Deep Brain Stimulation and other invasive strategies for Parkinson‘s disease

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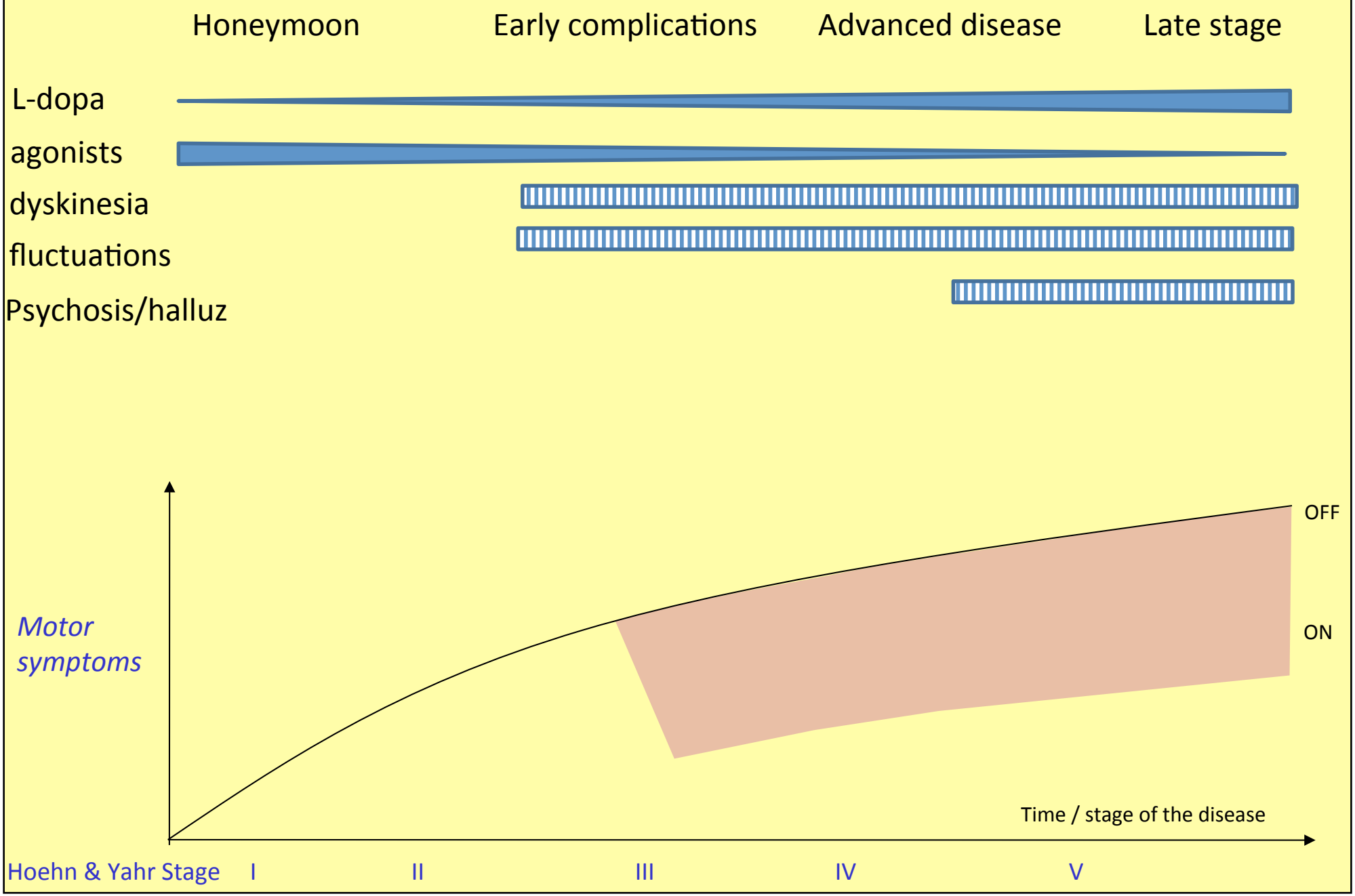
The treatment periods of Parkinson‘s disease



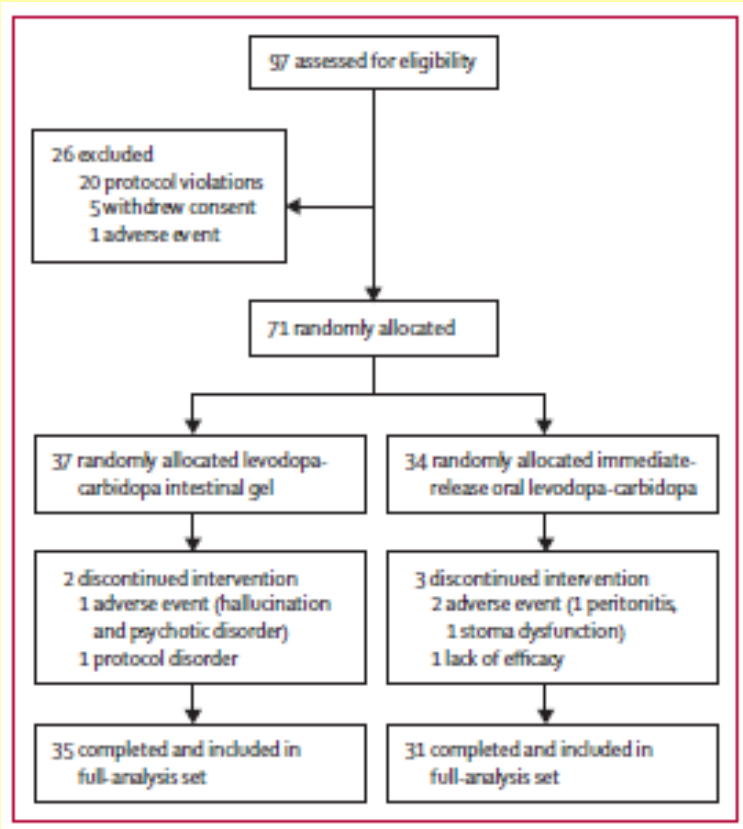
Treatment-resistent advanced PD

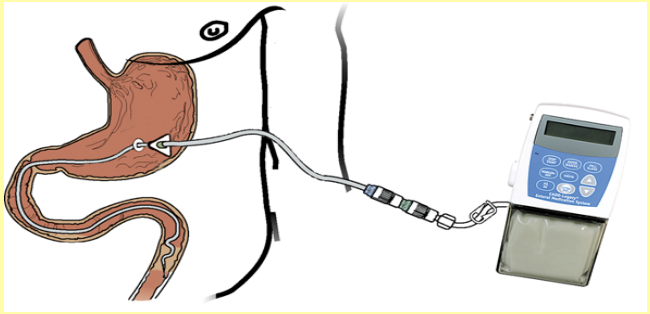
- Duodopa intrajejunal therapy
- Apomorphin subcutaneous injection
- Deep brain stimulation

