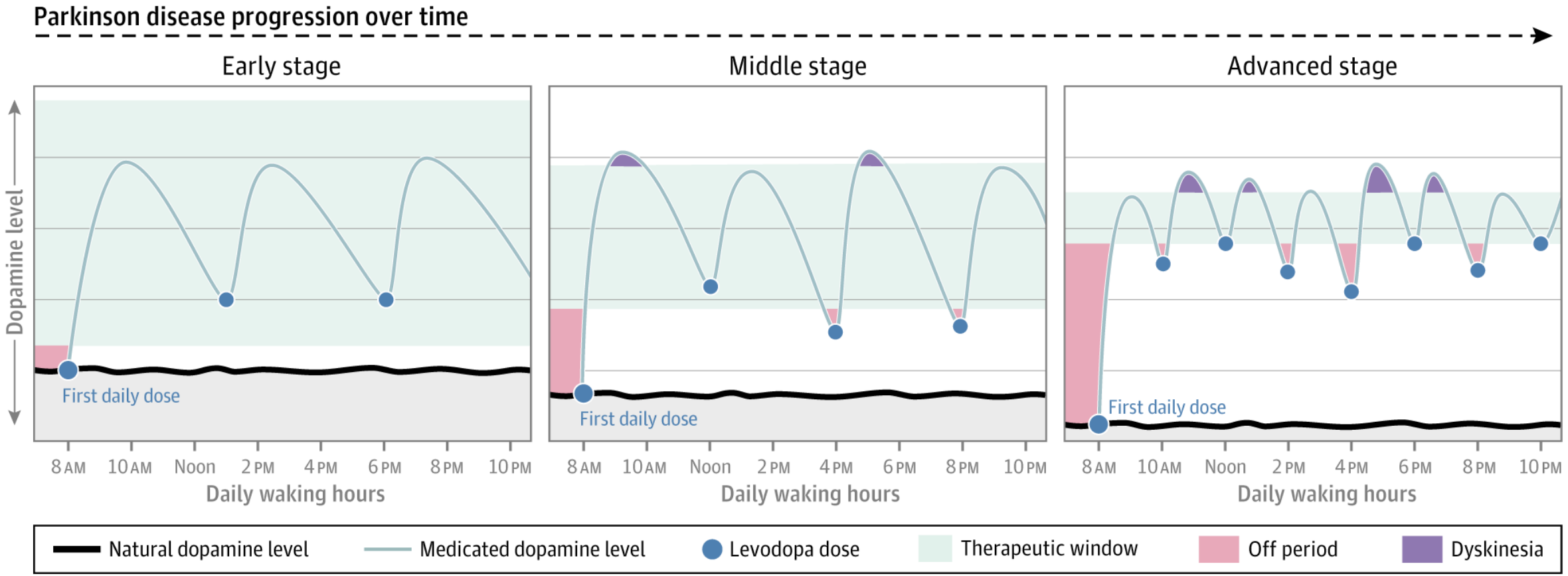
Afbouw Deanxit !

Levodopa

- Complicaties
  - Acuut
    - Constipatie, Nausea, Orthostatisme
  - Lange termijn
    - Responsfluctuaties ; ON/OFF
    - Dyskinesieën



