Therapies in advanced PD

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Disclosures

I have no conflict of interest related to this teaching course.

Learning objectives

- To describe the selection criteria and beneficial effects of patients for the device-aided treatment
- To learn how to use and manage infusion therapies
- To recognize frequents problems and side effects during infusions therapies and deep brain stimulation
- To identify factors able to help in selection one device over another

Key messages

- Any patient with APD:
  - Levodopa >5 times daily
  - Troublesome ‘off’ periods (>1-2 h/day) despite optimal oral/transdermal levodopa or non-levodopa-based therapies
  - Relatively preserved cognitive-behavioral status

- Since device-aided therapies are now being offered increasingly around the world, it is important for neurologists to be comfortable in discussing and managing problems of these therapies

- In advising on one interventional therapy over another:
  - Consider patient’s clinical profile: cognitive impairment, frailty, presence of troublesome dyskinesias, medication-refractory tremor, age, availability of support and follow up
  - More studies are needed to better personalize treatment

Introduction

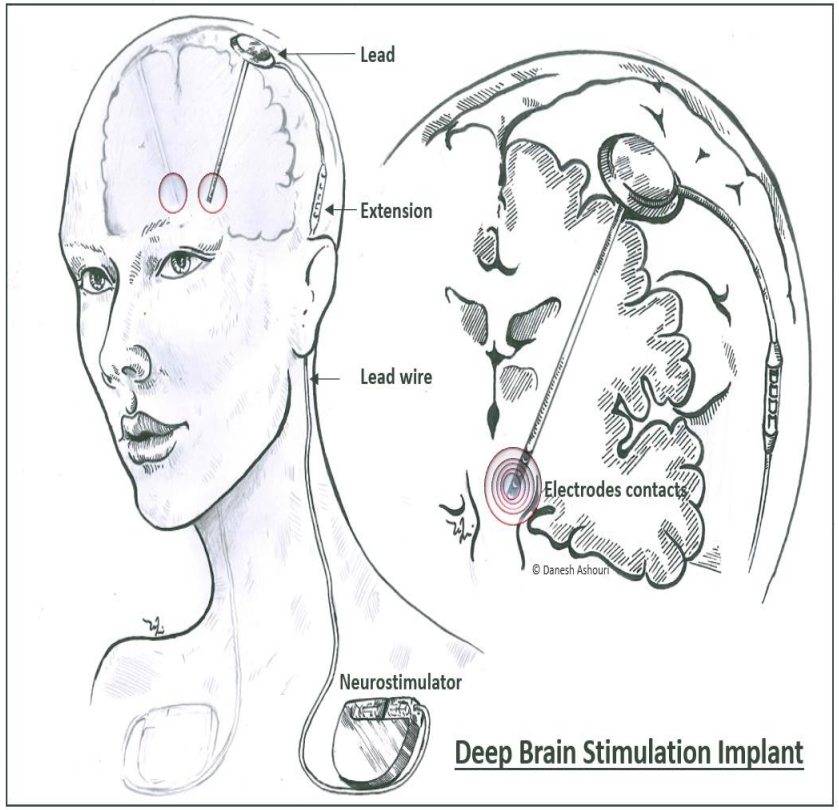
- Concept of “advanced Parkinson’s disease” (APD): controversial and unclear
- Need to include our growing knowledge of the heterogeneity of PD underpinned by motor and nonmotor subtypes

- Dyskinesia and motor fluctuations present major challenges in the long-term treatment of PD.

