K Ray Chaudhuri

Parkinson’s Foundation Centre of Excellence at King’s College Hospital and King’s College London London, UK
THE GUIDING PRINCIPLES OF INITIATING LCIG

• Selection of the “right” patient
  Motor and Nonmotor aspects, Functional aspects
  The 5-2-1 paradigm, Navigate PD real life guidelines

• NG tube vs direct implantation

• Medium and Long term aims
  • Managing Expectations
  • Carer perspectives

• Provision for continuing care locally

• MDT team and dedicated gastroenterologist
Non-motor features of Parkinson disease

Anthony H. V. Sadowski!, K. Ray Chaudhuri! and Peter Jenner!

Advanced Parkinson’s?
Advanced Parkinson’s or “complex phase” Parkinson’s disease? 
Re-evaluation is needed

Nataliya Titova¹ · Pablo Martínez-Martín² · Elena Katunina¹ · K. Ray Chaudhuri³
Among 1,300 patients who were classified as having advanced PD:

- **73–74%** never received information from their treating doctor about the different treatment options for advanced Parkinson’s disease.
- **74–81%** were aware of the different treatment options for advanced Parkinson’s disease.
- **61%** indicated that they were interested in being evaluated as to suitability for treatment with one of the advanced treatment options.

Candidates for invasive techniques require more informational support from a doctor.
The patient perspective: Parkinson’s disease (PD) symptoms

- In a study of 265 outpatients with PD in the UK, participants were asked to name the three most troublesome symptoms they experienced in the past 6 months.

### EARLY PD Group
(<6 years of PD symptoms)

<table>
<thead>
<tr>
<th>Rank</th>
<th>Symptom</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Slowness</td>
<td>51.1</td>
</tr>
<tr>
<td>2</td>
<td>Tremor</td>
<td>42.4</td>
</tr>
<tr>
<td>3</td>
<td>Stiffness</td>
<td>43.5</td>
</tr>
<tr>
<td>4</td>
<td>Pain</td>
<td>25.0</td>
</tr>
<tr>
<td>5</td>
<td>Loss of smell/taste</td>
<td>16.3</td>
</tr>
</tbody>
</table>

### ADVANCED PD Group
(>6 years of PD symptoms)

<table>
<thead>
<tr>
<th>Rank</th>
<th>Symptom</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fluctuating response to medication</td>
<td>28.3</td>
</tr>
<tr>
<td>2</td>
<td>Mood</td>
<td>28.3</td>
</tr>
<tr>
<td>3</td>
<td>Drooling</td>
<td>21.4</td>
</tr>
<tr>
<td>4</td>
<td>Sleep</td>
<td>23.1</td>
</tr>
<tr>
<td>5</td>
<td>Tremor</td>
<td>17.3</td>
</tr>
</tbody>
</table>

†Answers were weighted according to their ranking: most troublesome symptom was given 3 points, second most troublesome symptom was given 2 points, third most troublesome symptom was given 1 point.

‡Rankings were based on the weighted sum for each symptom.

APD, advanced Parkinson’s disease; PD, Parkinson’s disease.

Carers of People living with Parkinson, the 2019 European realities
Helene Rossinot MD MPH¹, Pablo-Martinez Martin², Per Odin MD PhD³, K Ray Chaudhuri DSc FRCP MD⁴, Catherine Billoet MD⁵, Susanna Lindwall⁶

Presented: Virtual Movement Disorders Congress, USA 2020
Treatment should be selected based on symptoms not stage\textsuperscript{1-3}

This is often around H&Y stage 3...end-stage disease is too late!
Течение БП: от стабильного ответа на ДА-препараты до развития моторных осложнений

Indications

**LCIG:**
- Severe disease
- Pronounced motor fluctuations
- Dyskinesias
- Nocturnal akinesia

**LCIG:**
- Young/Heathy aged
- No dementia
- Troublesome fluctuations

**LCIG:**
- Pronounced dementia
- Lack of levodopa response
- Inability to handle device
- Contraindications for abdominal surgery
Patients with dyskinesia and motor fluctuations that can no longer be controlled by oral medication