Levodopa

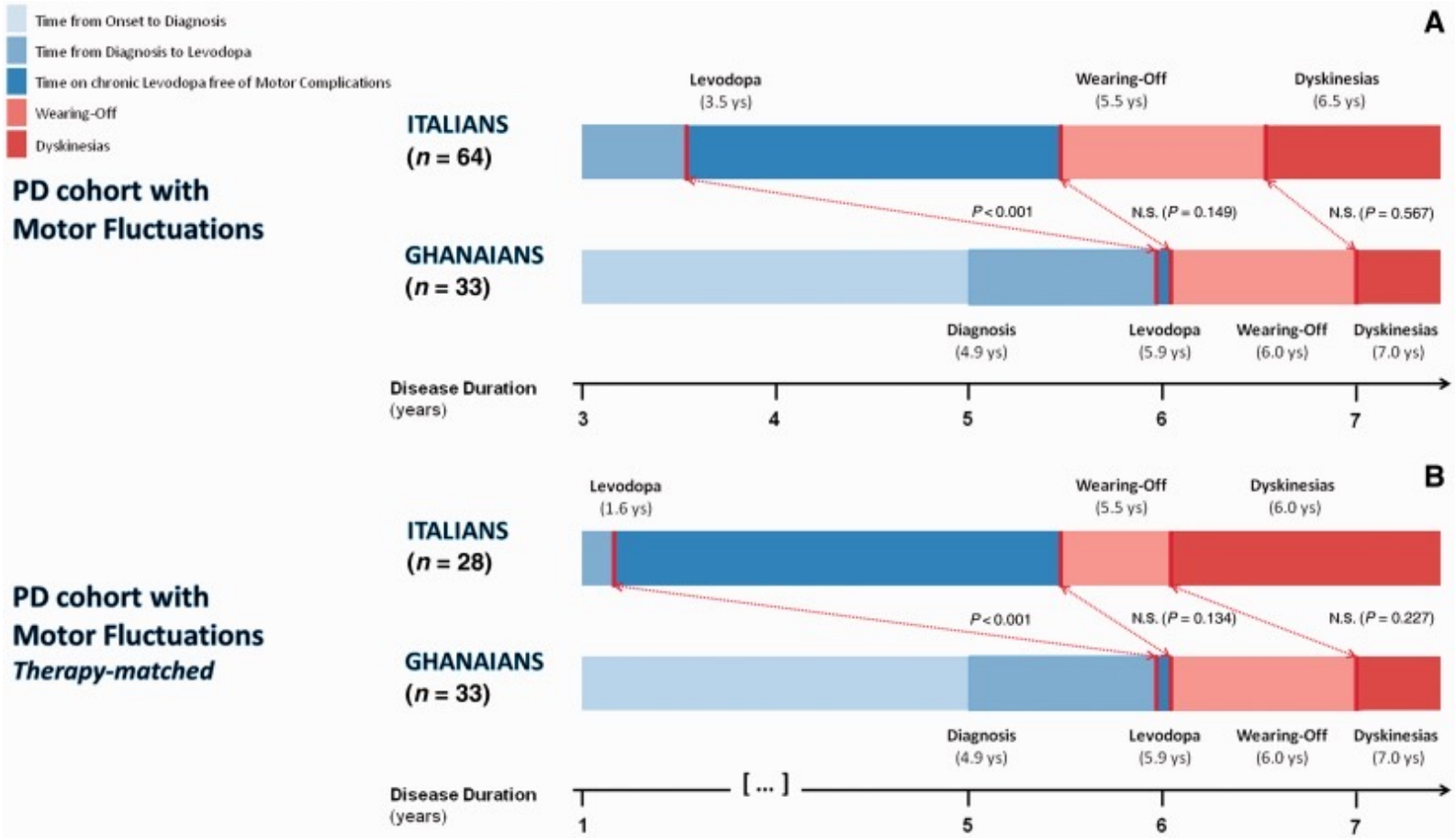


Armstrong MJ, Okun MS. Diagnosis and Treatment of Parkinson Disease: A Review. *JAMA.* 2020;323(6):548–560. doi:10.1001/jama.2019.22360

BRAIN
A JOURNAL OF NEUROLOGY

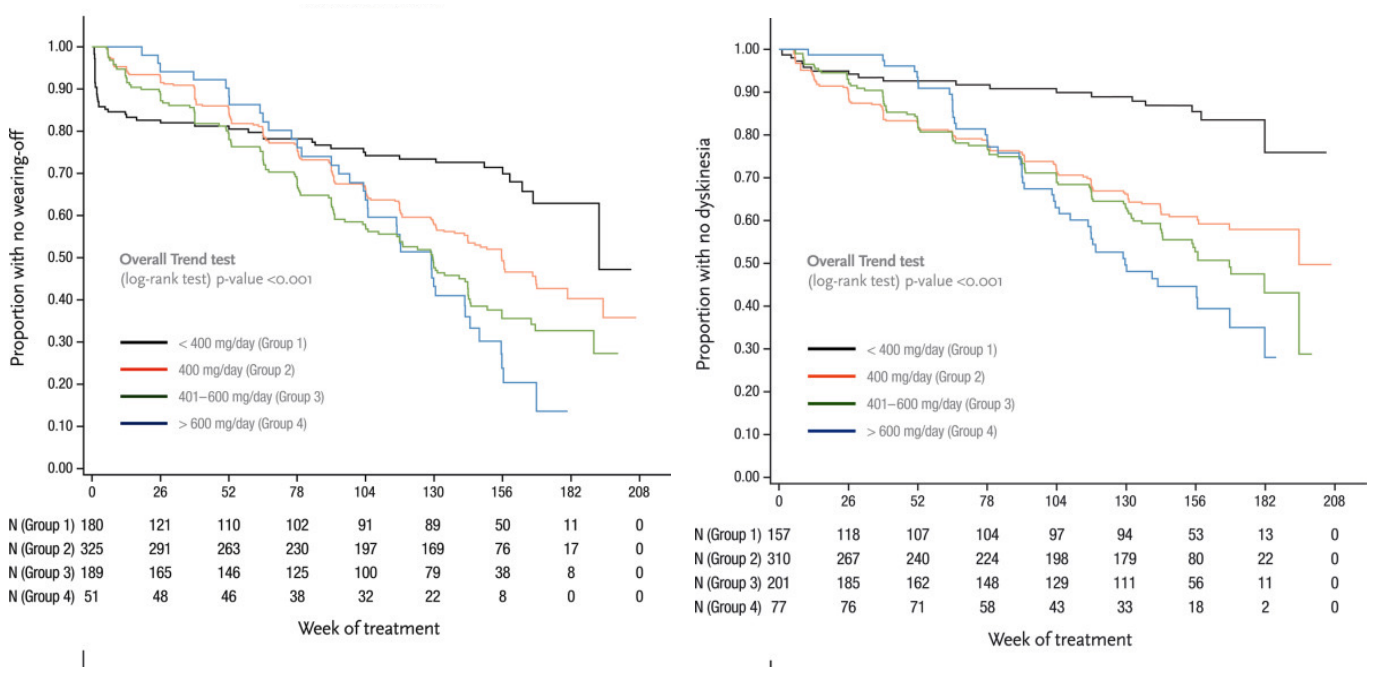
The modern pre-levodopa era of Parkinson's disease: insights into motor complications from sub-Saharan Africa