- In APD, these motor complications may be insufficiently controlled by oral medication regimens and require device-aided therapeutic strategies:
  - Deep brain stimulation of the subthalamic nucleus (STN-DBS) or other targets
  - Intrajejunal levodopa infusion
  - Apomorphine infusion

Deep brain stimulation (DBS)

- Invasive functional surgery, *Benabid et al 1993*
- In contrary to ablative surgery:
  - Reversibility
  - Less tissue damage
  - Bilateral
- Success of DBS:
  - patient selection
  - DBS surgery
  - postoperative management



Beneficial effects

- **Responsive Parkinson Disease Symptoms:**
  - Motor symptoms that respond to the best on state (rigidity, bradykinesia, tremor
  - Motor fluctuations (dose wearing off, on-off, dose failures)
  - Reducing ‘off’ time by 25-68%
  - Dyskinesias reduced by 40-60%
  - Non motors symptoms: impulse control disorders, anxiety, pain, noctural sleep, weight loss (*Kurtis et al, 2017)*
- **Reduction of LED** by 31-68%
- Improvement: Qol >70%, ADL approximatively 50%
- **Symptoms that do not respond:**
  - Axial: speech, dysphagia, gait and posturak instability if not levodopa responsive
  - Autonomic symptoms
  - Cognition, mood and behavior
- **Timing:** Early vs Late stimulation

Patient selection criteria

Indications

- > 30% improvement in UPDRS III following levodopa challenge except for tremor
- Normal neuropsychological evaluation
- No psychiatric troubles
- Age <70 years (70-75)
- Family support

Absolute Contraindications

- Dementia
- Acute psychosis, major depression
- Severe brain atrophy or lesions interfering with trajectory planning
- Serious comorbidities
- General contraindication to undergo neurosurgical interventions

Christian J. Hartmann et al. Ther.Adv Neurol Disord. 2019

Surgical procedure and intraoperative management

- **Medication-off state**
- **Two stages:**
  - DBS lead placement
    - Direct identification of target and trajectory: stereotactic coordinates
    - Microelectrode recording (MER)
    - Macrostimulation: clinical testing
  - The IPG placement
- **Perioperative protocols of anesthesia**
- **Targets:**
  - STN: target of choice
  - Gpi: mild cognitive decline, severe hyperkinesia
  - ViM nucleus: disabling tremor only, not apply for STN or GPI DBS

Postoperative management

- **Initial programming session:**
  - Microlesion effects
  - Testing adverse and beneficial effects
  - Best contact:
    - low amplitude thresholds for beneficial effects
    - large therapeutic window
    - Monopolar stimulations: frequency 130 Hz, pulse width 60 μs, constant current mode

- **Reduction of anti-PD medication:** gradually step-wise increase amplitude by 0.5 mA
- **Side effects at low stimulation amplitudes:** pulse width 30-40 μs, bipolar
- **Symptoms not well controlled:** several contacts as cathodes
- **Axial symptoms:** frequency 60–80 Hz
- **Tremor insufficiently suppressed:** Increase frequency

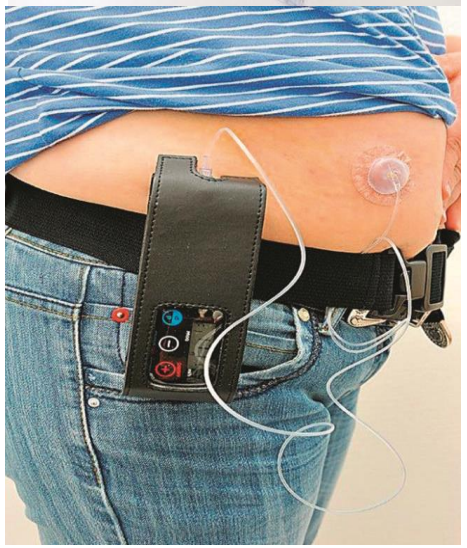
Complications and side effects

Surgery-related	Hardware-related	Stimulation-related
Seizure: <1 to 3%	Device malfunction	Paresthesias
Hemorrhage: 2–3%	Lead fracture	Muscle contractions
Fatal cerebral hemorrhage: <1%	Lead migration	Dysarthria
Infection: 2–25% (vast majority are superficial)	Lead disconnection	Diplopia
Permanent neurologic deficit: 0–0.6%	Skin erosion	Cognitive changes
Misplaced leads: 0–12.5%		Depression
Venous air embolism		Mania
		Suicide
		Pseudobulbar affect
		Obsessive/compulsive thoughts
		Anxiety/panic attacks
		Aggressive behavior