Clinical Considerations in Advanced Therapy Patient Selection

- **CSAI**
  - Age: No age limitation (caveat: hallucinations and psychosis in patients aged > 70 years)
  - Psychiatric status: No limitation; however, careful monitoring is advisable
  - Cognitive impairment: No or mild cognitive impairment
  - Follow-up treatment: Technical adjustments by patients or caregiver possible, regular check by physician

- **LCIG**
  - Age: No age limitation
  - Psychiatric status: No limitation, but treat patients with past/current psychosis with caution
  - Cognitive impairment: No limitation, nurse/caregiver support advisable in case of suspected or diagnosed dementia
  - Follow-up treatment: Technical adjustments by patients or caregiver possible, regular check by physician

- **DBS**
  - Age: Patients should not be older than 70 years
  - Psychiatric status: No psychiatric medical history
  - Cognitive impairment: No cognitive impairment (MMSE > 24)
  - Follow-up treatment: Technical adjustments only by physician

**MMSE**: Mini-Mental State Examination

2. Duodopa intestinal gel - Summary of Product Characteristics (SPC).
Investigations to Consider Before Advanced Therapy

- Patient history
- General physical/neurological examination
- Patient diary/Wearable Sensor Record
- L-dopa challenge (if doubt about responsiveness)
- Evaluation by:
  - Physiotherapy
  - Occupational therapy
  - Speech therapy
  - Abdominal Xray (constipation)
- Individual investigations depending on health status
  - Vit B12, Folate, Homocysteine
  - ?? Wearable Sensor Recording
  - ? NCS in low body weight subjects

Need to use a wearable sensor?
PKG: Indication for Advanced Therapy

- 8 doses L-dopa per day
- Oral medications causing peak dose dyskinesia
- Bradykinesia with a number of unpredictable “off” periods
- Extreme fluctuations from “on” with bradykinesia IV to “off” dyskinesia IV

Which patient should not be considered for each or any device-aided therapy?

<table>
<thead>
<tr>
<th>Device-aided therapy</th>
<th>Increasing risk</th>
<th>Absolute contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBS</td>
<td>• Non-compliance with non-invasive therapies&lt;br&gt;• Biological age &gt;70–75 years&lt;sup&gt;a&lt;/sup&gt; &lt;br&gt;• Severe depression&lt;br&gt;• Condition that increases surgical risk, including cardiomyopathy</td>
<td>• Lack of levodopa response, with the exception of rest tremor&lt;br&gt;• Dementia&lt;br&gt;• Severe brain atrophy or lesions interfering with trajectory planning</td>
</tr>
<tr>
<td>SC apomorphine</td>
<td>• Non-compliance with non-invasive therapies&lt;br&gt;• MCI or dementia&lt;br&gt;• Previous or current dopamine dysregulation, punding or impulse control disorders&lt;br&gt;• Moderate-to-severe dementia</td>
<td>• Lack of levodopa response&lt;br&gt;• Inability of patient and caregiver to handle medication and device</td>
</tr>
<tr>
<td>LCIG infusion</td>
<td>• Non-compliance with non-invasive therapies&lt;br&gt;• Pre-existing peripheral neuropathies&lt;sup&gt;c&lt;/sup&gt;&lt;br&gt;• Previous or current dopamine dysregulation and punding&lt;br&gt;• Moderate-to-severe dementia&lt;br&gt;• Patient frailty (unable to support device weight)</td>
<td>• Lack of levodopa response&lt;br&gt;• Inability of patient and caregiver to handle medication and device&lt;br&gt;• Absolute or relative contraindications to abdominal surgery</td>
</tr>
</tbody>
</table>
What is «5-2-1»?