Roberto Cilia,[1] Albert Akpalu,[2] Fred Stephen Sarfo,[3] Momodou Cham,[4] Marianna Amboni,[5,6] Emanuele Cereda,[7] Margherita Fabbri,[8] Patrick Adjei,[2] John Akassi,[3] Alba Bonetti[1] and Gianni Pezzoli[1]



Levodopa complicaties

- Risicofactoren
  - **Hogere Levodopa dosissen**
  - Jongere onset leeftijd
  - Vrouwelijk geslacht
  - Hogere ziektelast (UPDRS-score)
  - (Laag gewicht)*
  - (Langere ziekteduur)



Movement Disorders, Volume: 28, Issue: 8, Pages: 1064-1071, First published: 29 April 2013, DOI: (10.1002/mds.25364)

Levodopa complicaties

MOTOR FLUCTUATIES

- **Extra dosis** Levodopa
- **Fractioneren**
- **Associatie**
  - MAO-B (bv. Azilect, Xadago)
  - COMT inhibitor (Stalevo)
- Overweeg **gastro-intestinaal** nazicht
- Dieetadvies (cave eiwitten)
- Device-aided therapies

DYSKINESIEËN

- **Dosisreductie**
- **Fractioneren**
- Bv. Amantadine
- Device-aided therapies

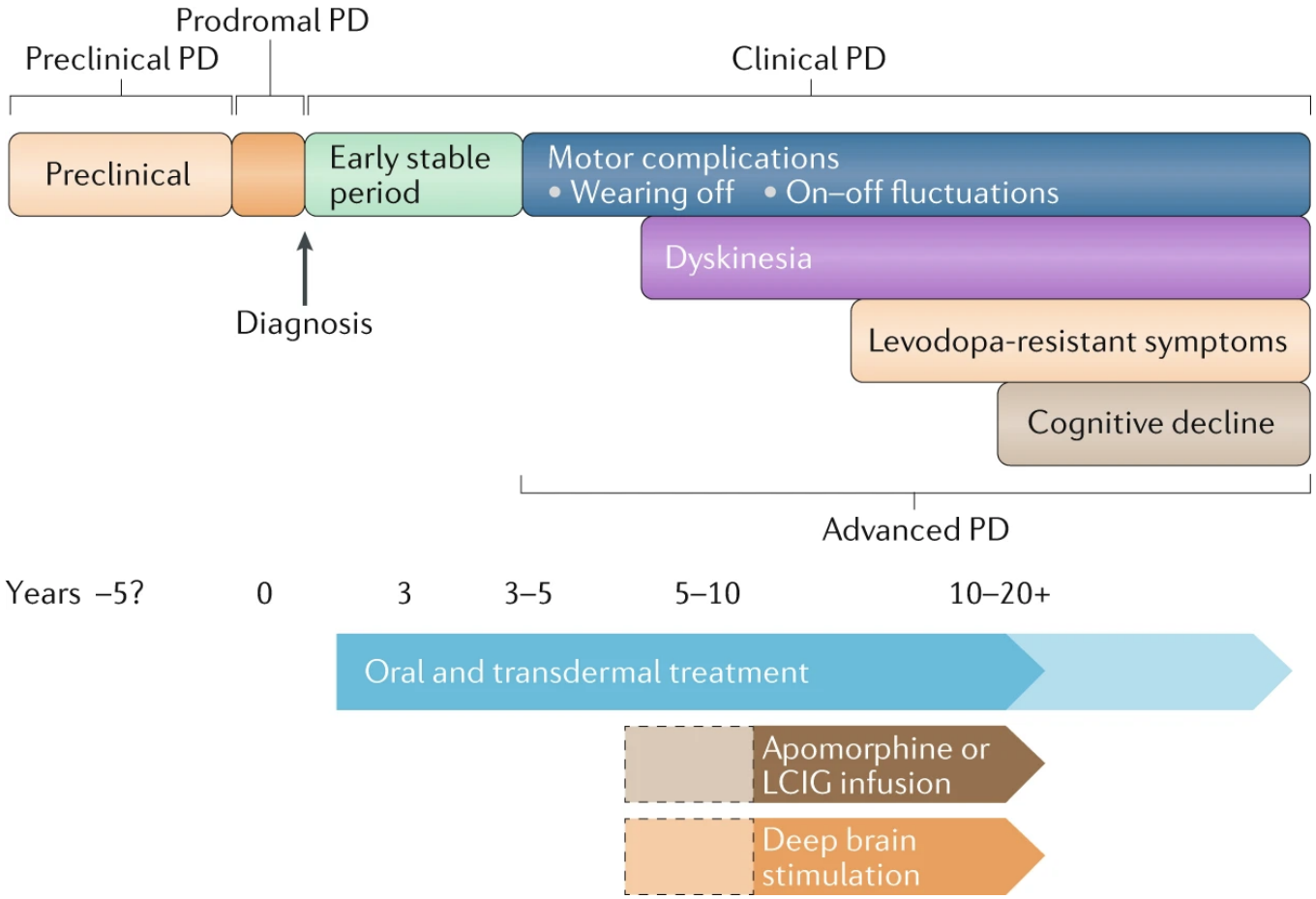
Device-aided therapies

Wanneer wel?

