De ziekte van Parkinson in 2022: De nieuwe kleren van de keizer ?

Prof.Dr.Patrick Santens

Bewegingsstoornissen

Dienst Neurologie

Universitair ziekenhuis Gent

The burden of neurological diseases in Europe: an analysis for the Global Burden of Disease Study 2017

Günther Deuschl, Ettore Beghi, Franz Fazekas, Timea Varga, Kalliopi A Christoforidi, Eveline Sipido, Claudio L Bassetti, Theo Vos, Valery L Feigin

Lancet Public Health 2020;
5: e551–67

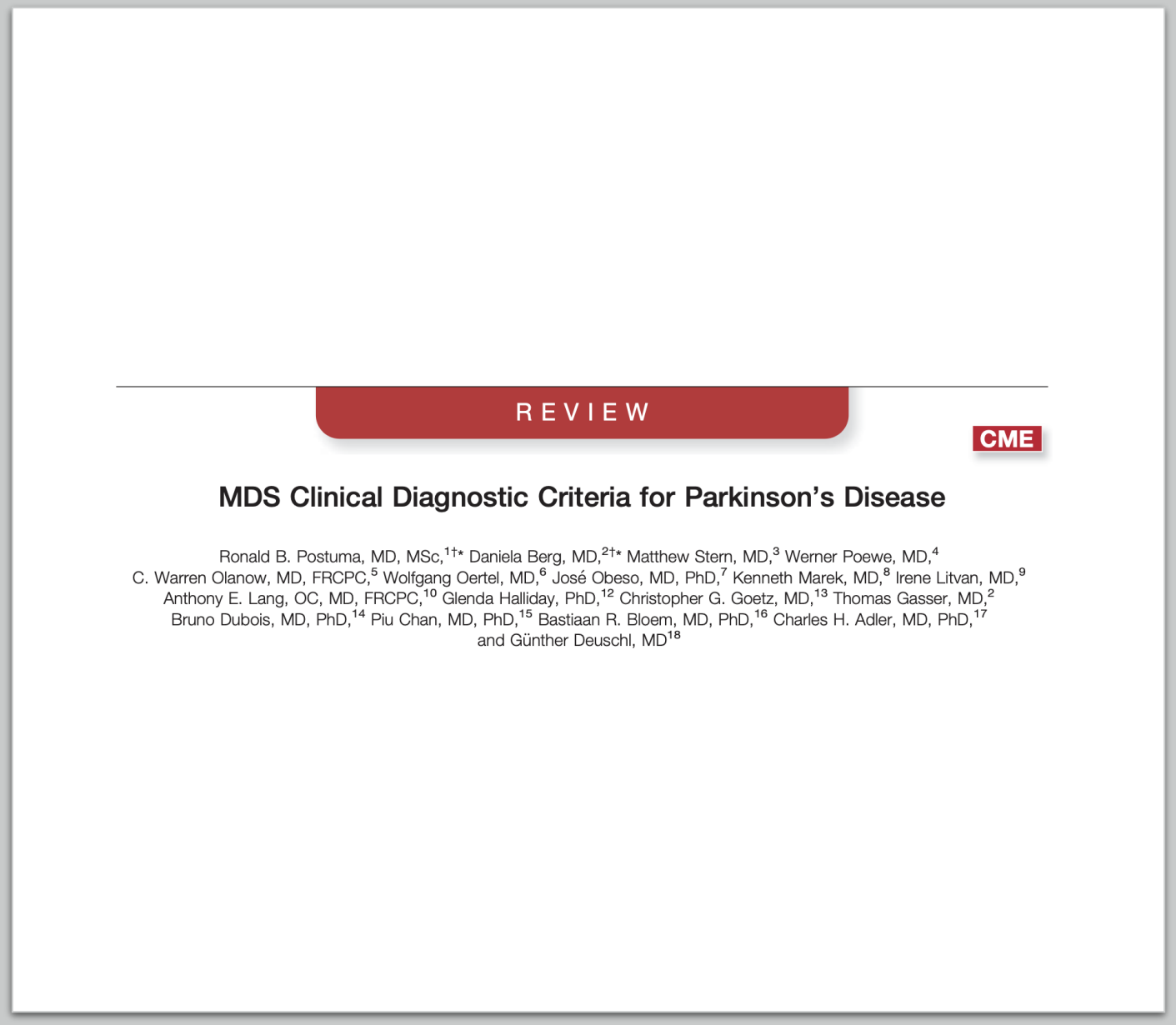
Another notable disease with a large increase in prevalence and DALYs was Parkinson's disease. The global burden of Parkinson's disease more than doubled during the study period.[20] The growth of the burden of Parkinson's disease surpassed that of Alzheimer's disease and other dementias. This increase has been attributed to the ageing of the European population, the reduction of rural populations, occupational exposures, and the declining smoking rates.[21,22] Although increased attention towards the disease might partially explain the increasing incidence observed, Parkinson's disease is still underdiagnosed, as shown in the USA[23] and by an online European survey that found that 40% of respondents had never seen a Parkinson's disease specialist.[24,25]

Recente evoluties

- Pathologie en pathofysiologie
- Focusverschuiving naar niet-motorische problemen
- Vroegtijdige diagnose
- Symptomatische behandelingen
- Niet-farmacologische behandeling

Motorische symptomen

- Hypokinesie/bradykinesie/akinesie
- Tandradrigiditeit
- Rusttremor
- Houdingsveranderingen



REVIEW

CME

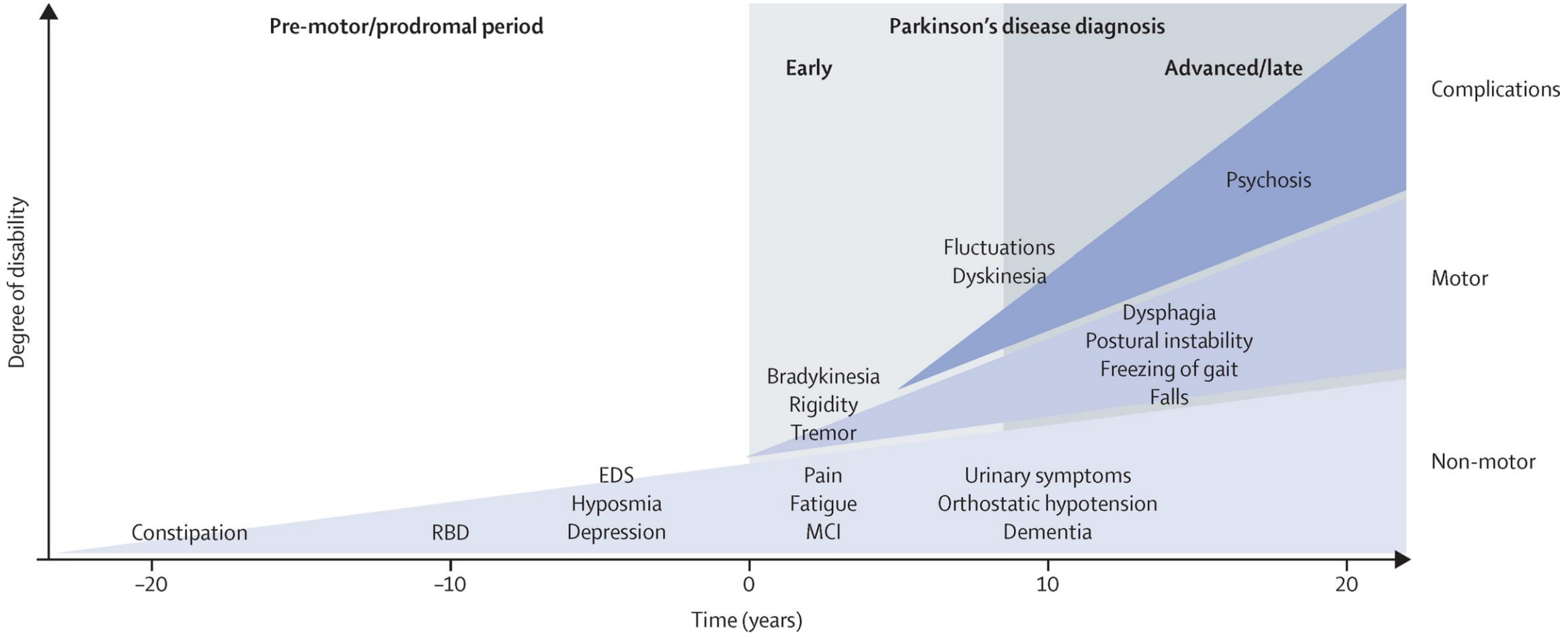
MDS Clinical Diagnostic Criteria for Parkinson's Disease