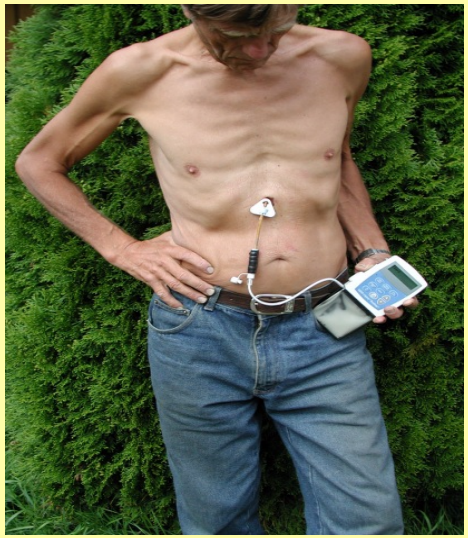
Jenunal application of L-DOPA

Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study

CWarren Olanow, Karl Kieburtz, Per Odin, Alberto J Espay, David G Standaert, Hubert H Fernandez, Arvydas Vanagunas, Ahmed A Othman, Katherine L Widnell, Weining Z Robieson, Yili Pritchett, Krai Chatamra, Janet Benesh, Robert A Lenz, Angelo Antonini, for the LCIG Horizon Study Group

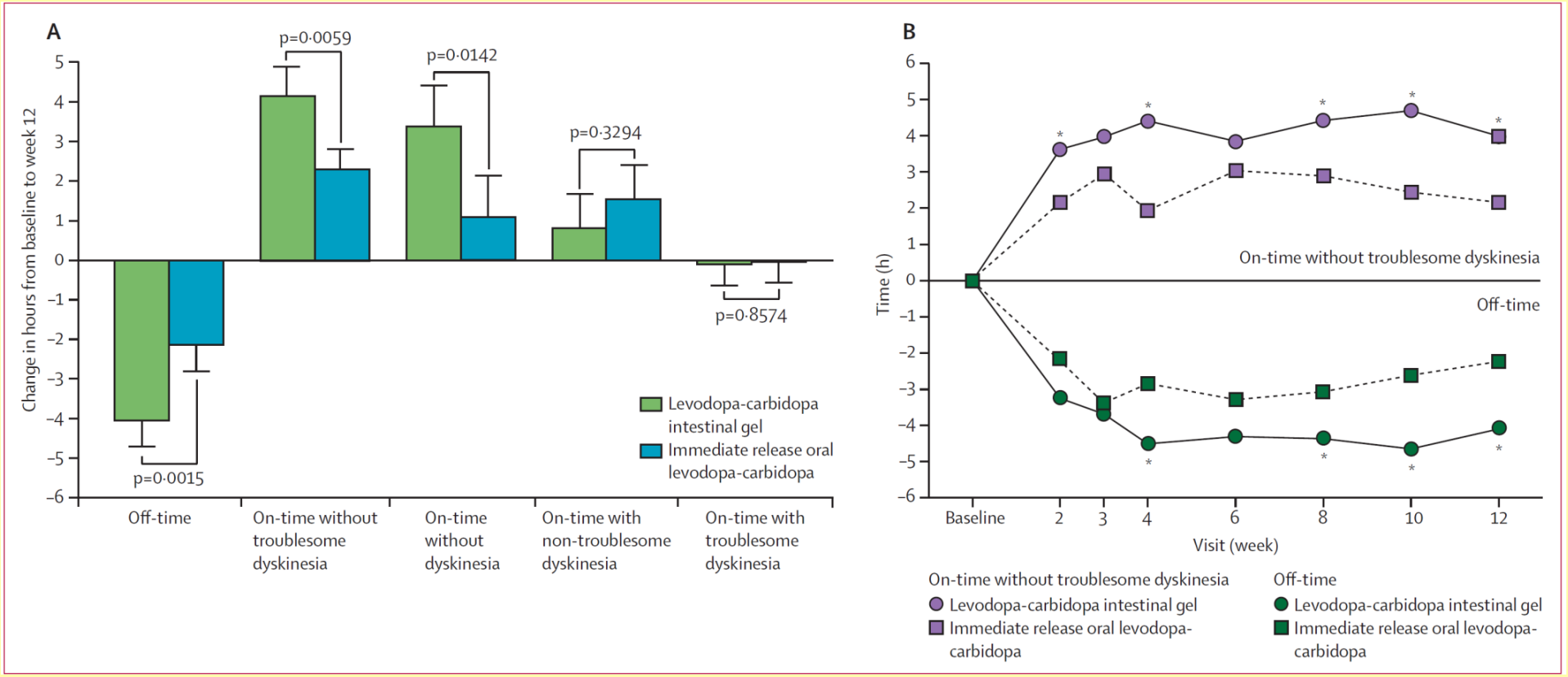






Olanow et al. Lancet Neurology 2014

Results (N = 66 patients)



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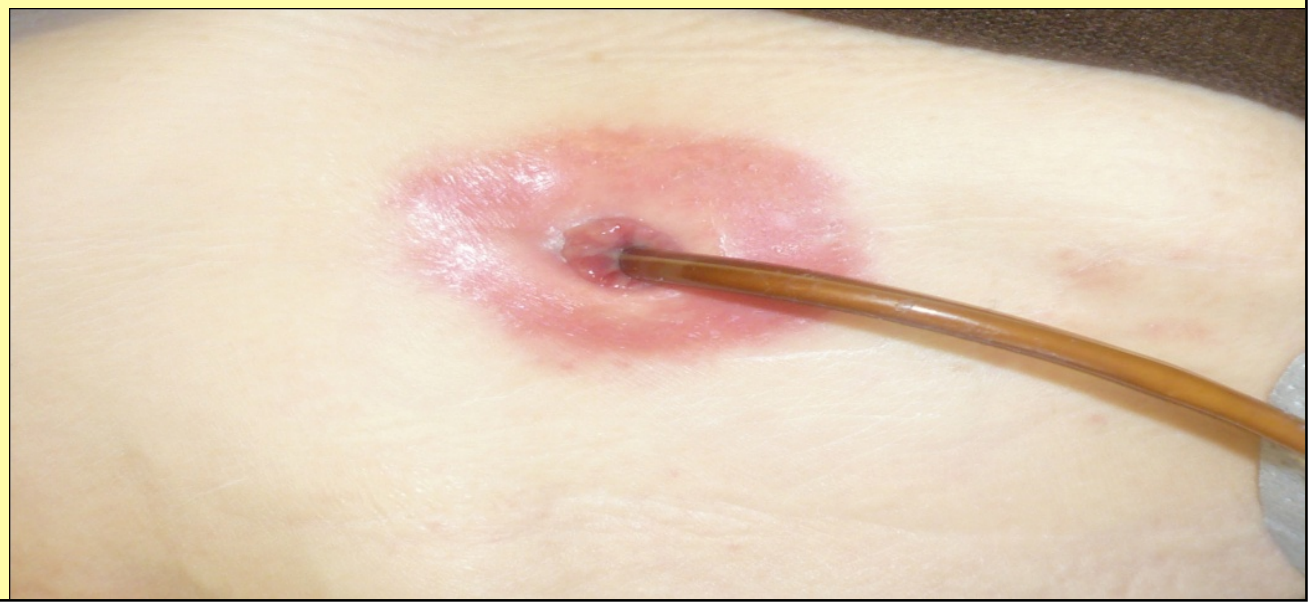
Jejunale Levodopa-infusion: side effects