Characteristics That Define a Patient with APD

**Motor**
1. Moderate level of troublesome motor fluctuations
2. ≥2 hours of the day with “off” symptoms
3. ≥1 hour of the day with troublesome dyskinesia
4. Moderate level of dyskinesia
5. Troublesome dysphagia
6. 5 times daily levodopa intake

**Non-Motor**
1. Mild level of dementia
2. Non-transitory troublesome hallucinations
3. Moderate level of psychosis
4. Non-motor symptom fluctuations
5. Moderate level of nighttime sleep disturbances

**Function**
1. Repeated falls (>1 fall) despite optimal treatment
2. Needs help with ADL at least some of the time
3. Not able to perform complex tasks – most of the time
4. Moderate impaired mobility

Motor Algorithm «5-2-1»

Levodopa–Carbidopa Intestinal Gel in Patients with Parkinson’s Disease: A Systematic Review

Karin Wirdefeldt\textsuperscript{1,2}, Per Odin\textsuperscript{3,4}, Dag Nyholm\textsuperscript{5}

25 studies addressing motor and Nonmotor Parkinson’s

All positive outcomes

Levodopa–Carbidopa Intestinal Gel in PD

<table>
<thead>
<tr>
<th>Study</th>
<th>Length of follow-up</th>
<th>NMSST, BL</th>
<th>NMSST, follow-up</th>
<th>NMSST, % improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Honig et al. [14]</td>
<td>6 mo</td>
<td>89.9 ± 56.5</td>
<td>39.4 ± 33.9</td>
<td>56*</td>
</tr>
<tr>
<td>Reddy et al. [39]</td>
<td>6 mo</td>
<td>113.9 ± 49.3</td>
<td></td>
<td>40*</td>
</tr>
<tr>
<td>Fasano et al. [13]</td>
<td>25 mo</td>
<td></td>
<td></td>
<td>14*</td>
</tr>
<tr>
<td>Sensi et al. [23]</td>
<td>24 mo</td>
<td>51.8 ± 37.3</td>
<td>38.0 ± 24.7</td>
<td>27*</td>
</tr>
<tr>
<td>Caceres-Redondo et al. [22]</td>
<td>24 mo</td>
<td></td>
<td></td>
<td>17*</td>
</tr>
<tr>
<td>Antonini et al. [11]</td>
<td>12 mo</td>
<td>75.3 ± 42.2</td>
<td>22.2 ± 50.6 reduction</td>
<td>29*</td>
</tr>
<tr>
<td>Bohlega et al. [49]</td>
<td>6 mo</td>
<td>237.1 ± 45.5</td>
<td>81.6 ± 25.7</td>
<td>65*</td>
</tr>
<tr>
<td>Martinez-Martín et al. [12]</td>
<td>6 mo</td>
<td>90.95 ± 45.00</td>
<td>53.66 ± 38.67</td>
<td>51*</td>
</tr>
</tbody>
</table>

BL: baseline, NMSST: Non-Motor Symptom Scale total score
* Significant ($p < 0.05$)
* Not significant
Burden of non-motor symptoms in Parkinson’s disease patients predicts improvement in quality of life during treatment with levodopa-carbidopa intestinal gel

K. Ray Chaudhuri, A. Antonini, W. Z. Robinson, O. Sanchez-Solino, L. Bergmann and W. Poewe on behalf of the GLORIA study co-investigators

Improvement of NMS baseline burden at month 24

- Worsening ≥5 score points
- Improvement/worsening <5 score points
- Improvement ≥10 score points
- Improvement ≥20 score points
- Improvement ≥30 score points

<table>
<thead>
<tr>
<th>NMS Score Range</th>
<th>0–20 (N = 28)</th>
<th>21–40 (N = 41)</th>
<th>41–60 (N = 39)</th>
<th>61–80 (N = 36)</th>
<th>&gt;80 (N = 89)</th>
<th>Total (N = 233)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement</td>
<td>18%</td>
<td>15%</td>
<td>18%</td>
<td>22%</td>
<td>28%</td>
<td>28%</td>
</tr>
<tr>
<td>≥10 score points</td>
<td>42%</td>
<td>49%</td>
<td>42%</td>
<td>47%</td>
<td>58%</td>
<td>46%</td>
</tr>
<tr>
<td>≥20 score points</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30 score points</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