Ronald B. Postuma, MD, MSc,[1†*] Daniela Berg, MD,[2†*] Matthew Stern, MD,[3] Werner Poewe, MD,[4]
C. Warren Olanow, MD, FRCPC,[5] Wolfgang Oertel, MD,[6] José Obeso, MD, PhD,[7] Kenneth Marek, MD,[8] Irene Litvan, MD,[9]
Anthony E. Lang, OC, MD, FRCPC,[10] Glenda Halliday, PhD,[12] Christopher G. Goetz, MD,[13] Thomas Gasser, MD,[2]
Bruno Dubois, MD, PhD,[14] Piu Chan, MD, PhD,[15] Bastiaan R. Bloem, MD, PhD,[16] Charles H. Adler, MD, PhD,[17]
and Günther Deuschl, MD[18]

Niet-motore symptomatologie

- Autonome stoornissen: constipatie, urinaire/sexuele stoornissen, hypotensie, zweten
- Cognitieve stoornissen/gedragsveranderingen: depressie, apathie, geheugenstoornissen, executieve problemen,…
- Sensorische symptomen: zinderingen, pijn, krampen,…
- Slaapstoornissen: fractioneren van de slaap, REM slaap gedragsproblemen, vermoeidheid en slaperigheid (excessive daytime somnolence)

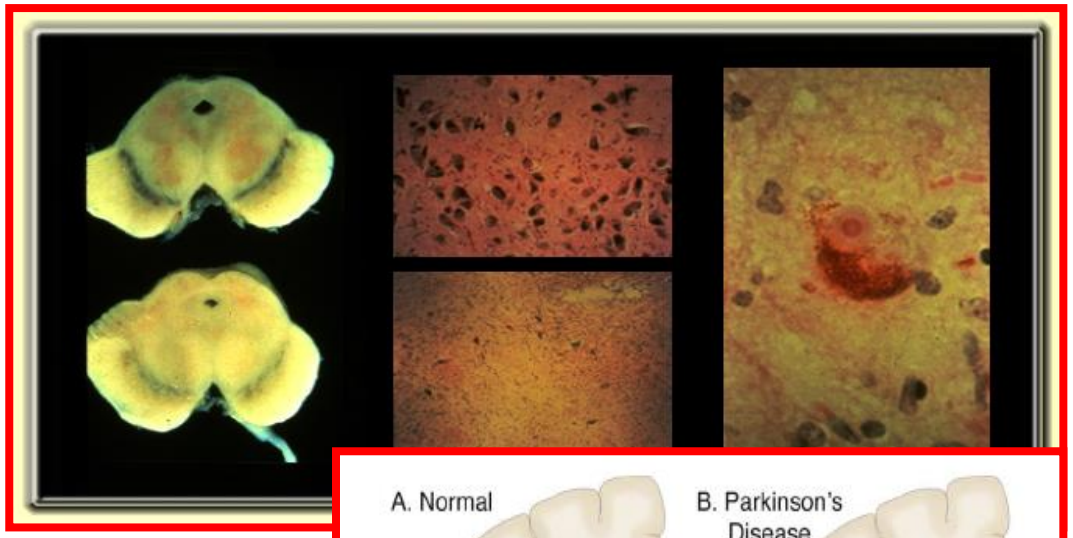
Premotore stadia
Niet-motorische symptomen

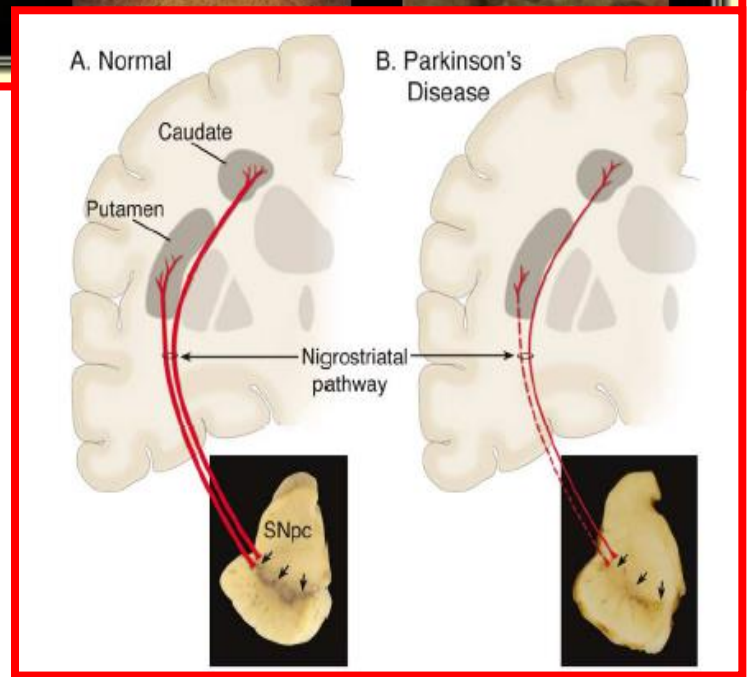


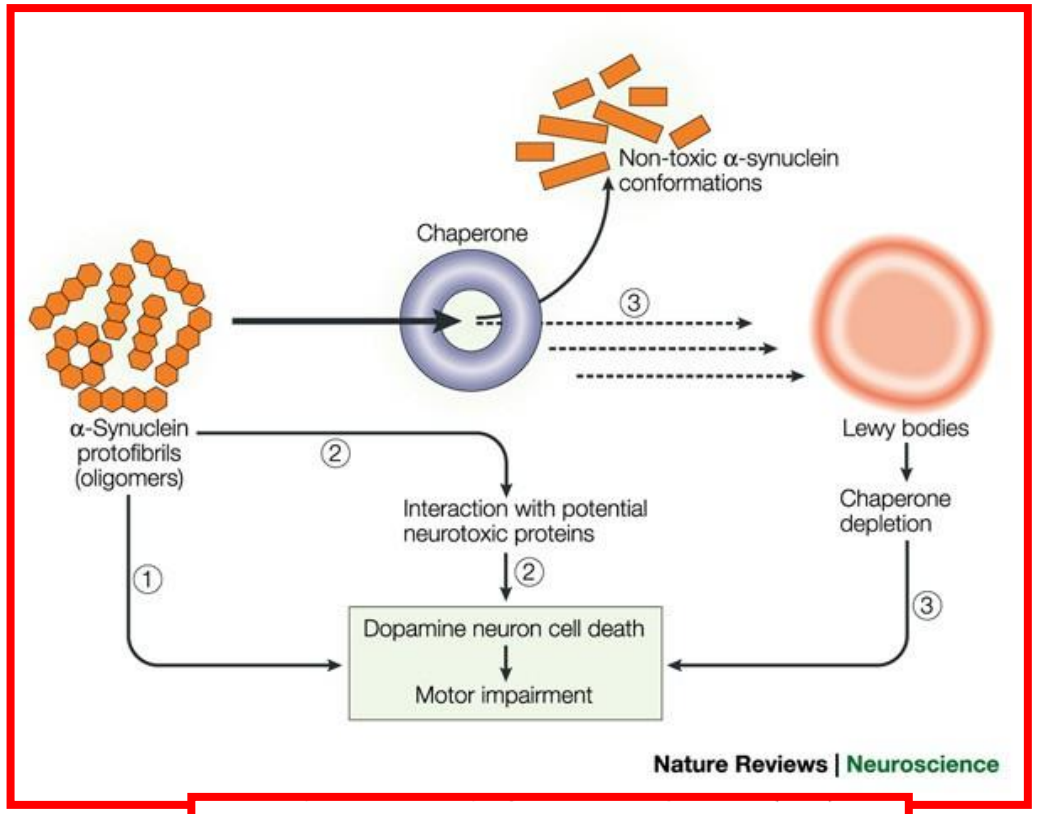
REM slaap gedragsstoornis (RSBD)

- Verlies van atonie die normaal is bij REM slaap
- Uitleven van dromen met (hevige) motorische en/of verbale activiteit, soms leidend tot letsel bij patiënt of bedpartner
- Vaak agressieve inhoud van de droom: vechten, vluchten, verdedigen
- Gaat niet steeds gepaard met ontwaken, waardoor patiënt geen herinnering heeft bij ontwaken
- Sterk verhoogde kans (>50%) op ontwikkelen van neurodegeneratieve ziekte (ZvParkinson, dementie) binnen de 12 jaar.
- Te behandelen met clonazepam (0.5-2mg) of melatonine (3-10mg)