- ✓ **PEG implantation**
  - ✓ pain
  - ✓ Abscesses/ peritonitis
- ✓ **Stoma**
  - ✓ Pain when the Stoma is mobilized unintended
  - ✓ Stomainfection
- ✓ **PEG**
  - ✓Disclocation of the jejunal tube
  - ✓Breaking of the tube
- ✓ **Polyneuropathy**



Complications of therapy

	Levodopa-carbidopa intestinal gel (n=37)	Immediate-release oral levodopa-carbidopa (n=34)	Overall (n=71)
Device complications	34 (92%)	29 (85%)	63 (89%)
Intestinal tube	14 (38%)	12 (35%)	26 (37%)
Leakage	2 (5%)	1 (3%)	3 (4%)
Insertion	3 (8%)	1 (3%)	4 (6%)
Dislocation	8 (22%)	9 (26%)	17 (24%)
Occlusion	5 (14%)	4 (12%)	9 (13%)
Unintentional removal	0	1 (3%)	1 (1%)
Percutaneous gastrojejunostomy	11 (30%)	12 (35%)	23 (32%)
Breakage	1 (3%)	0	1 (1%)
Insertion	8 (22%)	7 (21%)	15 (21%)
Dislocation	2 (5%)	3 (9%)	5 (7%)
Occlusion	0	1 (3%)	1 (1%)
Connection issue	1 (3%)	3 (9%)	4 (6%)
Unintentional removal	0	1 (3%)	1 (1%)
Pump	5 (14%)	8 (24%)	13 (18%)
Breakage	1 (3%)	0	1 (1%)
Malfunction	3 (8%)	3 (9%)	6 (8%)
Occlusion	1 (3%)	2 (6%)	3 (4%)
Stoma	15 (41%)	15 (44%)	30 (42%)
Leakage	2 (5%)	1 (3%)	3 (4%)
Insertion	2 (5%)	5 (15%)	7 (10%)
Dislocation	0	1 (3%)	1 (1%)
Connection issue	0	1 (3%)	1 (1%)

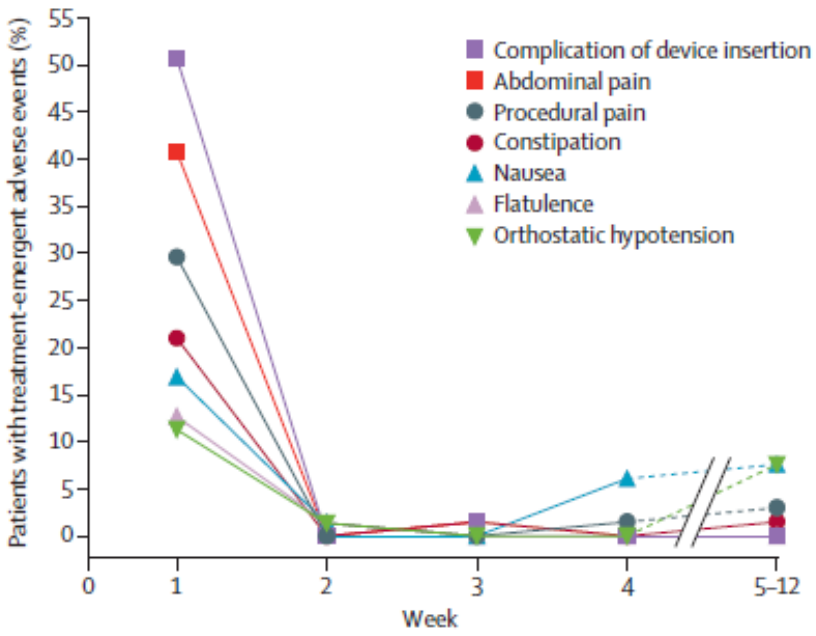


Figure 3: Timing of treatment-emergent adverse events reported by >10% of patients

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Review

Expert Consensus Group report on the use of apomorphine in the treatment of Parkinson's disease – Clinical practice recommendations

Claudia Trenkwalder [a, i, *], K. Ray Chaudhuri [b], Pedro J. García Ruiz [c], Peter LeWitt [d], Regina Katzenschlager [e], Friederike Sixel-Döring [a, j], Tove Henriksen [f], Ángel Sesar [g], Werner Poewe [h], on behalf of an Expert Consensus Group for the Use of Apomorphine in Parkinson's Disease, Mary Baker [k], Andres Ceballos-Baumann [l], Günther Deuschl [m], Sophie Drapier [n], Georg Ebersbach [o], Andrew Evans [p], Hubert Fernandez [q], Stuart Isaacson [r], Teus van Laar [s], Andrew Lees [t], Simon Lewis [u], Juan Carlos Martínez Castrillo [v], Pablo Martinez-Martin [w], Per Odin [x], John O'Sullivan [y], Georgios Tagaris [z], Karoline Wenzel [aa]

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[aa] *Medical University of Graz, Graz, Austria*

PEN

- Anticipated rescue when required during motor and non-motor off periods
- When absorption of oral levodopa is impaired or the patient has gastric emptying problems (gastroparesis)
- To treat delayed 'on'
- To treat early-morning motor problems (akinesia and dystonia)