Siddiqui MS et al, Continuum 2010

Apomorphine Subcutaneous Infusion

- Apomorphine (APO):
  - non narcotic derivate of morphine
  - highly potent DA
  - interacts with dopamine receptors D1-D5, D1 and D2 +++
  - equivalent anti-parkinsonian efficacy to oral levodopa
- Small infusion pump, fine-caliber tube, needle
- The least invasive: entirely reversible



Clinical Practice Recommendations
Expert Consensus Group Report

INDICATIONS

- Motor fluctuations that have become refractory to any changes in the oral or transdermal treatment
- Adjustments typically complicated by the emergence (or worsening) of dyskinesias
- Intolerable non motor symptoms associated with off periods
- Rescue doses of apomorphine injections required too frequently
- Simplify complex PD dosing regimen to improve convenience and compliance of therapy
- Absorption and gastric emptying of oral Ldopa impaired
- As alternative to DBS or LCIG if contraindicated or patient preference

Trenkwalder C et al, Parkinsonism Relat Disord. 2015

Beneficial effects

- **Motor symptoms:**
  - Reducing off time up to 40 %
  - Increase in on time without dyskinesias
  - improvement of ADL
  - Reduction in oral levodopa doses
- **Non-motor symptoms:**
  - Mean NMSS total score up 42%
  - Sleep/fatigue, mood/apathy, perceptual/hallucinations, attention/memory, gastrointestinal, urinary symptoms
  - No significant improvement was seen in the cardiovascular, sexual, and miscellaneous subscores.
- **Quality of life**

Katzenschlager R et al, Lancet Neurol 2018, Timpka J et al, Int Rev Neurobiol 2017

Contraindications

Relative	Absolute
• Non-compliance with non-invasive therapies • MCI • Moderate-to-severe dementia • Previous or current dopamine dysregulation, punding or impulse control disorders	• Lack of levodopa response • Inability of patient and caregiver to handle medication and device

P. Odin et al, Parkinsonism and Related Disorders, 2015

Starting patients on continuous apomorphine infusion

- Prior evaluations: ECG
  - exclude prolonged QT duration, tachy and bradyarrhythmias, atrial fibrillation, and premature ventricular contractions
  - exclusion of pre-existing hemolytic anemia
- Inpatient stay or in an outpatient setting
- 16-h daytime treatment (TOLEDO16+-2h)
- Domperidone 10mg three times daily 1 day before; total 3-7 days /Trimethobenzamide
- Starting dose 0,5 or 1mg per hour on first day
- Total daily dose divided into three subdoses: the morning dose, the maintenance dose, and the extra bolus dose.
- Maintenance doses: 4 - 7 mg/h (Toledo study: 3-8h)
- Discontinue all daytime PD medications

Adverse events

- **Subcutaneous nodules:**
  - Rotation of the choice of infusion sites
  - Teflon® needles
  - Delivery through the skin to an optimal angle (45-90)
  - Good skin hygiene / emollients
  - Lower concentration, e.g. 5 mg per ml
  - Massaging the infusion site (spiky rubber massage ball,vibrating device)
  - Ultrasound treatment
  - Silicone gel dressings

- **Visual hallucinations**
- **Confusion**
- **Impulse control disorders**
- **Postural hypotension**
- **Nausea**
- **Hemolytic anemia**
- **Eosinophilic syndrome**