De pathologie van de ziekte van Parkinson

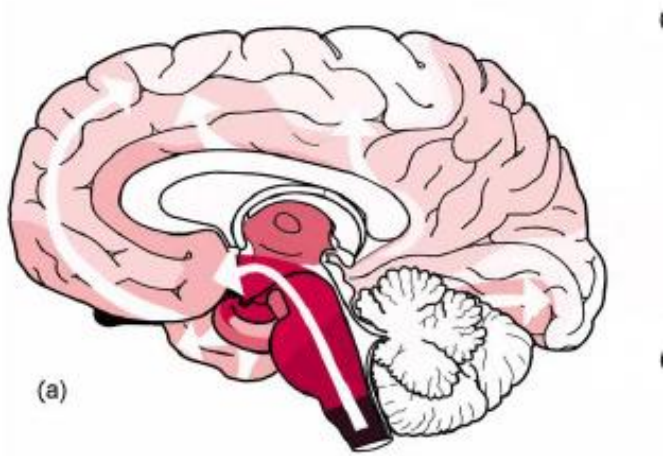


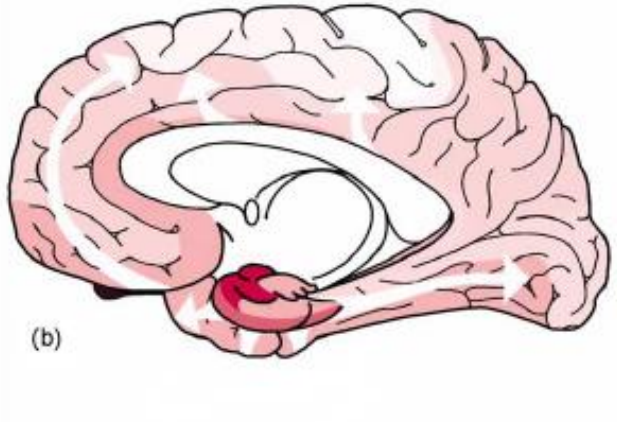


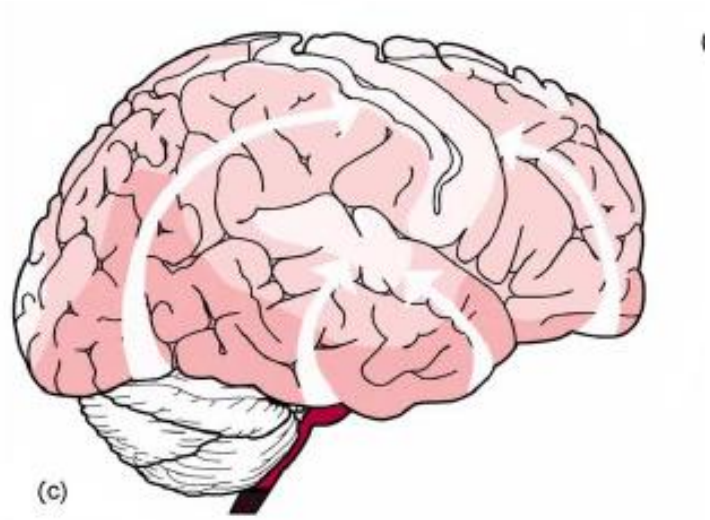


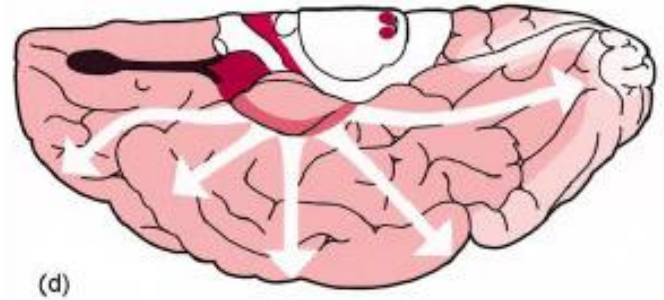
α-Synuclein in Lewy bodies

Pathologie van de ziekte van Parkinson

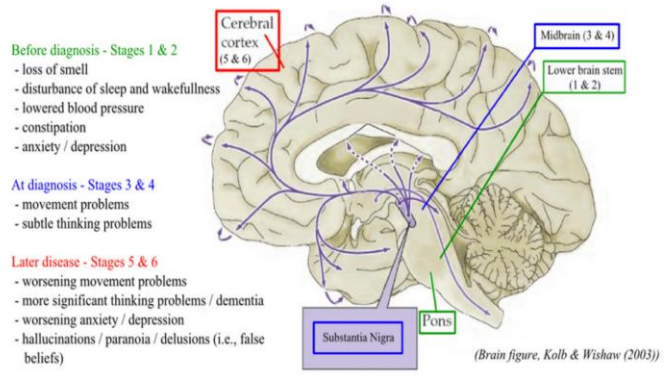








Nonmotore symptomen : pathofysiologie



- Neuronale degeneratie
- Depositie van alfa-synucleïne en lewy bodies
- Dysfunctie van neurotransmitter systemen

De pathologie van de ziekte van Parkinson

FEATURED ARTICLE

Is Alpha-Synuclein in the Colon a Biomarker for Premotor Parkinson's Disease? Evidence from 3 Cases

Kathleen M. Shannon, MD,[1]* Ali Keshavarzian, MD,[2] Hemraj B. Dodiya, MS,[3] Shriram Jakate, MD,[4] and Jeffrey H. Kordower, PhD[3]

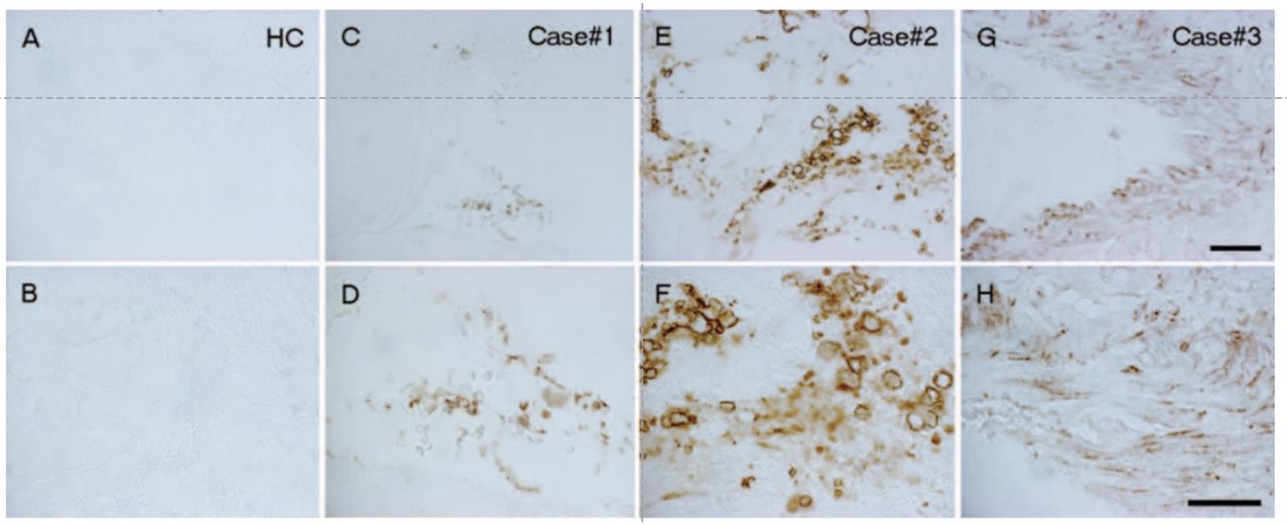


FIG. 1. Low- (A, C, E, and G) and high-power (B, D, F, and H) photomicrographs showing α-SYN histology through the colon from a healthy control (A and B), case 1 (2 years pre-PD diagnosis) (C and D), case 2 (2 years pre-PD diagnosis) (E and F), and case 3 (5 years pre-PD diagnosis) (G and H). Scale bar in (A, C, E, and G) represents 50 um and in (B, D, F, and H) represents 30 um.

Mov Disord. 2012 May;27(6):716-9.