EJN 2019
GLORIA: NMSS Subdomain Scores Change from Baseline

Antonini et al (2017) Parkinsonism & Related Disorders 45; 13-20

Levodopa-carbidopa intestinal gel in advanced Parkinson’s: Final results of the GLORIA registry
Angelo Antonini, Werner Poewe, K. Ray Chaudhuri, Robert Jech, Barbara Pickut, Zvezdan Pirtoski, Jozsef Szasz, Francesc Valldeoriola, Christian Winkler, Lars Bergmann, Ashley Yegin, Koray Onuk, David Barch, Per Odin on behalf of the GLORIA study co-investigators.
EuroInf 2: Comparison of apomorphine, DBS and LCIG

NMSS domains at:

- Baseline
- Follow-up

* Significant intragroup improvements of NMSS domains from baseline to follow-up
Figure 4. Percentage of Patients Requiring 0, 1, or 2 Component Replacements Occurring in the First 6 Months of Treatment Based on Type of Proceduralist that Performed the PEG-J Insertion.

A. All patients (n=27):
- Gastroenterologist: 81.5%
- Interventional radiologist: 14.8%
- Others: 3.7%

B. Gastroenterologist (n=16):
- All patients: 75%
- Gastroenterologist: 90.9%
- Interventional radiologist: 7.6%
- Others: 1.9%

C. Interventional radiologist (n=11):
- All patients: 9.1%
- Gastroenterologist: 9.1%
- Interventional radiologist: 9.1%
- Others: 90.9%
LONGTERM MANAGEMENT

1. Have a functional Multidisciplinary team in place
2. Aftercare post discharge
   1. Tube care
   2. Diet
   3. Body weight monitoring
   4. “Runaway” /diphasic dyskinesias
   5. DDS
3. Practicing neurologists involved in treatment follow-up
4. Patient information & setting together realistic treatment GOALS

Odin P, Chaudhuri KR et al, Parkinsonism Relat Disord. 2015
Effect of Device-Aided Therapies on Dyskinesias
Evidence for Impact of LCIG – Diphasic Dyskinesias

Some patients receiving LCIG may experience new-onset DDs

![Image: But...]

In a chart review of 33 patients with PD treated with LCIG at a movement disorders center in Italy:

- 4 patients (12.1%) reported persistent and disabling DDs
- DD symptoms were managed by increasing morning LCIG flow and adding ER dopamine agonist and levodopa-carbidopa at bedtime
- Within 1 month, all patients presented a gradual reduction in duration and severity of DDs

DDs were also reported for 2 patients in Spain with advanced PD after 7 to 24 months with stable doses of LCIG:

- Dyskinesias occurred in lower limbs 20 to 30 minutes after morning dose, coincided with improvement in bradykinesia (“on” time), and greatly interfered with gait
- Up-titration of maintenance dose or administration of extra doses worsened the symptoms; down-titration had no effect

DD, diphasic dyskinesia; ER, extended release.
Infusion Therapies and Development of Impulse Control Disorders in Advanced Parkinson Disease: Clinical Experience After 3 Years’ Follow-up

Antoniya Todorova, PhD,* Michael Samuel, MD, FRCP,* Richard G. Brown, PhD,†‡ and Kallol Ray Chaudhuri, DSc*†‡

<table>
<thead>
<tr>
<th>TABLE 2. Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Preexisting ICDs</td>
</tr>
<tr>
<td>Preexisting ICDs- resolved</td>
</tr>
<tr>
<td>Preexisting ICDs- attenuated</td>
</tr>
<tr>
<td>New troublesome ICDs</td>
</tr>
<tr>
<td>Treatment stopped due to ICDs</td>
</tr>
</tbody>
</table>
Post-LCIG Complications