- **Onvoldoende symptoomcontrole**
- **Fluctuaties**
- **Dyskinesieën**

Wanneer niet?

- Ernstige dementie
- Niet op levodopa reagerende symptomen
- Belangrijke posturale instabiliteit



Antonini, A., Jenner, P. Apomorphine infusion in advanced Parkinson disease. *Nat Rev Neurol* **14,** 693–694 (2018)

Device-aided therapies

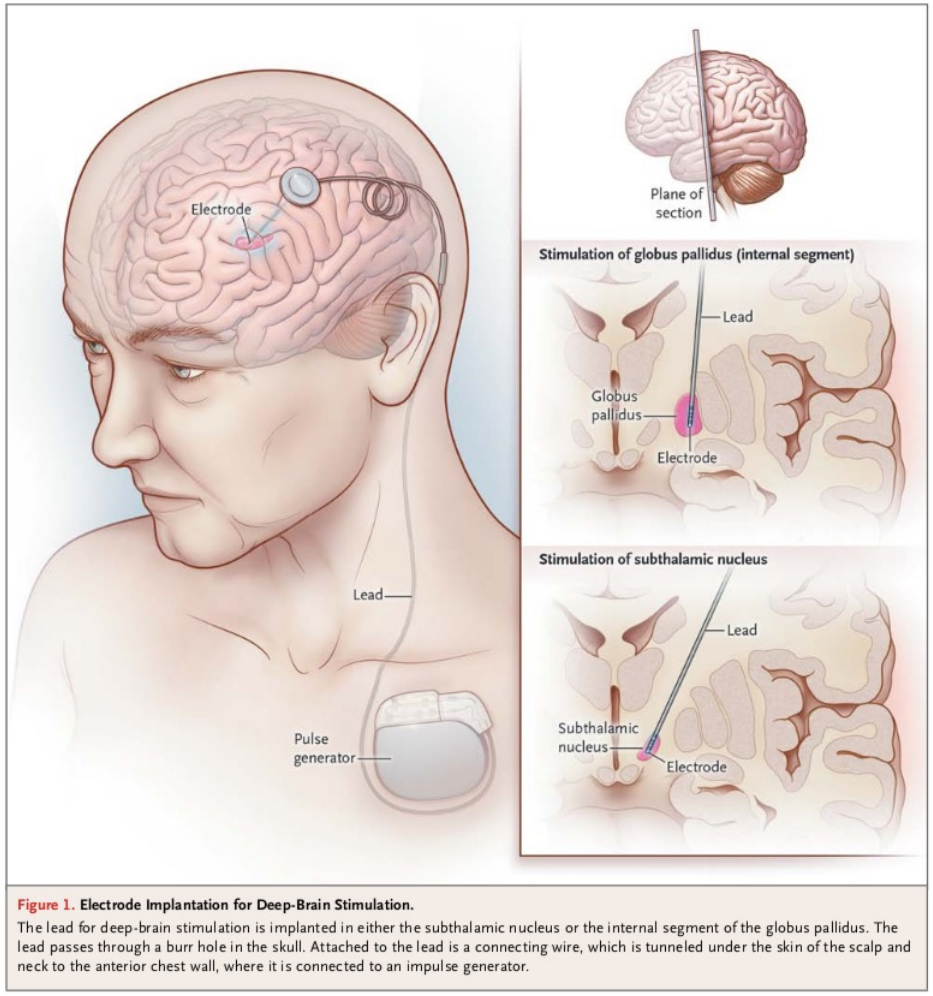
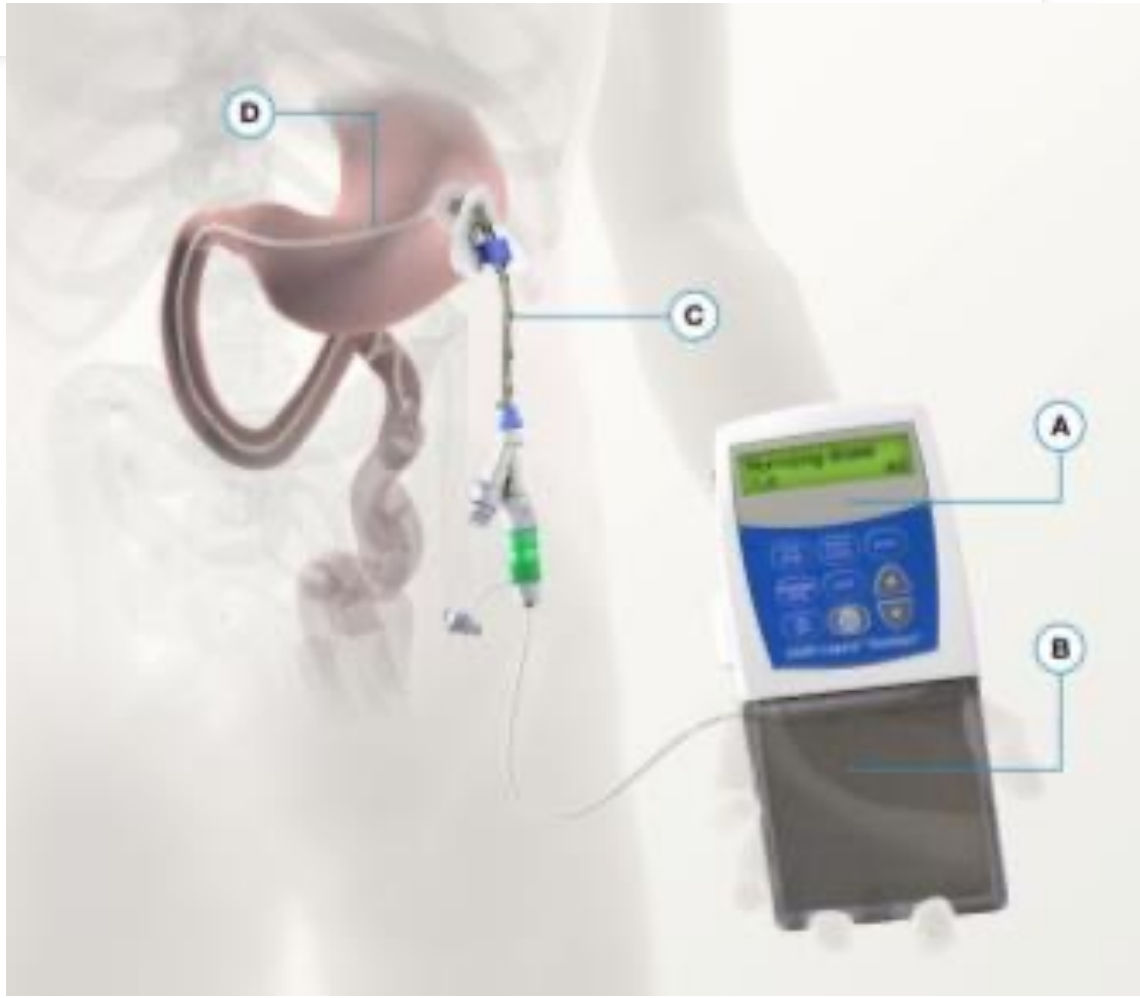
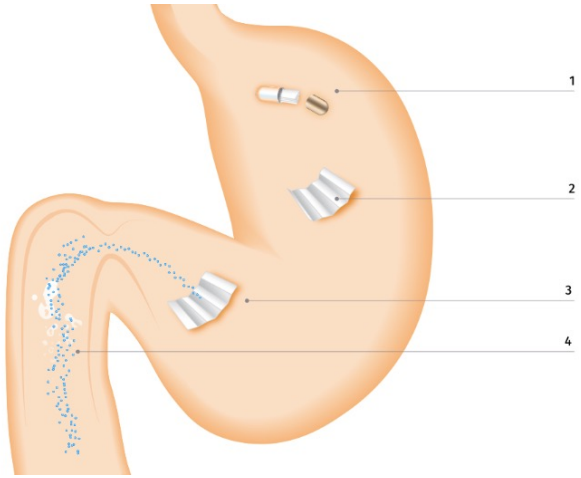