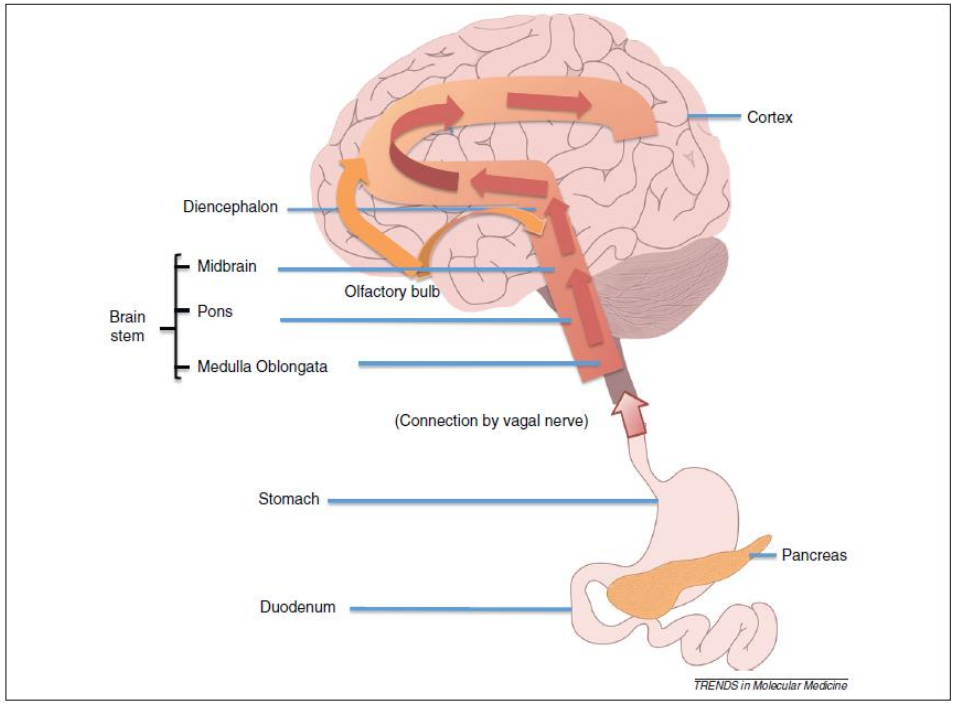
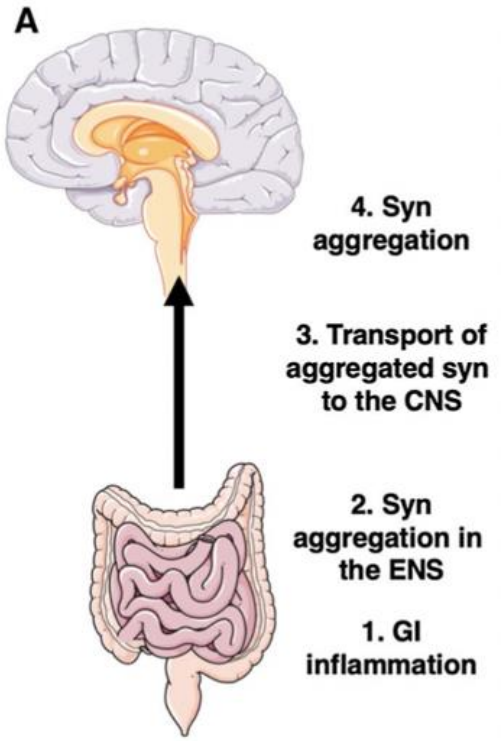
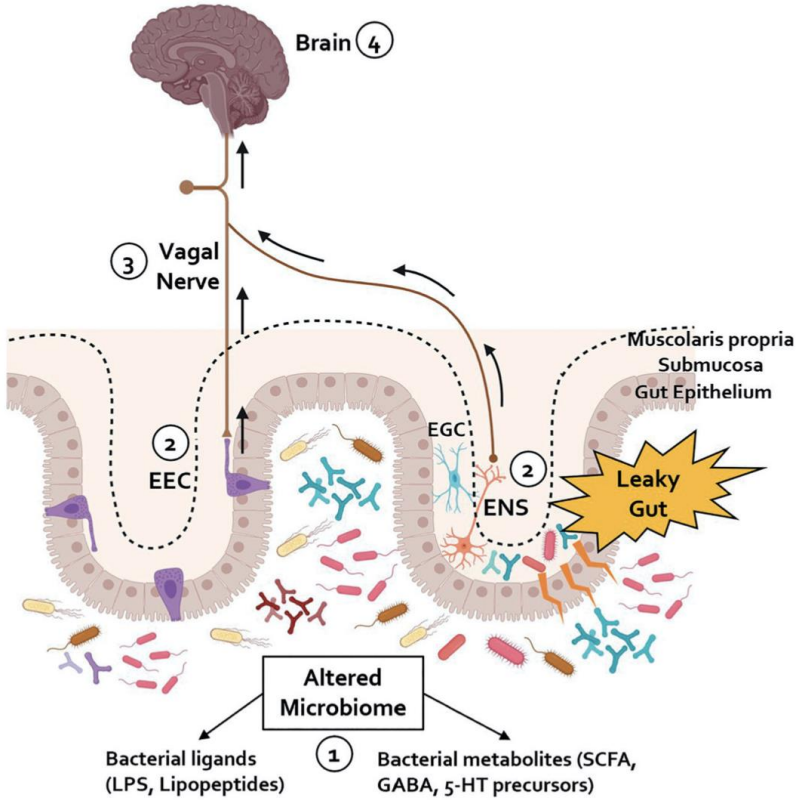


Figure 2. Spread of idiopathic PD pathology. As proposed by Braak and coauthors, Lewy body pathology may arise in the periphery/enteric nervous system, possibly in the gastrointestinal tract, and transfer to the brain stem via the glossopharyngeal and vagus nerves. Finally, it spreads to the cortex at a later stage of disease progression (red arrows). Alternatively, the pathology may initiate at the olfactory bulb and the anterior olfactory nucleus and from there spread to the midbrain and the cortex (orange arrows).





De gut-brain hypothese

De ziekte van Parkinson is een heterogene aandoening

Environmental risk factors

Increased risk (OR >1)
Pesticide exposure
Prior head injury
Rural living
Beta-blocker use
Agricultural occupation
Well water drinking

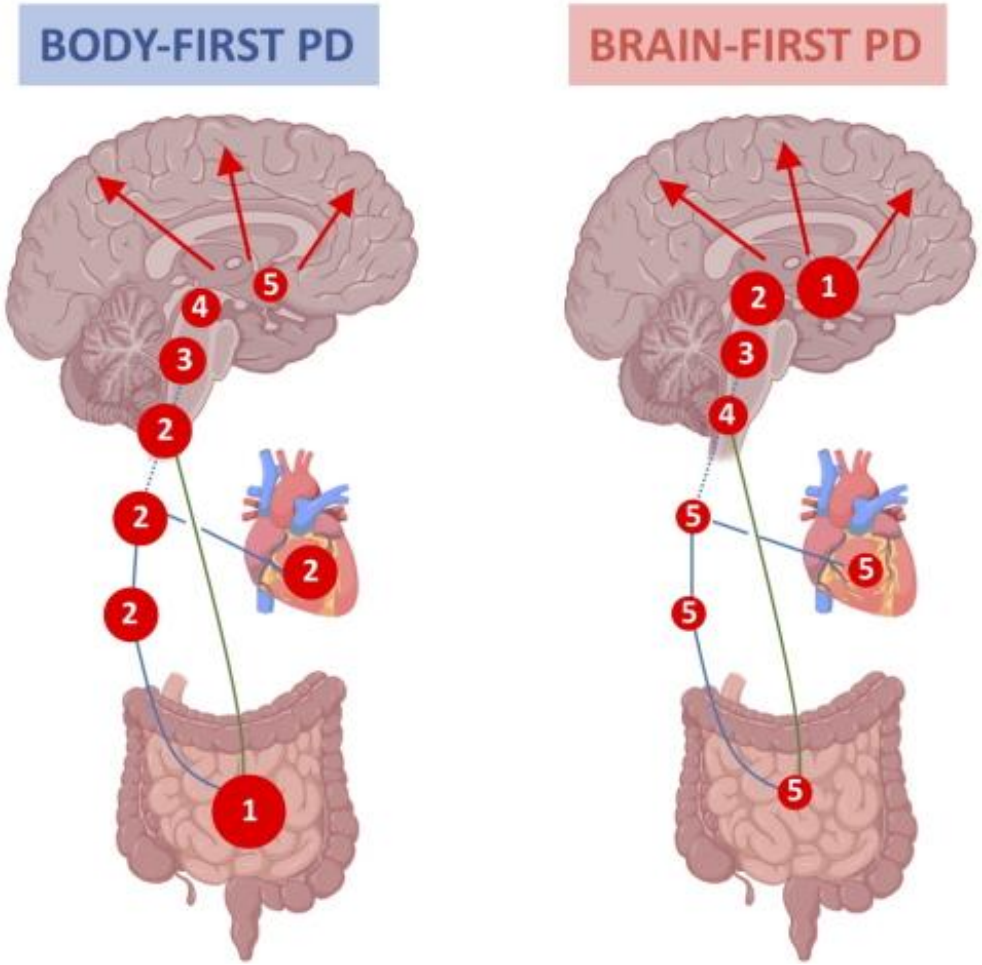
Decreased risk (OR <1)
Tobacco smoking
Coffee drinking
NSAID use
Calcium channel blocker use
Alcohol consumption

Interactions

Genetic risk factors

Increased risk (OR >1)
GBA (OR >5)
INPP5F
STK39
LRRK2
SIPA1L2
BST1
RAB7L1-NUCKS1
VPS13C
DDRGK1
GPNMB
CCDC62
MIR4697
BCKDK-STX1B

Decreased risk (OR <1)
SNCA
MAPT
TMEM175-GAK-DGKQ
HLA-DQB1
MCCC1
ACMSD-TMEM163
GCH1
RIT2
FAM47E-SCARB2
FGF20
SREBF1-RAI1



Diagnostiek

- Klinische diagnostiek : vnl motorische symptomen
- Differentiële diagnostiek
  - Tremoren bv essentiële tremor
  - Gangstoornissen
  - Parkinson plus syndromen
- Beeldvorming
  - Structurele beeldvorming
  - Functionele beeldvorming