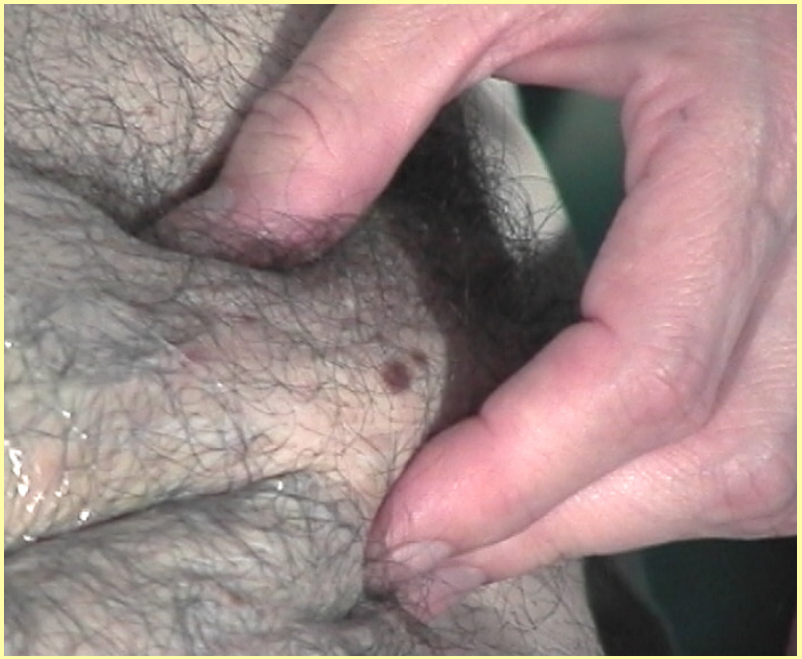
PUMP

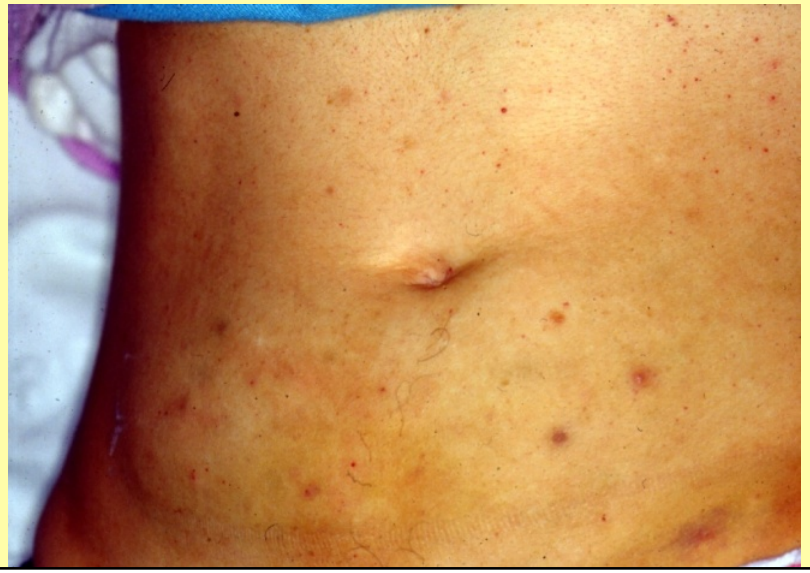
- Patient considers that rescue doses required too frequently
- Dyskinesias limit further therapy optimisation
- Non-motor symptoms associated with 'off' periods
- Simplify complex PD dosing regimens to improve convenience and compliance with therapy
- As an alternative to surgical therapy or LCIG if these are contraindicated or because of patient preference
- Absorption or gastric emptying of oral levodopa are impaired

Continuous apomorphine-therapie: Side effects

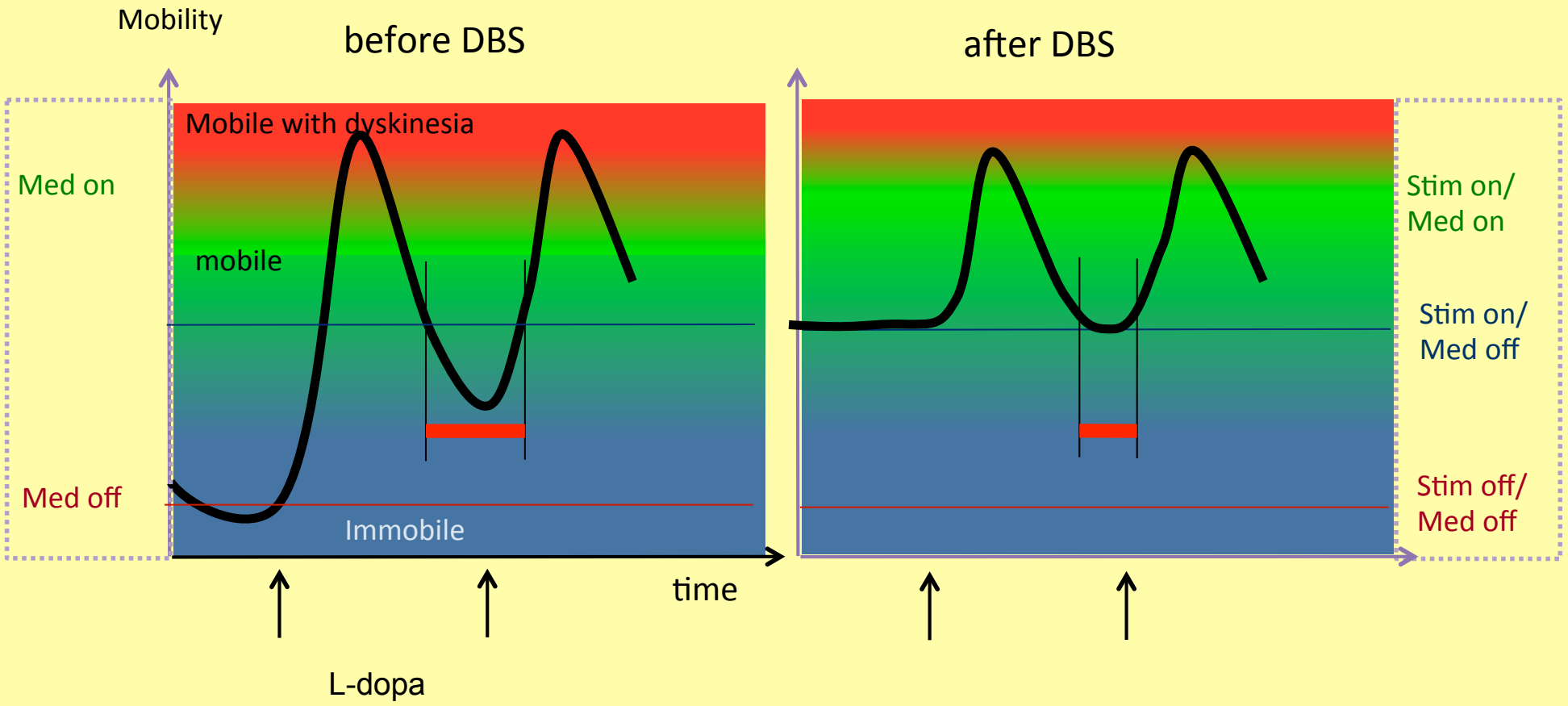
Odin et al. 2004 (n=118)