- Stoma irritation
- Stoma pain
- Tube dislocation

Progress and Course of Action

The problems

- Weight Loss
- Reflux
- Generally Unwell
- Abdominal pain and bloating

1. Review endoscopy
   - Check Tube status

2. Check Blood for B12/Folate
   - Malabsorption markers

3. Analgesia
   - Rule out peritoneal complications
   - Rule out constipation
Long-term safety and efficacy of LCIG in advanced Parkinson’s

Integrated Safety of Levodopa-Carbidopa Intestinal Gel From Prospective Clinical Trials

Anthony E. Lang, MD, FRCP,1 Ramon L. Rodriguez, MD,2 James T. Boyd, MD,3 Sylvain Chouinard, MD, FRCP,4 Cindy Zadkoff, MD,5 Alberto J. Espay, MD,6 John T. Stevin, MD, MBA,7 Hubert H. Fernandez, MD,8 Mark F. Lew, MD,9 David A. Stein, MD,10 Per Odin, MD, PhD,11 Victor S.C. Fung, MBBS, PhD, FRACP,12 Fabian Klostermann, MD, PhD,13 Alfonso Fasano, MD, PhD,14 Peter V. Draganov, MD,2 Nathan Schmelzleit, MD,6 Weinig Z. Robieson, PhD,15 Susan Eaton, PharmD,14 Kari Chatamra, PhD,17 Janet A. Beneah, BSMT,17 and Jordan Dubow, MD14

a. Prevalence of procedure/device associated AEs reported by ≥5% of subjects (All PEG-J)

- Complication of Device Insertion
- Abdominal Pain
- Procedural Pain
- Postoperative Wound Infection
- Excessive Granulation Tissue
- Incision Site Erythema
- Incision Site Pain
- Abdominal Discomfort
- Reaction

b. Prevalence of procedure/device associated SAEs reported by ≥1% of subjects (All PEG-J)

- Complication Device Insertion
- Abdominal Pain
- Peritonitis
- Pneumoperitoneum
- Device Dislocation
- Postoperative Wound Infection
- Small Intestinal Obstruction
- Device occlusion

Time Post-PEG Procedure (days)

n = 395 375 356 348 342 298 254 244 237 222 218 202 186
Device aided therapies may reduce comedication: Evidence for LCIG

- Results from a 2-center, retrospective, open-label study of 14 patients receiving LCIG\(^1\)
- Follow-up at 24.9 ± 14.4 months (range, 6-52 months)

\(\text{LEDD (mg/d)}\)

<table>
<thead>
<tr>
<th></th>
<th>PRE</th>
<th>POST</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1500 ± 300</td>
<td>1000 ± 200</td>
<td>.01</td>
</tr>
<tr>
<td>Levodopa</td>
<td>900 ± 150</td>
<td>700 ± 130</td>
<td>.02</td>
</tr>
<tr>
<td>Dopamine agonist</td>
<td>60 ± 15</td>
<td>30 ± 10</td>
<td></td>
</tr>
</tbody>
</table>

Number of pills taken daily:

- PRE: 9.7 ± 5.5
- POST: 1.7 ± 2.0 \((P = .00001)\)

But beware of DAWS

In the GLORIA study, \textbf{36\% to 40\%} of the 375 enrolled patients achieved monotherapy with LCIG over 2 years\(^2\)

LCIG, levodopa-carbidopa intestinal gel;
• First real-life case series of PD patients with COVID-19

• **Older PD patients with comorbidity and possibly those on advanced therapies should be recognised as a high-risk group (three in this series on IJI died)**

• **Motor and non-motor features, such as anxiety, fatigue, orthostatic hypotension, cognitive impairment, and psychosis, worsened during the infection**

• Need for setting a roadmap for health care professionals to the specific needs and therapeutic decisions required to personalise management
Patient selection is the key

An experienced MDT team is important to maintain therapy

A dedicated gastroenterologist enhances outcome

Consideration motor, nonmotor issues at baseline and managing expectations as well as carer issues are important

Baseline parameters may predict medium term and long term management (body weight, carer support, personality, diet)