Intrajejunal levodopa infusion therapy

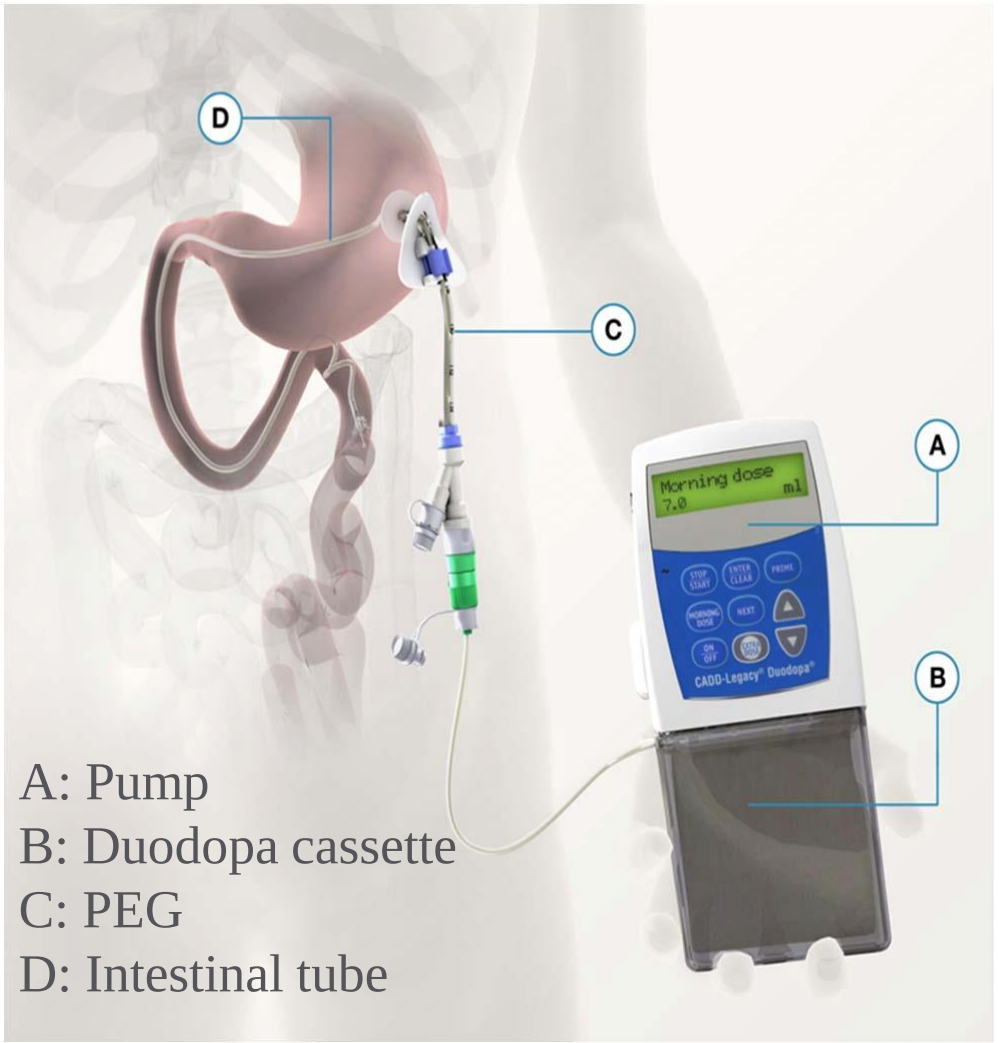
- Levodopa-carbidopa intestinal gel (LCIG) (AbbVie, North Chicago, IL)
  Sweden 1991- Europe (Duodopa) 2004, USA (Duopa) 2015

- Levodopa-entacapone-carbidopa (LECIG) (Lecigon, lobsor pharmaceuticals AB)
  October 2018 Swedish MPA

- **LCIG:**
  - Carboxymethylcellulose aqueous gel: 20 mg L-dopa and 5mg carbidopa per ml
  - Continuous dopaminergic delivery to the upper intestine
  - Overcome the inherent variability in absorption related to gastric emptying
  - More stable levodopa plasma levels than standard oral levodopa therapy