Noduli	94
Orthostatic hypotension	10
Eosinophilia	9
Nausea	7
Hämolytic anemia	4
Dizziness	3
Others	10



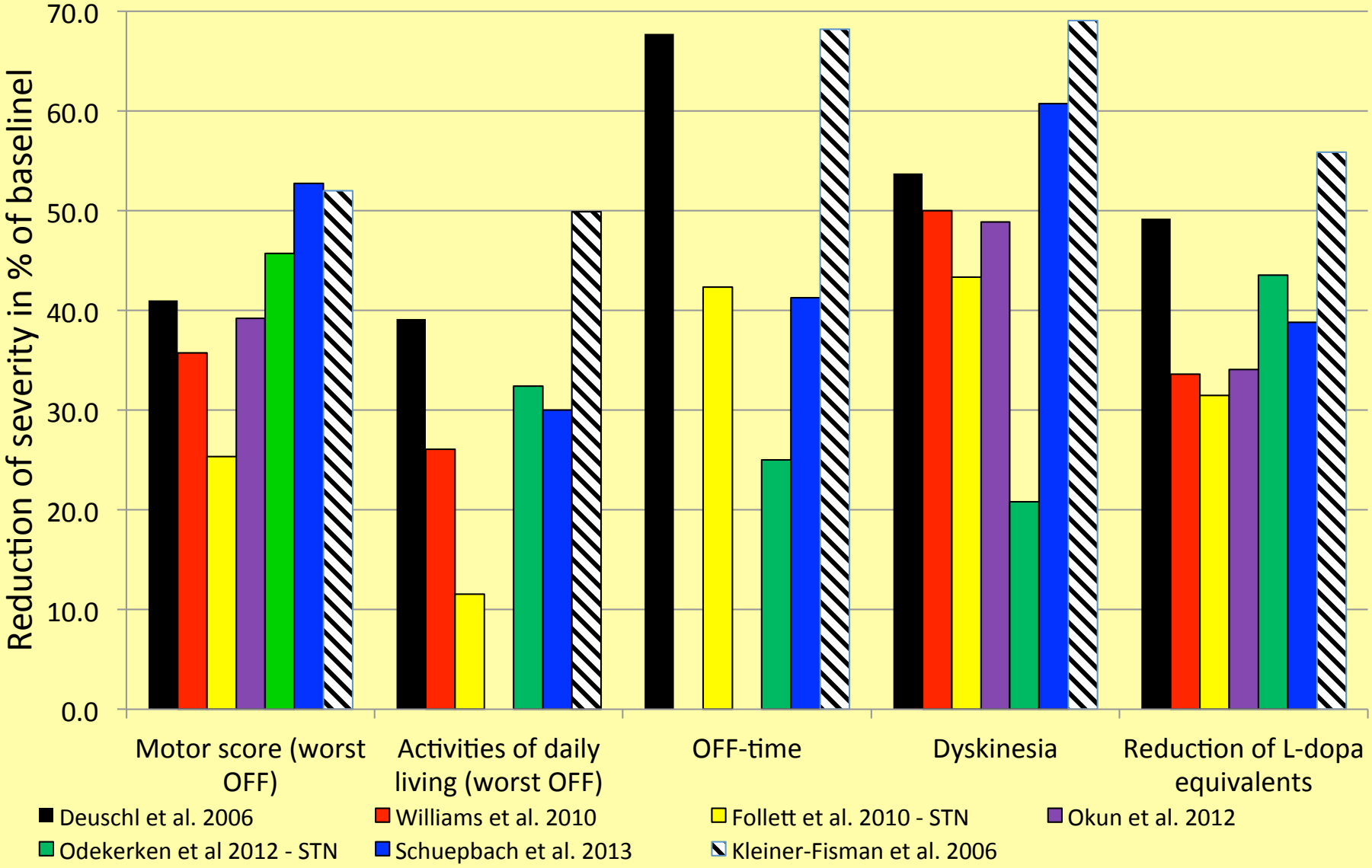


Deep brain stimulation of the subthalamic nucleus



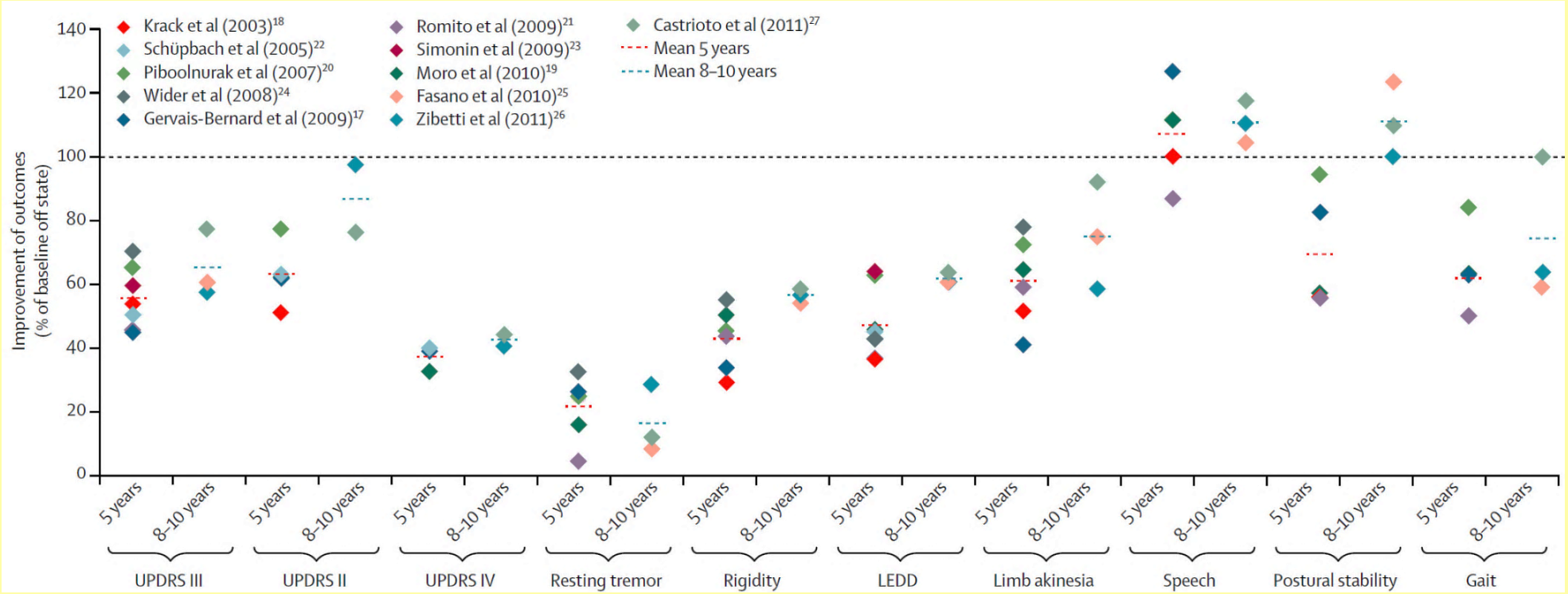
Deuschl and Agid 2013

The effects are strong and consistent across different studies



Deuschl and Agid 2013

The effects are sustainable for 5 and 8-10 years



Deuschl and Agid 2013

Side effects in advanced disease

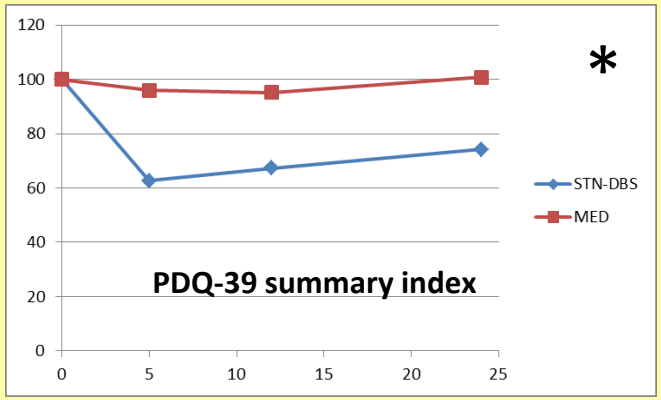
- Mortality: ~ 0,4% (Voges et al. 2007)
- Permanent sequelae: ~ 1%
- Infections of the system: up to 10%
- Hardware problems ~ 3 %
- Suicides: 0.45% (not related to DBS)
- Stimulation-evoked side effects: 5-20% (mostly reversible)

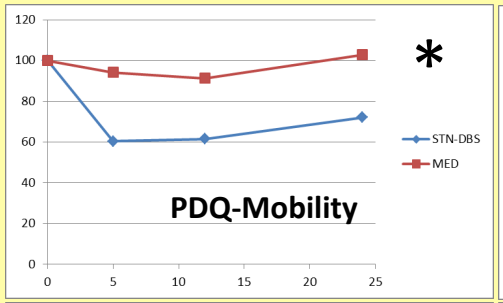