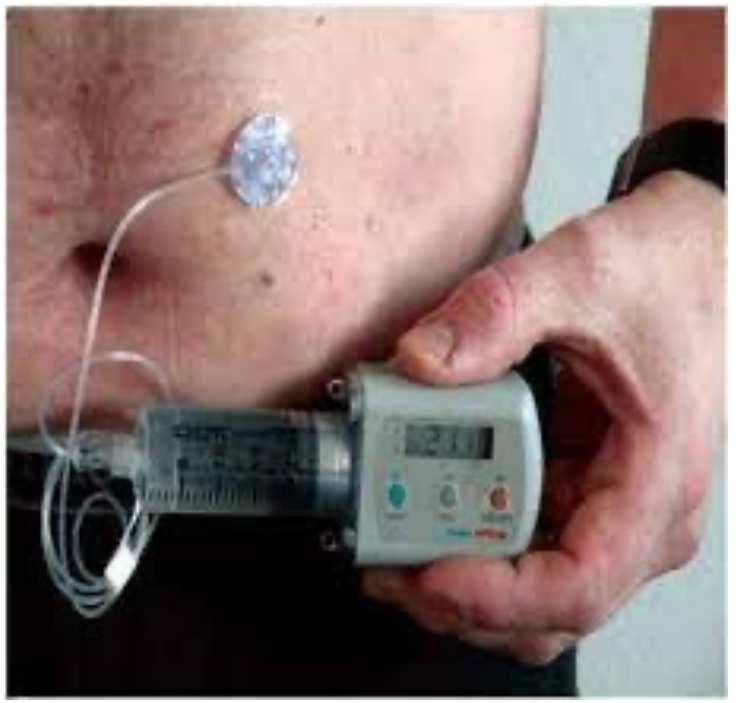


Figure 1. Electrode Implantation for Deep-Brain Stimulation.
The lead for deep-brain stimulation is implanted in either the subthalamic nucleus or the internal segment of the globus pallidus. The lead passes through a burr hole in the skull. Attached to the lead is a connecting wire, which is tunneled under the skin of the scalp and neck to the anterior chest wall, where it is connected to an impulse generator.