Dopamine transporter (DaT)scan

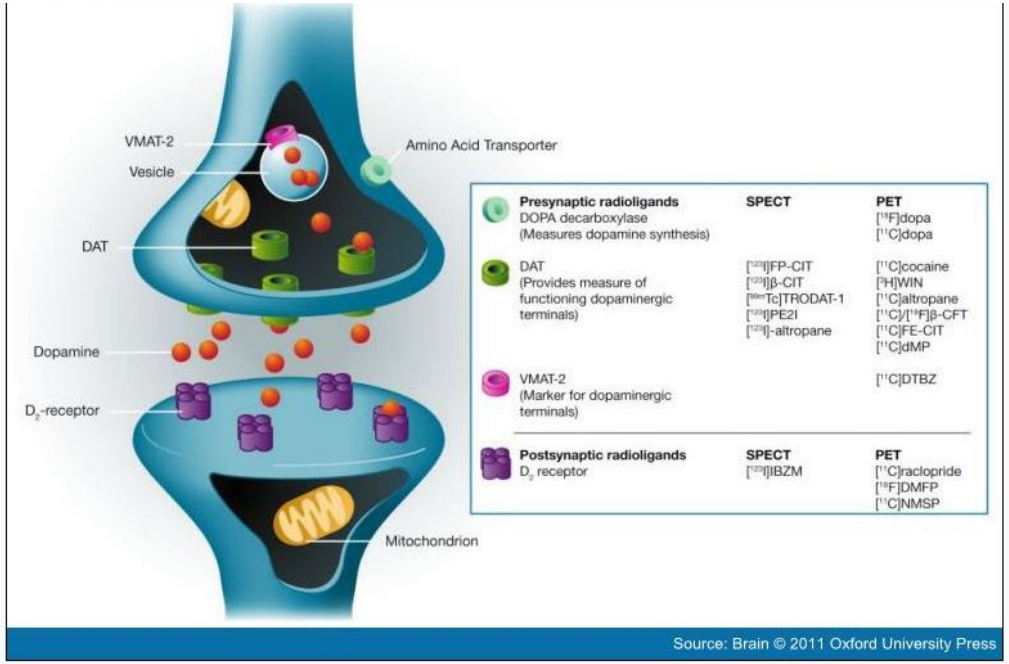
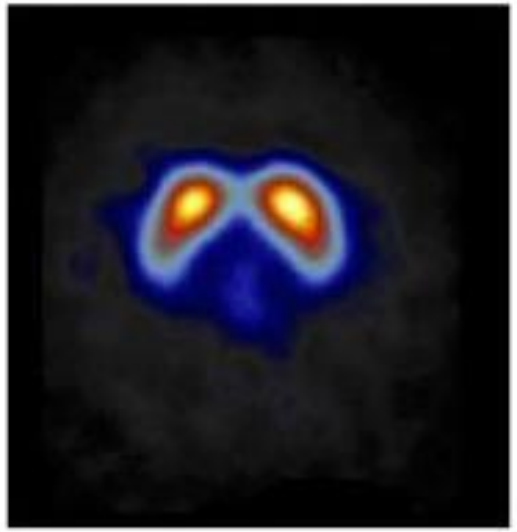
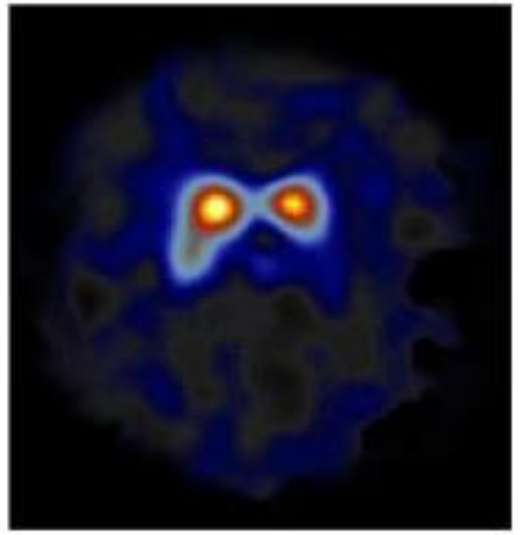


Figure 1.

Dopaminergic radioligands for SPECT and PET. β-CFT = 2β-carbomethoxy-3β-(4-fluorophenyl)tropane; DAT = dopamine transporter; dopa = dihydroxyphenylalanine; DMFP = desmethoxyfallypride; dMP = d-threo methylphenidate; DTBZ = dihydrotetrabenazine; FE-CIT = (*N*-(2-fluoroethyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane; IBZM = iodobenzamide; NMSP = 3-*N*-methylspiperone; PE2I = *N*-(3-iodoprop-(2E)-enyl)-2β-carboxymethoxy-3β-(4'-methylphenyl)nortropane; TRODAT-1 = [2-[[2-[[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo]3.2.1]oct-2-yl]methyl](2-mercaptoethyl)amino]ethyl]amino]ethanethiolato(3-)-*N*2,*N*20,*S*2,*S*20]oxo-[1R-(exo-exo)]; VMAT = vesicular monoamine transporter; WIN = WIN 55,212-2 cannabinoid receptor agonist.



Healthy subject

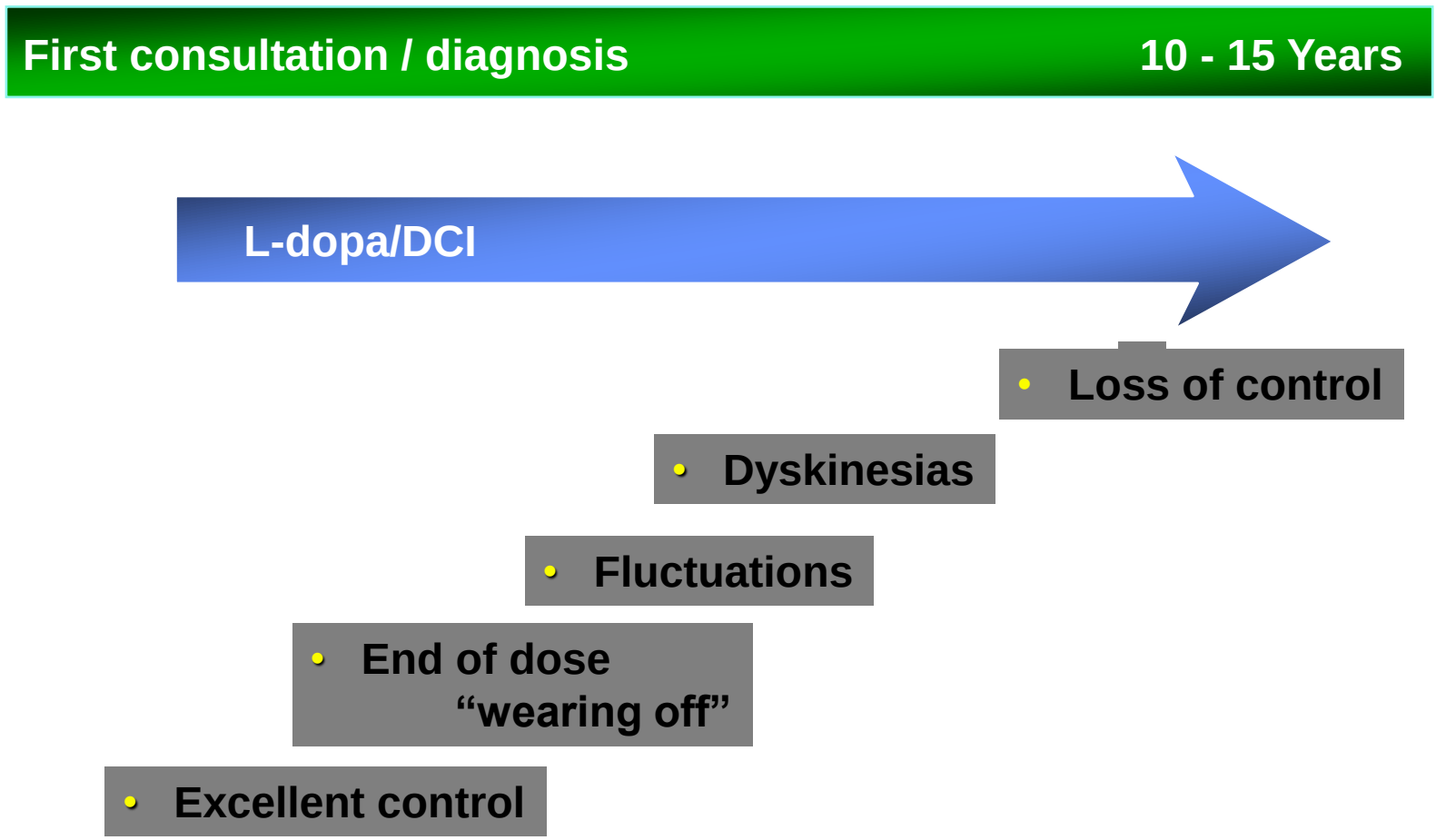


PD patient – Stage 1

Symptomatische medicamenteuze behandelingen voor de ziekte van Parkinson

- Dopaminerge strategieën :
  - Levodopa met decarboxylase remmer : Prolopa
  - Dopamine receptor agonisten : bromocriptine (Parlodel), ropinirole (Requip), pramipexole (Mirapexine), rotigotine (Neupro pleister), (apomorfine)
  - Remmen van de afbraak van L-DOPA en dopamine door
    - MAO-B remmers : selegiline (Eldepryl), rasagiline (Azilect), safinamide (Xadago)
    - COMT remmers : entacapone (Comtan) – combinatie entacapone-levodopa (Stalevo/Corbilta)
- Anticholinergica : Akineton, Artane, Kemadrin
- Amantadine*