Administration of LCIG

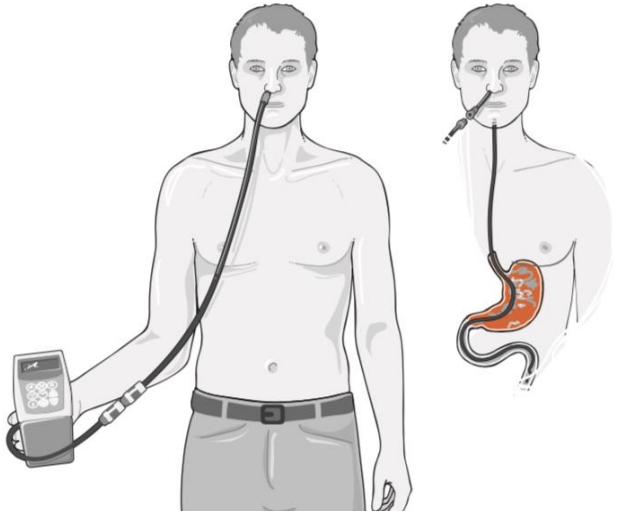
- Gel infused continuously through the abdominal wall with the help of a percutaneous endoscopic gastrostomy (PEG) inserted in local anesthesia
- Gel passes through the duodenum within an intestinal tube that has its distal end in proximal part of jejunum(PEG-J)
- Portable, programmable infusion pump (CADD Legacy® Duodopa Pump, Smiths Medical, St Paul, MN, USA)
- Cassette 100ml gel: 2000 mg Levodopa, 500 mg carbidopa, weight 500g

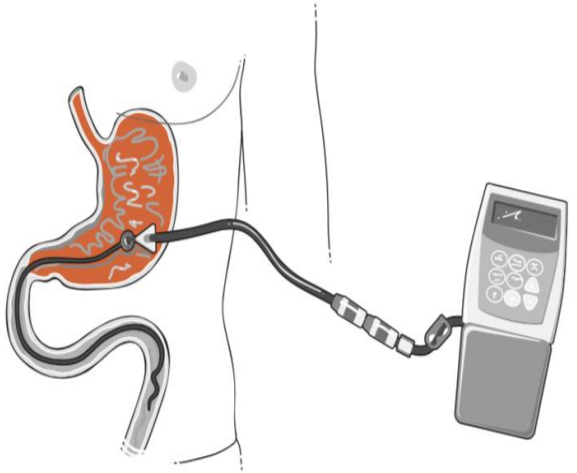


A: Pump
B: Duodopa cassette
C: PEG
D: Intestinal tube

Administration of LCIG

- Nasoduodenal phase before initiating the final equipment
- 16h regimen +++ / Continuous treatment
- Total daily dose :
  - morning bolus dose: 100–200 mg L-dopa, effect within 10-30 min
  - continuous dose: 20–200 mg/h, titrated after response to the clinical symptomatology, 1 to 2 week inpatient stay
  - extra bolus dose at demand: 10–40 mg
- Monotherapy / additional treatment





The “Ideal” Patient

Indications

- Severe motor fluctuations (more than 1–2 h of off) and dyskinesia with insatisfactory results in spite of at least 5 doses of peroral L-dopa per day
- Dyskinesia not required in the US license
- High age, depression: not excluded

Relative contraindications

- Pre-existing peripheral neuropathies
- Previous or current dopamine dysregulation and punding
- Moderate to severe dementia
- Patient frailty
- Concurrent medications that may cause orthostatic hypotension
- Well-controlled wide angle glaucoma
- Severe CV or pulmonary disease, renal, hepatic or endocrine disease, ulcers, convulsion

Absolute Contraindications

- Hypersenitivity to levodopa-carbidopa
- Lack of levodopa response
- Absolute or relative contraindications to abdominal surgery
- Narrow angle glaucoma
- Severe heart failure, cardiaarrhythmia
- Acute stroke
- Non selective-MAO inhibitors, IMAO type A
- Conditions in which adrenergics are contraindicated: pheochromocytoma, hyperthyroidism, Cushing’s syndrome.
- History of melanoma.
- Inability of patient and caregiver to handle medication and device

J Virhammar and Dag Nyholm, Ther Adv Neurol Disord (2017)
M.J. Catalán et al, eNeurologicalSci 8 (2017)

Beneficial effects

GLORIA Registry 2017
24-month, multinational, prospective, non- interventional, observational registry, 357 patients

Motor symptoms

••At least, 50% reduction in off time at every study visit

•• Significant and sustained reductions in "On" time with dyskinesia by 25% despite increase in LED over the 24 months follow up period