Wat brengt de toekomst?



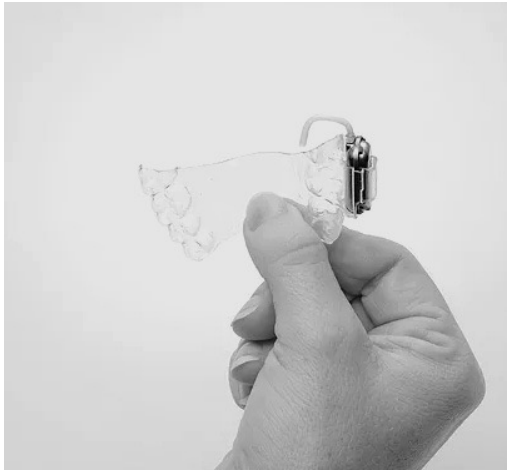


Journal of Parkinson's Disease 11 (2021) 1695–1702
DOI 10.3233/JPD-212813
IOS Press

Research Report

Foslevodopa/Foscarbidopa Is Well Tolerated and Maintains Stable Levodopa and Carbidopa Exposure Following Subcutaneous Infusion

Matthew Rosebraugh[a,*], Wei Liu[a], Melina Neenan[b] and Maurizio F. Facheris[c]



The NEW ENGLAND JOURNAL of MEDICINE

Monoclonal Antibody Therapy in Parkinson's Disease — The End?

Alan Whone, F.R.C.P., Ph.D.

RESEARCH SUMMARY

Trial of Prasinezumab in Early-Stage Parkinson's Disease

Pagano G et al. DOI: 10.1056/NEJMoa2202867

CLINICAL PROBLEM

Aggregated α-synuclein has a prominent role in the pathogenesis of Parkinson's disease. Prasinezumab, a humanized monoclonal antibody that binds to aggregated α-synuclein, has been proposed as a potential treatment for Parkinson's disease, but clinical trial data are needed.

CLINICAL TRIAL

Design: A phase 2, multinational, double-blind, randomized, placebo-controlled trial examined the efficacy and safety of low- and high-dose prasinezumab in patients with early-stage Parkinson's disease.

Intervention: 316 patients who had not previously received treatment for symptoms of Parkinson's disease or who were receiving stable doses of a monoamine oxidase B inhibitor were assigned to receive intravenous prasinezumab (1500 mg or 4500 mg) or placebo every 4 weeks for 52 weeks. The primary end point was the change from baseline to week 52 in the Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total score; scores range from 0 to 236, with higher scores indicating greater symptom severity.

RESULTS

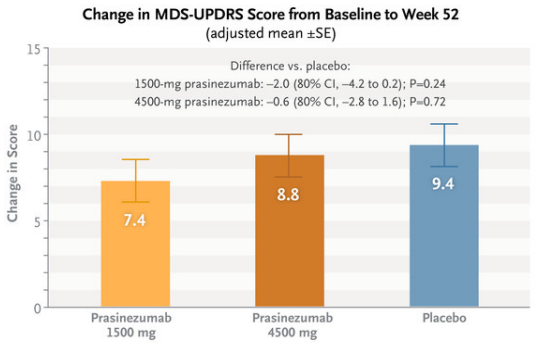
Efficacy: The mean change in the MDS-UPDRS score at week 52 did not differ significantly between either prasinezumab dose and placebo.

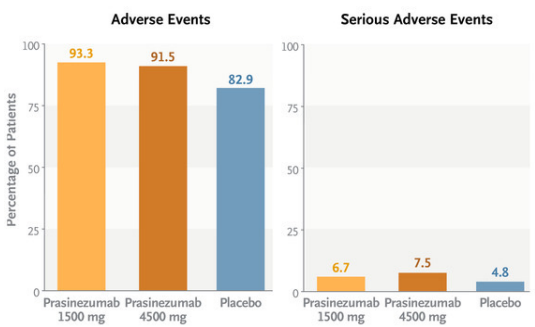
Safety: Infusion reactions were common and were reported most frequently in the 4500-mg group. Serious adverse events occurred more often with prasinezumab than with placebo.

LIMITATIONS AND REMAINING QUESTIONS

- Nearly one third of the participants were excluded from the 52-week efficacy analysis because they had started treatment for symptoms of Parkinson's disease.
- Non-White and non-U.S. or non-European populations were underrepresented in the trial.
- Testing for target engagement of prasinezumab was not performed.

Links: Full Article | NEJM Quick Take | Editorial





CONCLUSIONS

The monoclonal antibody prasinezumab, as compared with placebo, did not slow disease progression in patients with early-stage Parkinson's disease over a 52-week treatment period.

RESEARCH SUMMARY

Trial of Cinpanemab in Early Parkinson's Disease

Lang AE et al. DOI: 10.1056/NEJMoa2203395

CLINICAL PROBLEM

Existing therapies for Parkinson's disease are limited. The targeting of α-synuclein aggregates has been proposed as a potential disease-modifying strategy. Cinpanemab, a human-derived monoclonal antibody that binds to aggregated α-synuclein, showed promise in a mouse model and in a phase 1 study of Parkinson's disease.

