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 frequent 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

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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

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

## Contraindications

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

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## 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
- Hypersensitivity to levodopa-carbidopa
- Lack of levodopa response
- Absolute or relative contraindications to abdominal surgery
- Narrow angle glaucoma
- Severe heart failure, cardioarrhythmia
- 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)
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
• 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 effects, 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

• 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
References


• Maria José Catalán, Angelo Antonini, Matilde Calop et al. Can suitable candidates for levodopa/carbidopa intestinal gel therapy be identified using current evidence? eNeurologicalSci 8 (2017) 44–53


• Regina Katzenschlager, Werner Poewe, Olivier Rascol et al. Apomorphine subcutaneous infusion in patients with Parkinson’s disease with persistent motor fluctuations (TOLEDO): a multicentre, double-blind, randomised, placebo-controlled trial. Lancet Neurol 2018 Sep;17(9):749-759