Problemen met L-dopa

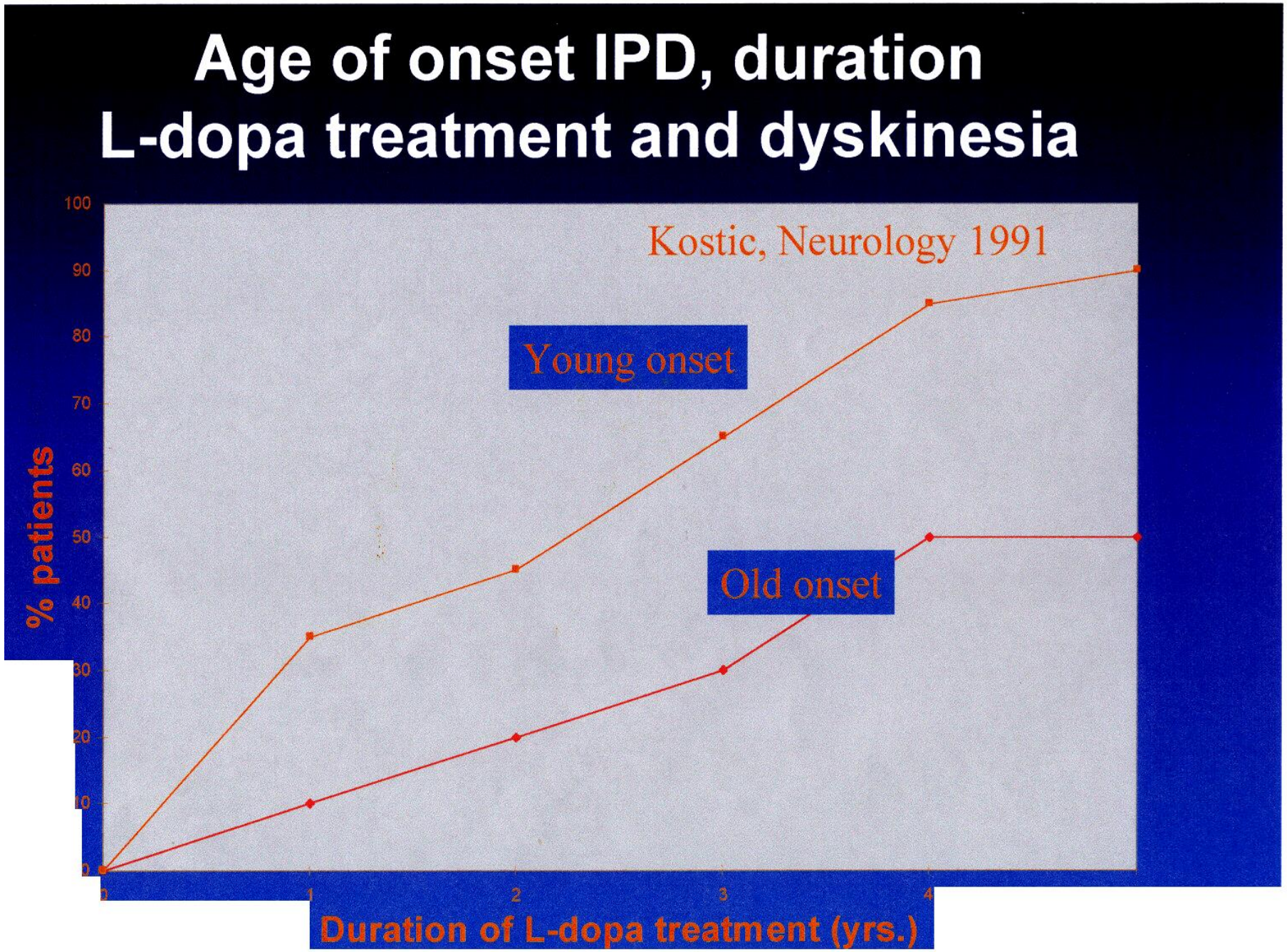


Fluctuaties en problemen na langdurige behandeling

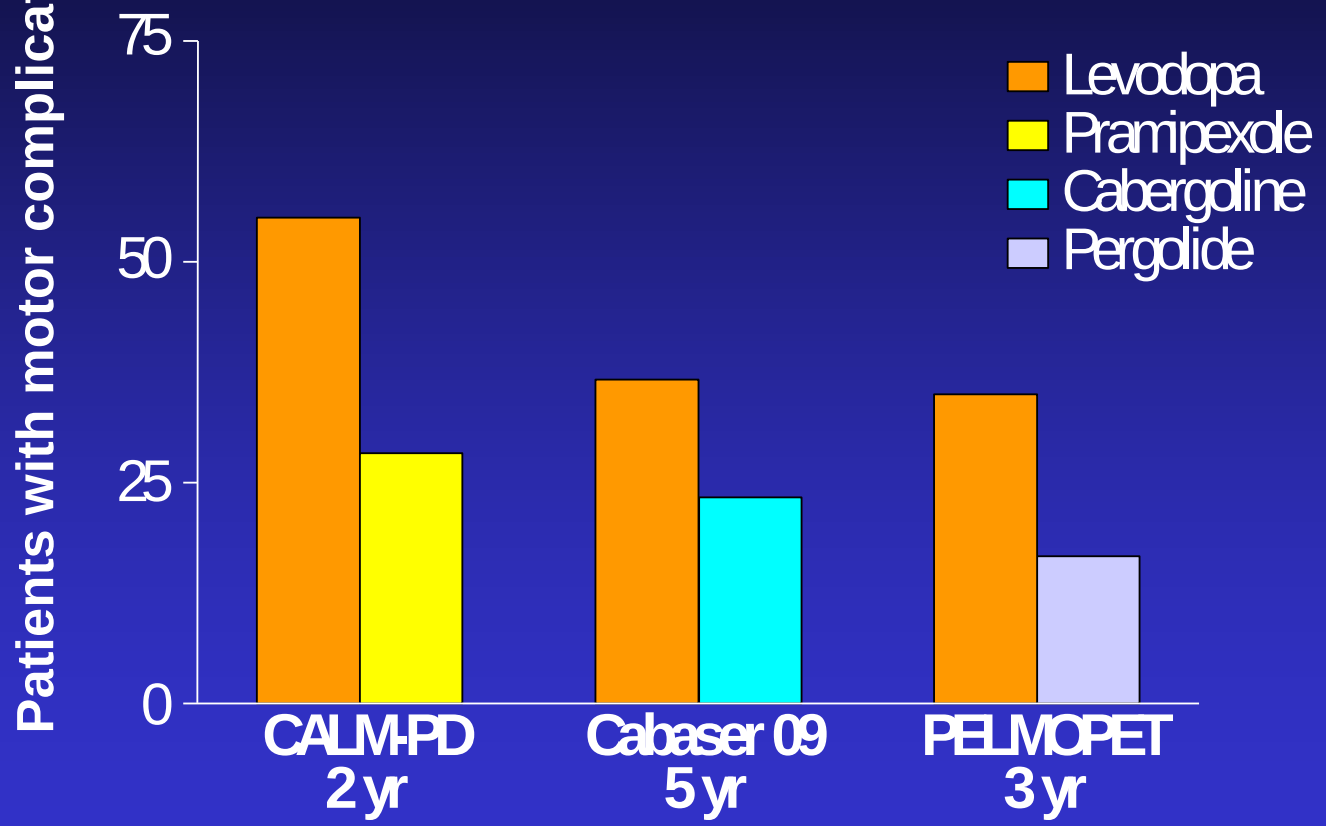
- Motorische Fluctuaties :
  - End-of-dose
  - On-off
  - Delayed on
  - No on
- Dyskinesieën
  - Peak dose
  - Bifasische
  - Early morning dystonie

- Niet-motorische fluctuaties
  - Pijn
  - Krampen
  - Gemoedsschommelingen
  - Angst/hyperventilatie
  - Plasdrang
  - Slaperigheid