CLINICAL TRIAL

Design: A phase 2, international, double-blind, randomized, placebo-controlled trial examined the efficacy and safety of cinpanemab in persons with early-stage Parkinson's disease.

Intervention: 357 participants who were not receiving treatment for Parkinson's symptoms were assigned to receive intravenous cinpanemab at one of three doses (250 mg, 1250 mg, or 3500 mg) or placebo (control) every 4 weeks for 52 weeks, after which placebo recipients switched to cinpanemab. The primary end points included the change from baseline to weeks 52 and 72 in the total score on the Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS); scores range from 0 to 236, with higher scores indicating greater symptom severity.

RESULTS

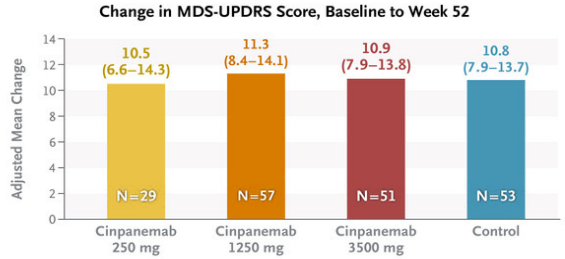
Efficacy: At 52 weeks, the change in MDS-UPDRS total score did not differ significantly between any cinpanemab dose and placebo. Results at 72 weeks, when the trial was stopped early for lack of efficacy, were consistent with the results at 52 weeks.

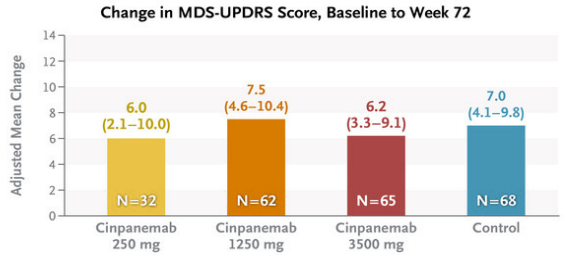
Safety: Adverse events occurred in similar proportions of cinpanemab and placebo recipients and were usually mild to moderate in severity. The most common adverse events with cinpanemab included headache, nasopharyngitis, falls, and back pain.

LIMITATIONS AND REMAINING QUESTIONS

- 40% of the participants were not included in the 52-week analysis because they had started other treatments for Parkinson's symptoms.
- Clearance of α-synuclein in cinpanemab recipients could not be verified.

Links: Full Article | NEJM Quick Take | Editorial





Adverse Events to Week 52

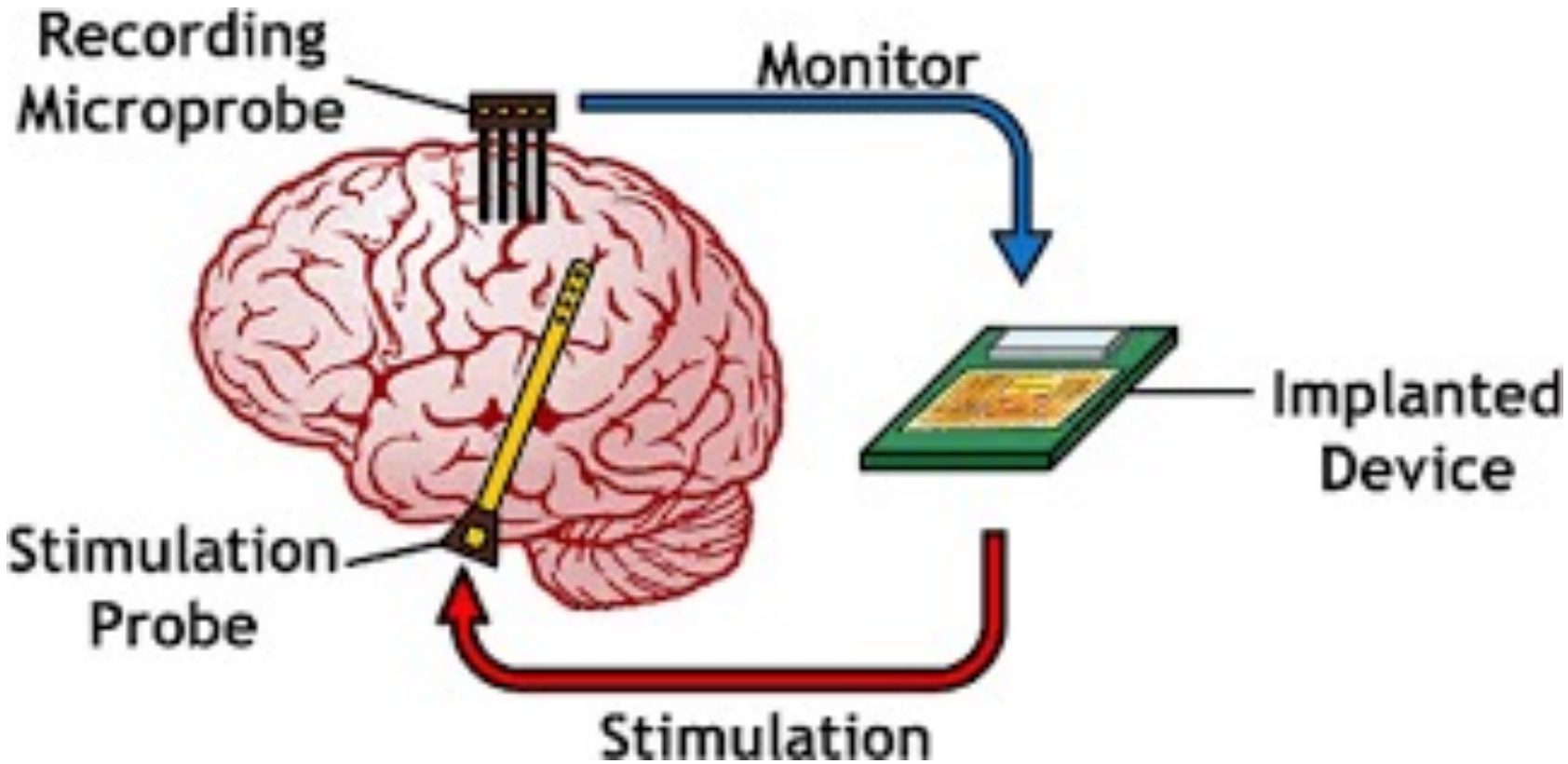
Adverse Event	Cinpanemab 250 mg (N=55)	Cinpanemab 1250 mg (N=102)	Cinpanemab 3500 mg (N=100)	Control (N=100)
Any adverse event	42 (76)	83 (81)	86 (86)	80 (80)
Adverse events occurring in ≥5% of participants				
Headache	6 (11)	19 (19)	21 (21)	18 (18)
Nasopharyngitis	10 (18)	10 (10)	13 (13)	12 (12)
Fall	5 (9)	6 (6)	15 (15)	5 (5)
Back pain	3 (5)	8 (8)	13 (13)	9 (9)