Non motor symptoms

• NMSS total score significantly reduced at all study visits

•At last visit, 5/9 NMSS domain scores were significantly reduced compared to baseline: cardiovascular, sleep/fatigue,

mood/cognition, gastrointestinal tract, miscellaneous

QoL (PDQ8)

Significantly improved **at every study visit**

Antonini, Poewe, et al. Parkinsonism and Related Disorders 2017 Dec;45:13-20

Safety

Integrated data from 4 studies *(Lang et al, Mov Disord 2016)*

412 patients, median exposure 911 days, Total exposure 963 patient-years

Procedure/device adverse events

- 76% patients, Titration and maintenance periods
- Most common in > 5% of patients :
  - Device insertion: 41%
  - Abdominal pain: 36%
  - Procedural pain: 27%
  - Postoperative wound infection: 26%
  - Incision site erythema: 22%
  - Excessive granulation tissue: 22%
  - Procedural site reaction: 16%
- Serious AEs occurring in > 1% : 17%
  - Device insertion: 8%
  - Abdominal pain: 4%
  - Peritonitis : 2, 8%
  - Device dislocation, Pneumoperitoneum : 2,3%
- Possibly related death: 0,5%

Non procedure/device adverse events

- 92% of patients, Maintenance period +++
- Most common in > 10% of patients :
  - Insomnia, falls +++: both in 23%
  - Constipation: 20%
  - Nausea: 20%
  - Urinary tract infection : 17%
  - Vitamin B6 decreased : 16%
  - Anxiety: 15%
  - Dyskinesia:15%
  - Weight decreased: 14%
  - Blood homocysteine increased:14%
- Serious AEs occurring in > 1% : 42%
  - Pneumonia: 5%
  - Polyneuropathy: 5,8%
  - Hip fracture, Weight decreased: 2,4%
  - Death: 1,2%

Which device should be used? Treatment decisions

- Overlapping indications / Differences in exclusion criteria

- Assessing patient's suitability on a case by case:
    - Response to optimal oral therapy
    - Comorbidities
    - Caregiver support, and patient/caregiver preference
    - Costs

- No definitive criteria for one device over another

- No RCTs directly comparing device-aided therapies, but expert consensus opinions discussing the pros and cons of each approach have been published

International Parkinson and MDS EBM Review, 2018
Pan-European Educational Program, 'Navigate PD', 2015

- **Cognitive decline:**
  - Related to non-motor fluctuations: indication for device-aided therapies.
  - Mild cognitive impairment: DBS with caution, LCIG or SC apomorphine if adequate caregiver support
  - Cognitive impairment or dementia: LICG
- **Balance problems** due to dyskinesias or levodopa-responsive postural instability: all 3 devices
- **Off fluctuations**: comparable effetcs , although for SC apomorphine, only data from uncontrolled studies
- **Dyskinesias:** effects of 3 therapies, best documented with DBS
- **Age:**
  - < 70 years with motor fluctuations or dyskinesias: any of the device
  - > 70 years: DBS is a second-line among the device-aided therapies (although patients can be operated on in the presence of a normal MRI and preserved cognitive function)
  - > 70 years with mildly or moderately impaired cognition (or other contraindications to DBS): LCIG infusions or SC apomorphine

Odin P et al, Parkinsonism and Related Disorders (2015)

- **NMS**
  - Without fluctuations: not considered as a specific indication for device-aided therapies
  - However, clinical experience and some clinical data suggest that NMS, particularly those with a dopaminergic basis, respond.
  - NMS might be considered for helping select the type of device-aided therapy in individual cases

- **Dafsari et al, 2019:**
  - First report of motor, nonmotor, and QoL outcomes in patients with PD undergoing bilateral STN-DBS, LCIG, and APO infusion treatment in a real-life observational design
  - Beneficial effects of all three treatment on global NMS burden and specific aspects of NMS
  - STN-DBS, LCIG: total NMS burden
  - APO infusion: neuropsychological and neuropsychiatric NMS domains

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