Age of onset IPD, duration L-dopa treatment and dyskinesia

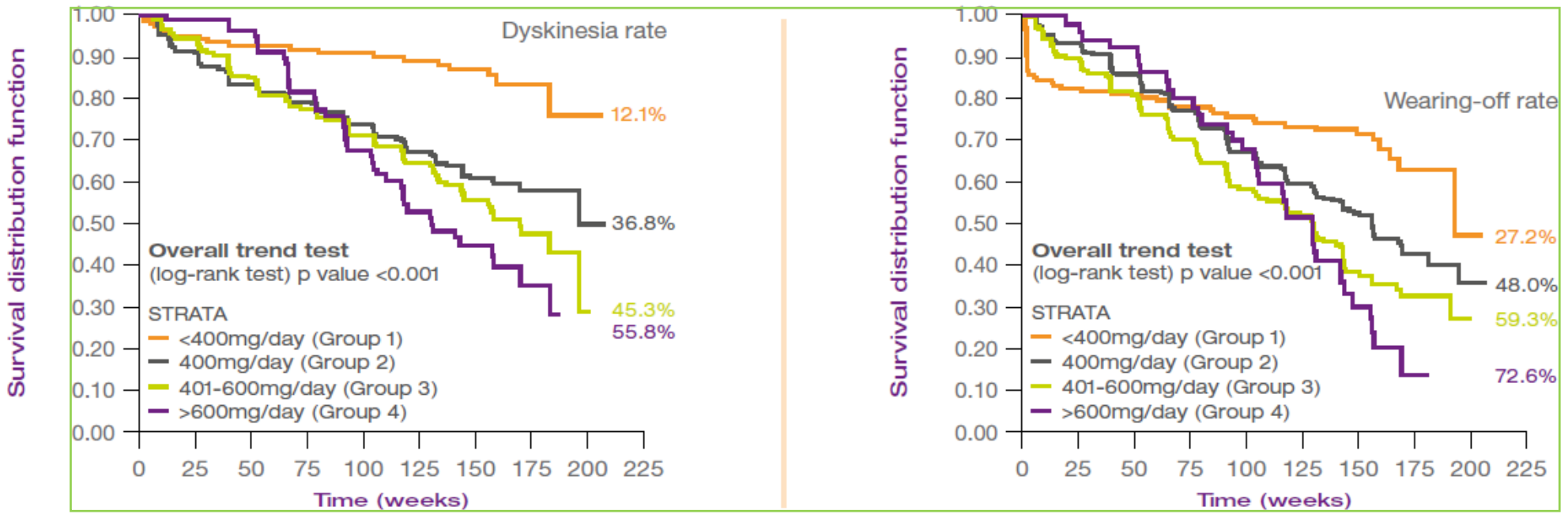


Levodopa Induces a Higher Incidence of Motor Complications Than Dopamine Agonist Therapy



Adapted from Hubble J. *Neurology*. 2002;58(suppl 1):S42-S50.

STRIDE-PD studie: The dose of L-dopa is associated with occurence of dyskinesia and wearing-off



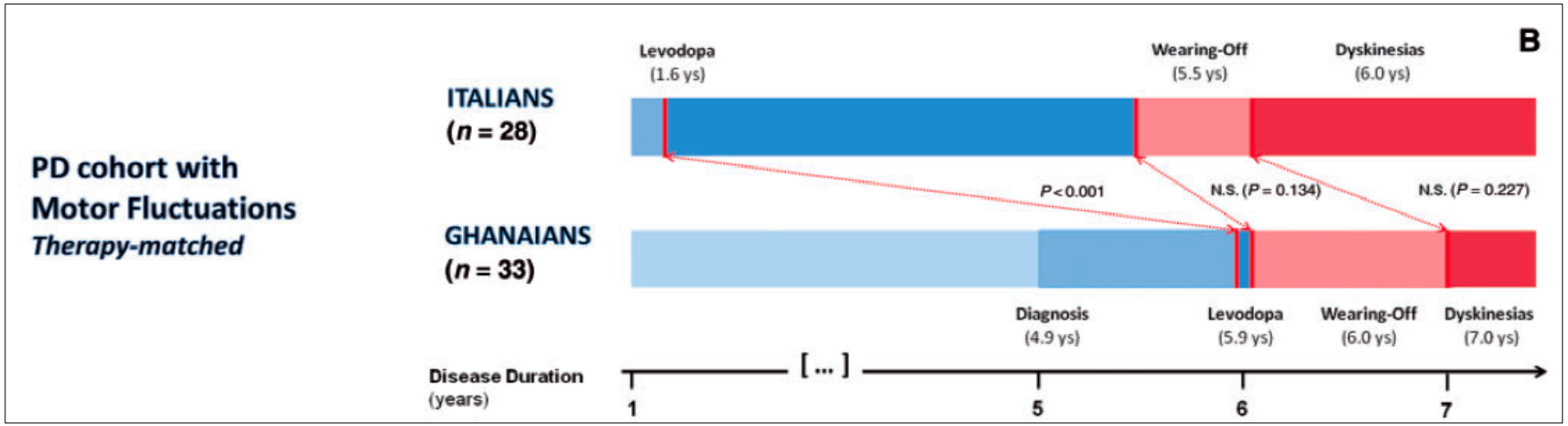
A significant increase in the risk for motor complications was observed at doses ≥400 mg/day.

Adapted from Warren Olanow C et al. Mov Disord 2013;28:1064–71

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

Brain 2014: 137; 2731–2742

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]



Logistic regression analyse ➔ wearing-off & dyskinesia are related to the duration of the disease + daily dosis L-Dopa, but not with the duration of the L-dopa treatment

Duration of disease "itself" + UPDRS-III (= bigger loss of SNpc-neurons) Are important factors causing motor complications .

It's not so important to not give L-Dopa (*to delay motor complications*) **BUT IT's IMPORTANT** to treat PD with lowest possible doses L-dopa.

Continue Dopaminerge Stimulatie in praktijk

- Vermijden levodopa monotherapie in hoge doseringen
- Snel combinatiebehandeling
    - COMT-remmers
    - Agonisten
    - MAO-B remmers
- Frequentie doseringen ?
- Snel herkennen van fluctuaties ook niet-motorische

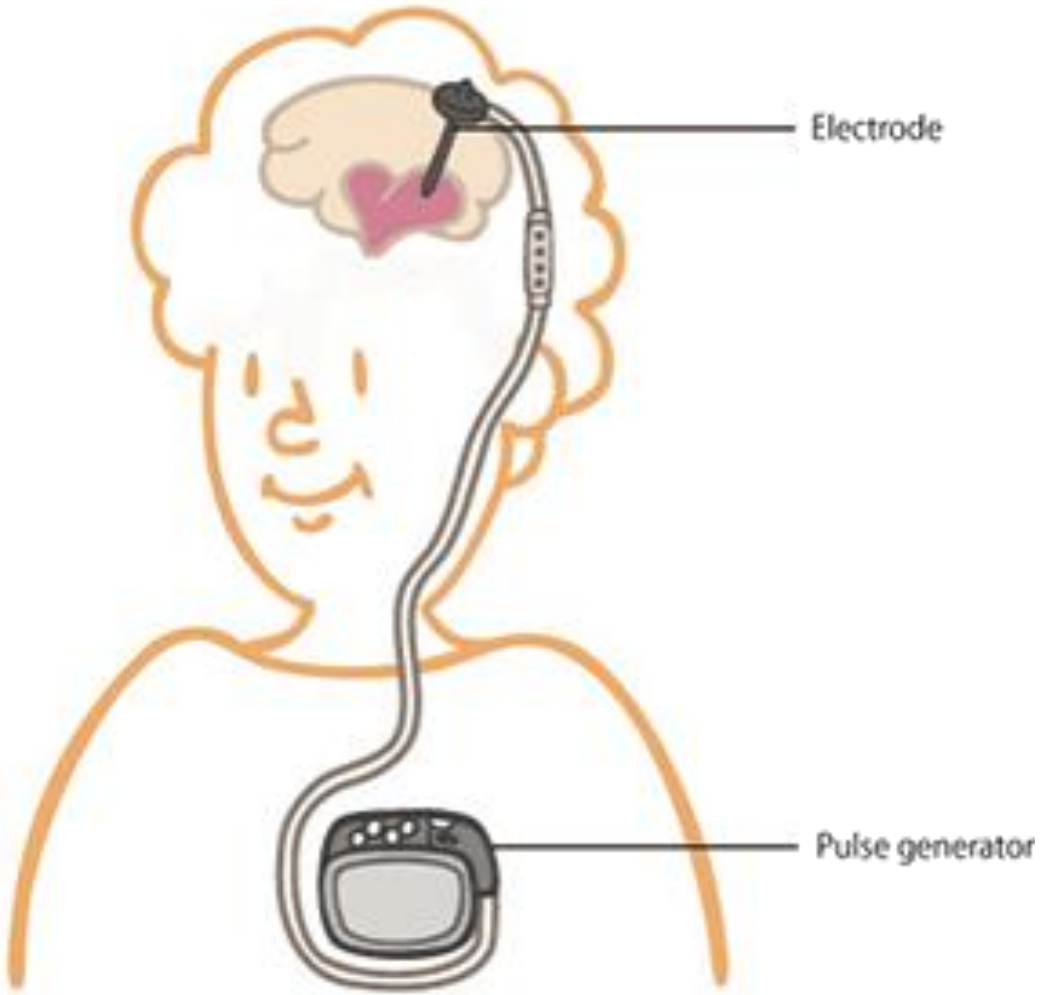
Selectieve behandelingen voor gevorderde ziekte