Serious, nonfatal adverse events most likely related to surgery in a series of 1096 patients with Parkinson's disease who underwent subthalamic nucleus or globus pallidus pars interna deep brain stimulation collected from six randomized controlled trials performed between 2006 and 2013

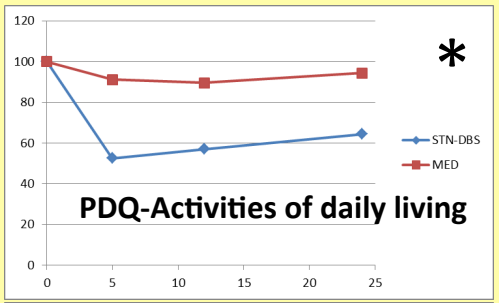
Serious adverse events	Neurostimulation (STN and GPi)	Events per 100 patients*
Infection	48	4.49
Nonfatal cerebral hemorrhage	16	1.50
Medical device complication	9	0.84
Dislocation of device	7	0.65
Disturbed wound healing	7	0.65
Reoperation necessary	4	0.37
CSF leakage	1	0.09

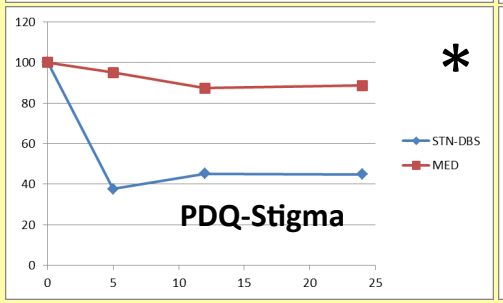
Deuschl et al. 2014

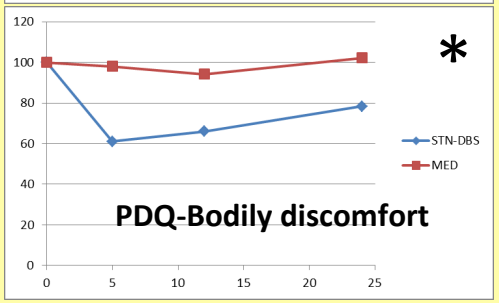
Earlystim: Quality of life (primary outcome) and handicap