Data are no. of participants (%).

CONCLUSIONS

The monoclonal antibody cinpanemab, as compared with placebo, did not slow progression of Parkinson's disease in patients with early-stage disease.

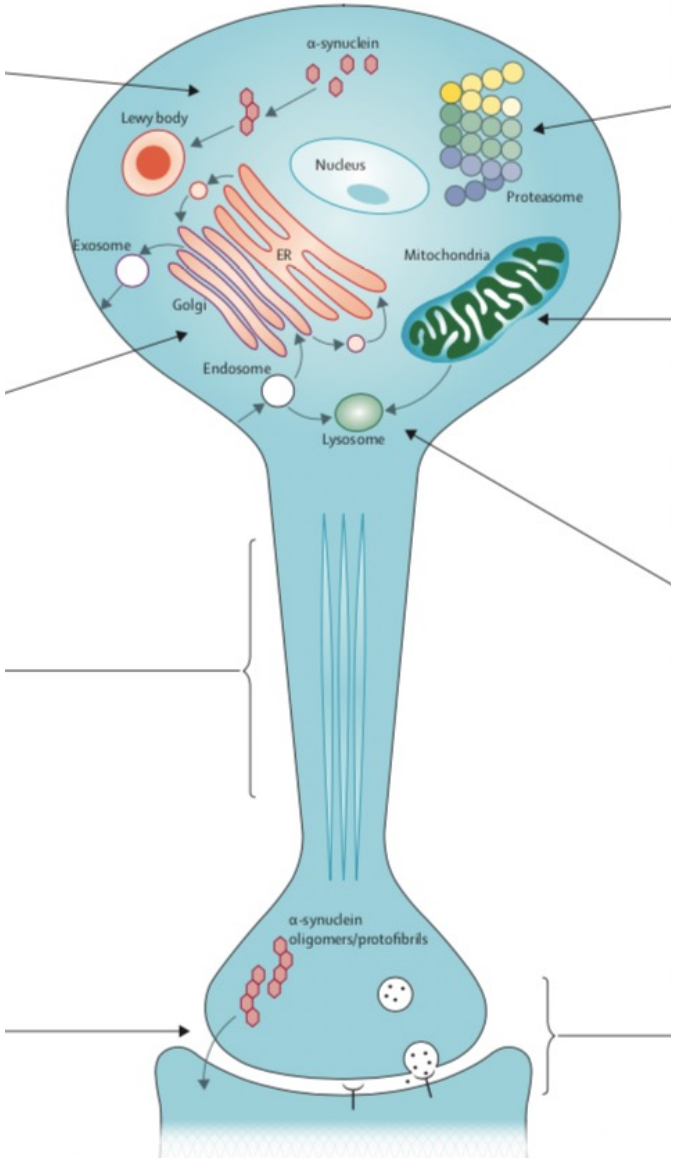
DBS - evoluties



Gepersonaliseerde geneeskunde

- Timing studies
  - Biomarkers

- One size fits all vs subtypes
  - Genotype (LRRK2, GBA)
  - Pathologie-type
  - Fenotype



Praktische tips

- Aangifte waarborg ernstige ziektes hospitalisatieverzekering

- Multidisciplinaire revalidatiesessies Parkinson AZG
- Parkinsondagziekenhuis AZG (> 70j)
- Parkinsonverpleegkundige@azgroeninge.be

- www.vlaamseparkinsonliga.be
- www.parkili.be


Bedankt voor jullie aandacht!