- Apomorfine SC als rescue behandeling voor off-episodes
- Diepe hersenstimulatie
- Duodopa : continue intraduodenale toediening van levodopa

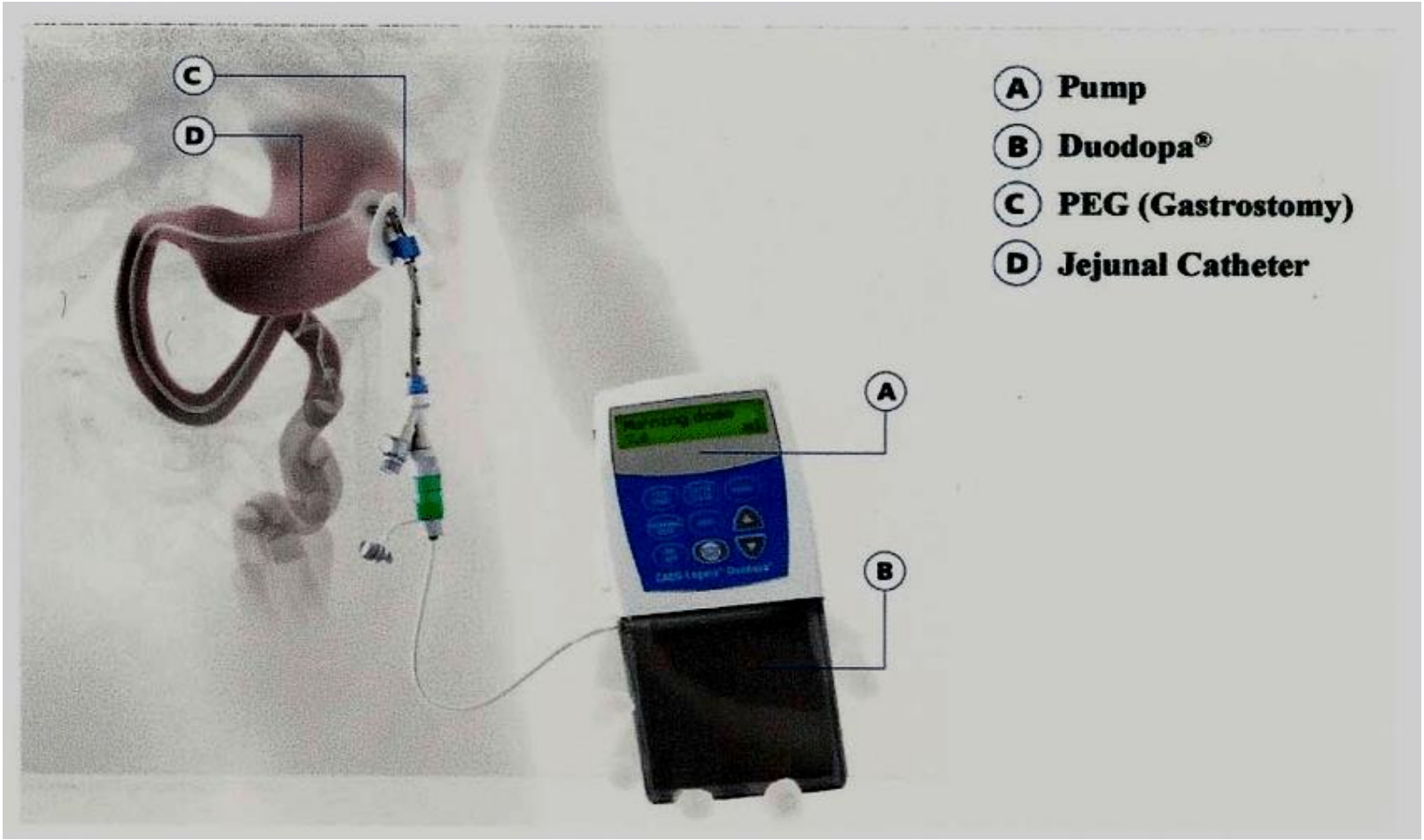
De apomorfine pen

Diepe hersenstimulatie

- Directionele stimulatie
- Brain sensing
- Closed loop stimulatie



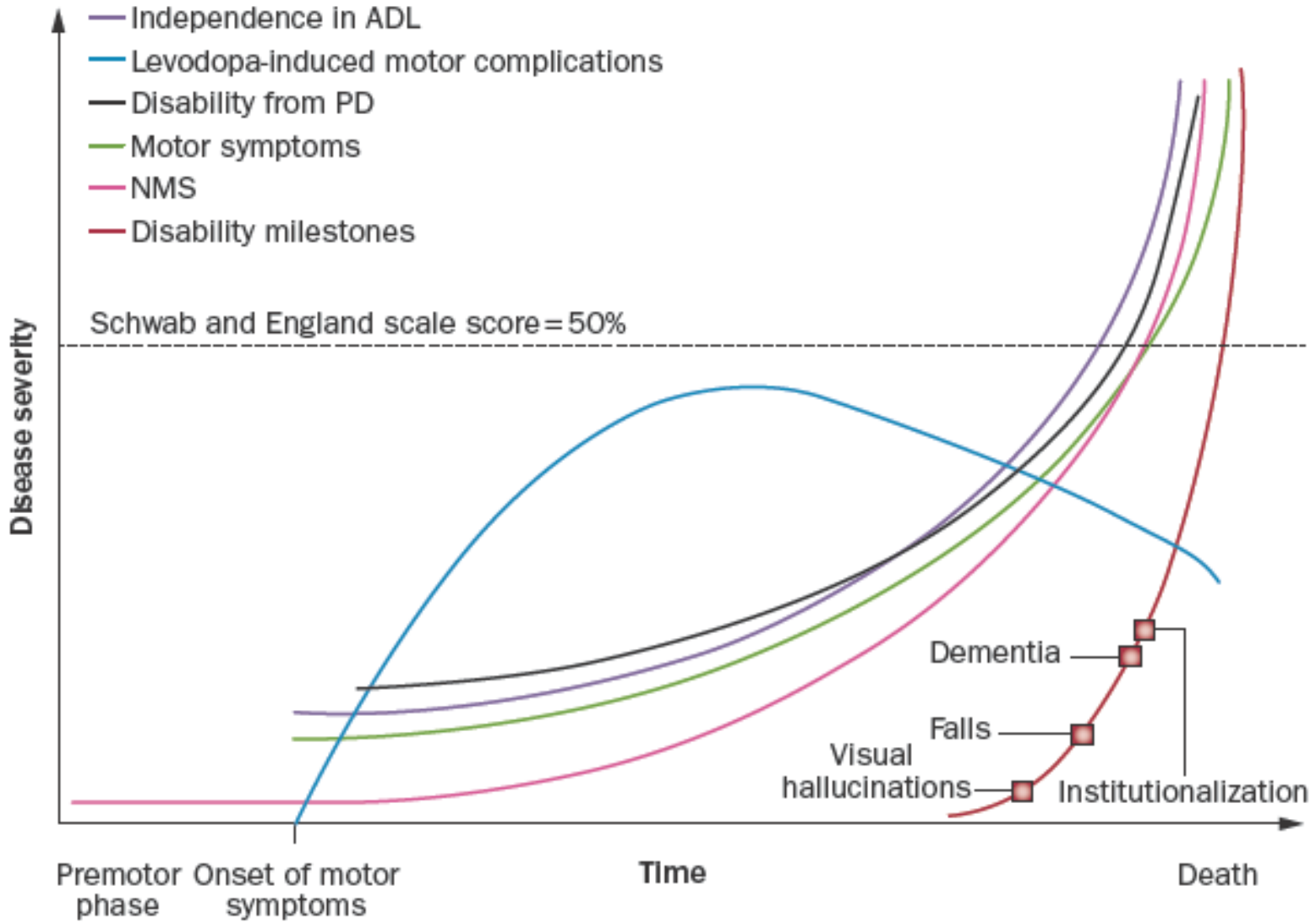
Duodopa/Lecigimon



Toekomstige symptomatische farmaca ?

- Alternatieve vormen van bestaande farmaca
  - Alternatieve toedieningen van apomorfine: transdermaal, oraal, suppo,…
  - Alternatieve vormen van levodopa
    - IPX-066 (Rytary)
    - Foslevodopa/ND0612 voor subcutane of transdermale toediening
    - CVT301 (Inbrija) inhalatie als rescue medicatie voor off-episodes
- Repurposing van bestaande medicijnen/nanoparticle toediening
    - Nilotinib, exenatide, terazosine,…
- Andere neurotransmitters: adenosine receptor antagonisten, cannabinoïden,…

Paramedisch en interdisciplinair werken



Coelho et al 2012 *Nat. Rev. Neurol.* 8, 435–442

ZIJN ER NOG VRAGEN