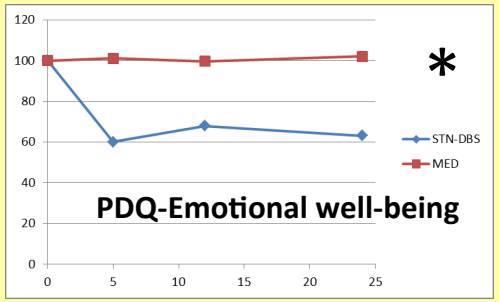


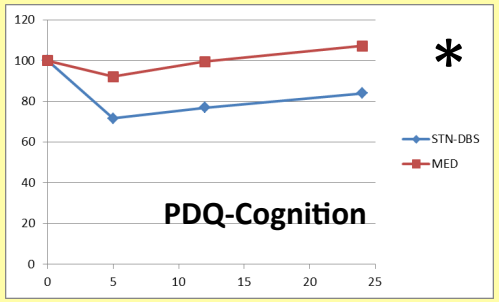


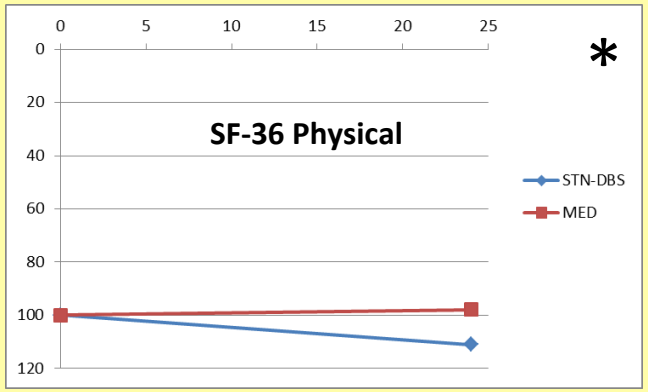


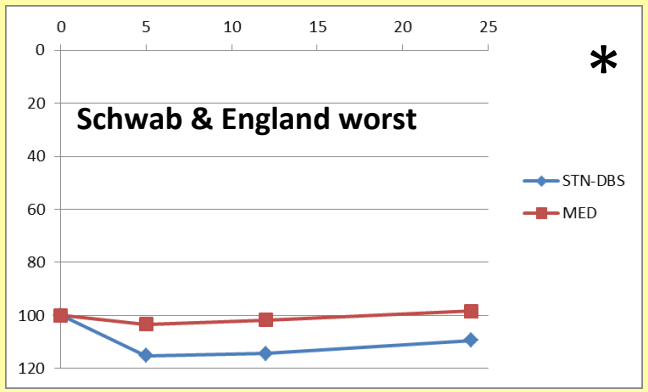








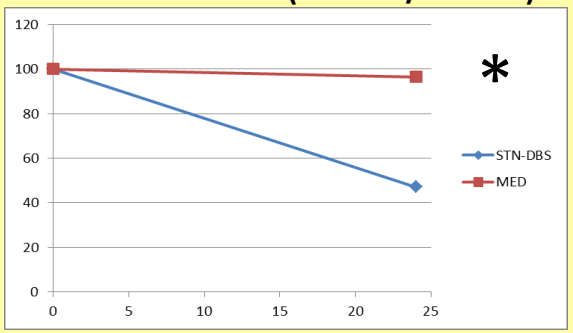




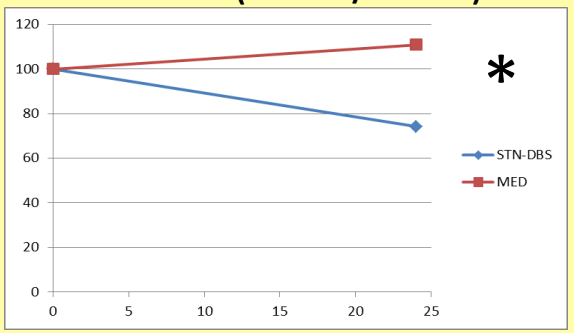
Figures: courtesy M. Schuepbach

Earlystim: Motor outcomes

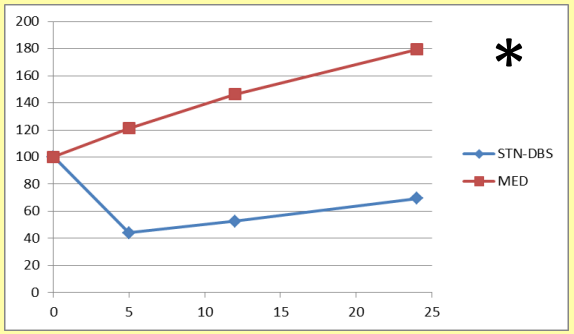
UPDRS III (Med off/Stim on)



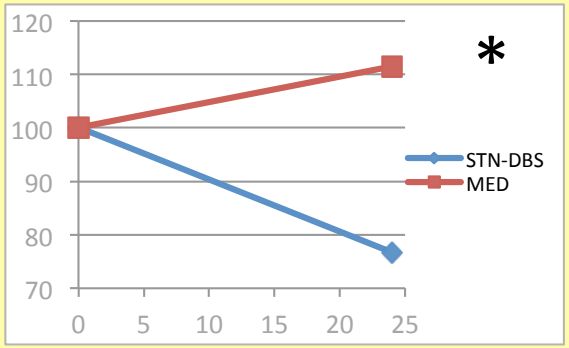
UPDRS III (Med on/Stim on)



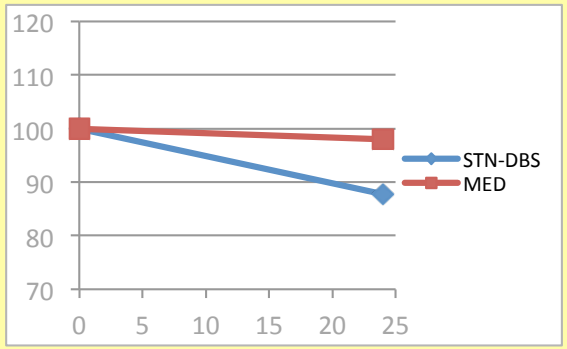
Marconi dyskinesia scale (Med on/Stim on)



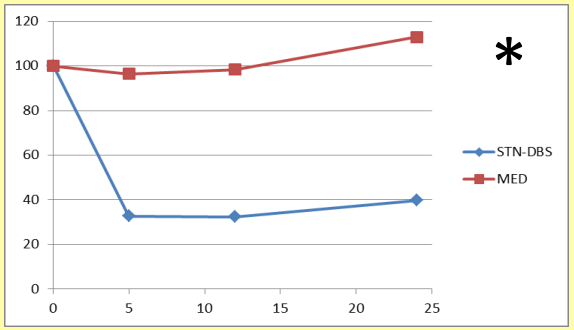
UPDRS II worst



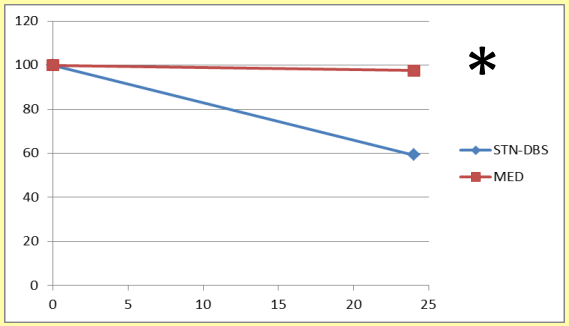
UPDRS II (best)



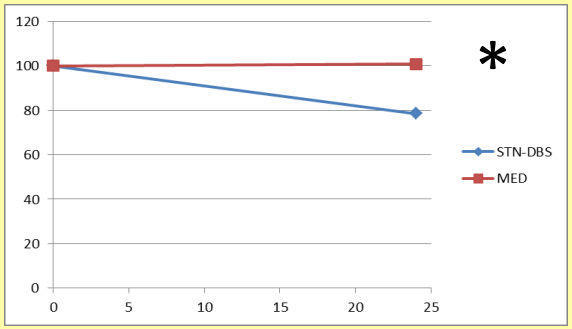
UPDRS IV



Diary: bad mobility



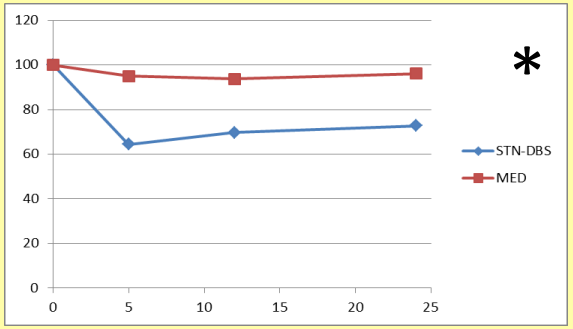
Walking test (steps) S+M-



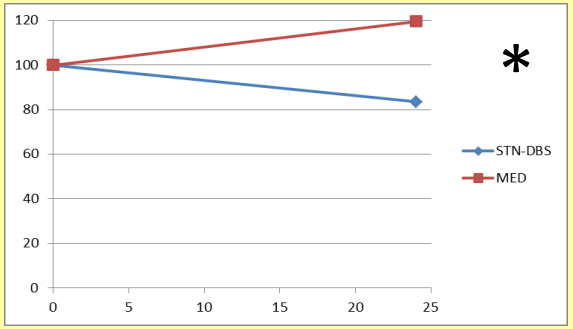
Figures: courtesy M. Schuepbach

Earlystim: Cognition, emotion and psychosocial

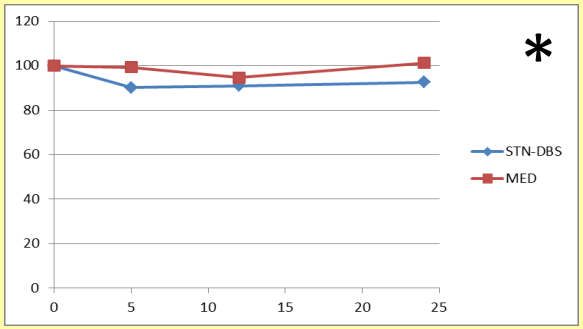
SCOPA-psychosocial



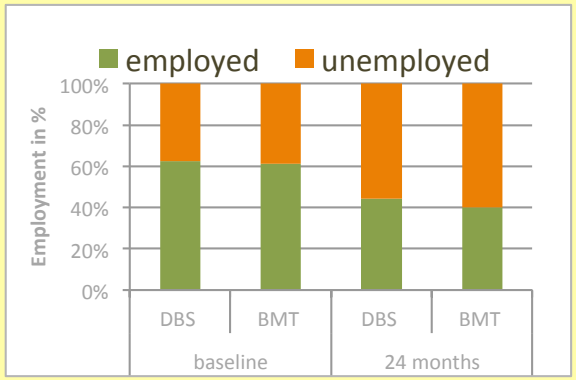
MADRS



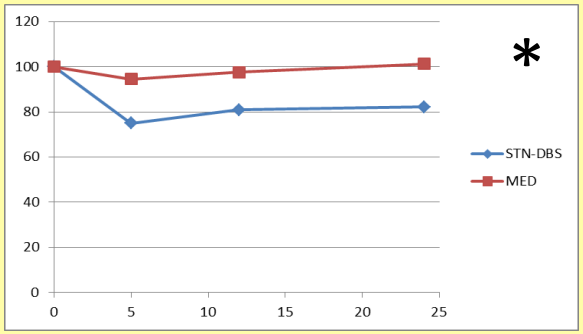
BPRS



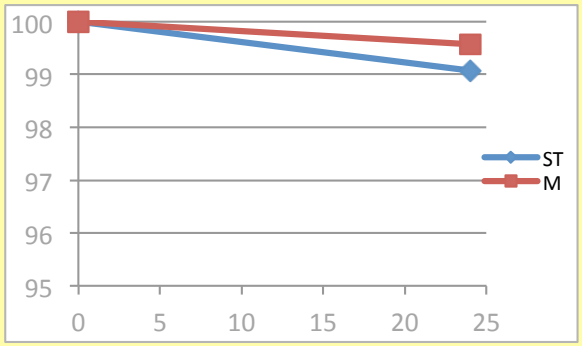
Employment



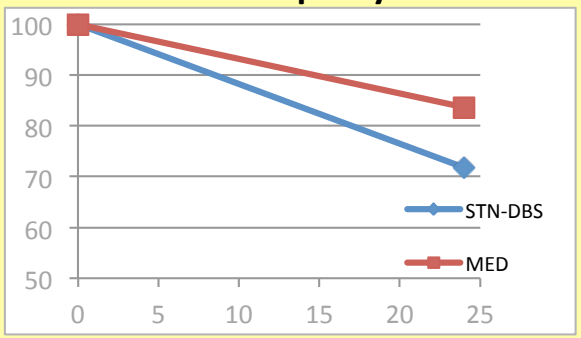
BDI-II



Mattis dementia reating scale



Starkstein Apathy Scale



Figures: courtesy M. Schuepbach

Safety within Earlystim

- 27 Surgery-related SAE resolved at 2 yrs
- Suicides higher in the study population than in the general PD population
- Completed and attempted suicides equally distributed among both groups (5:4 events in DBS:BMT)
- More medication related SAE in the BMT group

The essence: Suggested criteria for neurostimulation of Parkinson's disease at an earlier disease stage (after the honeymoon)

‚Treat only patients which have a high probability to improve'

- Definite diagnosis of Parkinson's disease (>4 years)*
- Excellent response to levodopa (≥50%)*
- Fluctuating disease, even if only mild*
- No cognitive disturbances (Mattis score ≥130)*
- No major comorbidities*
- No major depression (Beck Depression score II <25)* or other psychiatric contraindications*
- No neurosurgical contraindications*
- Stable social situation and realistic expectations from surgery
- Access to an experienced multidisciplinary team for patient selection, surgery, programming, and long-term care*

*Inclusion criteria for EARLYSTIM

Criteria to decide on the differential indication (expert opinion)

Symptom	STN-DBS	Levodopa intestinal Gel	Apomorphine pump
Dyskinesia	++	+	+
L-dopa unresponsive gait	-	+/-	+/-
Impulse control disorders	++	+	-
Hallucinations	+	+/-	-
Mild cognitive impairment	+/-	+	*/-
Dementia	-	+/-	-
Non-motor fluctuations	++	+	+
Orthostatic hypotension	+	-	-
Constant efficacy during daytime	++	+	+
Long-term experience	++	+	+

Summary

- Advanced PD is sometimes no longer treatable with oral medication
- Apomorphin, levodopa-infusion therapies and deep brain stimulation are options
- Scientific evidence is best for DBS, less good for LID and even for Apomorphin
- All three options do have possible side effects
- Individual characteristics of patients mainly determine the treatment to chose