Understanding the Advanced Treatments in Parkinson's Disease

Onanong Phokaewvarangkul, MD, PhD.

Assistant Professor of Neurology, Chulalongkorn Centre of Excellence for Parkinson's Disease and Movement Disorders, Chulalongkorn University and King Chulalongkorn Memorial Hospital

Working Definition

The definition of Advanced Treatments for Parkinson's disease in this talk will cover solely on device-aided therapies. Device-aided therapies refer to subcutaneous infusion of apomorphine and levodopa-carbidopa intestinal gel infusion (LCIG), and functional neurosurgical intervention, including ablative surgery and deep brain stimulation (DBS).

Outline of Talk

- Understanding on device-aided therapy strategies for Parkinson's disease
- In-depth understanding of Apomorphine treatment
- In-depth understanding of Levodopa-carbidopa intestinal gel treatment
- In-depth understanding of functional neurosurgery
- The impact of COVID-19 pandemic and device-aided therapy patients
- How to implement device-aided therapy in clinical practices

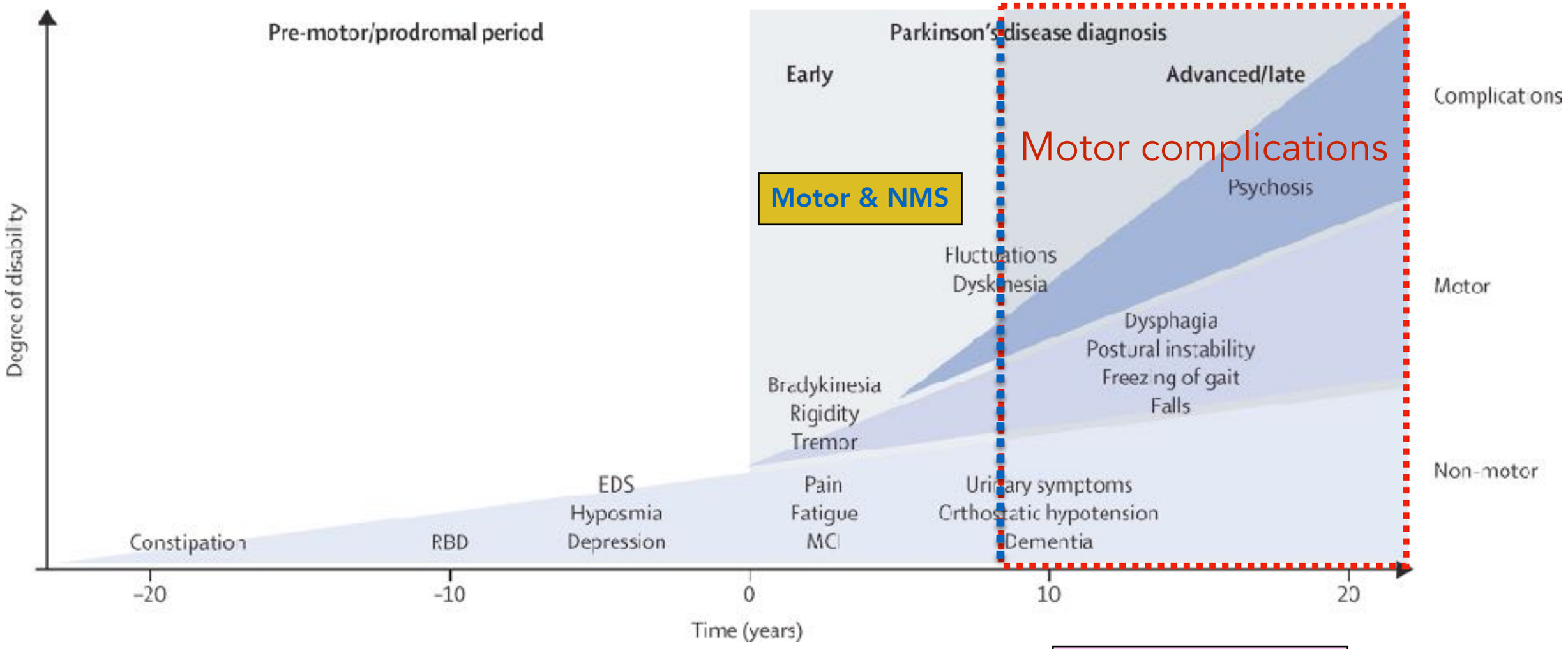
1

Understanding device-aided treatment strategies for Parkinson's disease

When should physicians recommend device-aided therapy for PD patients?

Severe motor complications

Natural history of Parkinson's disease



Early stage

- Oral medication

Advanced stage

- Oral medication
- Non-oral medication
- Infusion treatment
- Surgery* (various targets)

* Ablative surgery & DBS

Kalia L, et al. Lancet 2015;386:896-912.

Early PD

Early complications

Advanced complications

Honeymoon

Predictable

Unpredictable

Oral medications

Oral medications

Patch

Apomorphine

Oral medications

Patch

Apomorphine

LCIG

DBS

Best medical therapy

* adapt from NICE guideline 2017

Central mechanism for development of motor complications

Central mechanism for development of motor complications (1)

Intermittent doses of a short-acting levodopa

Parkinson's disease progression

loss of striatal dopamine terminals (normally store dopamine and buffer)

Large and uncontrolled oscillations in striatal dopamine levels

↓

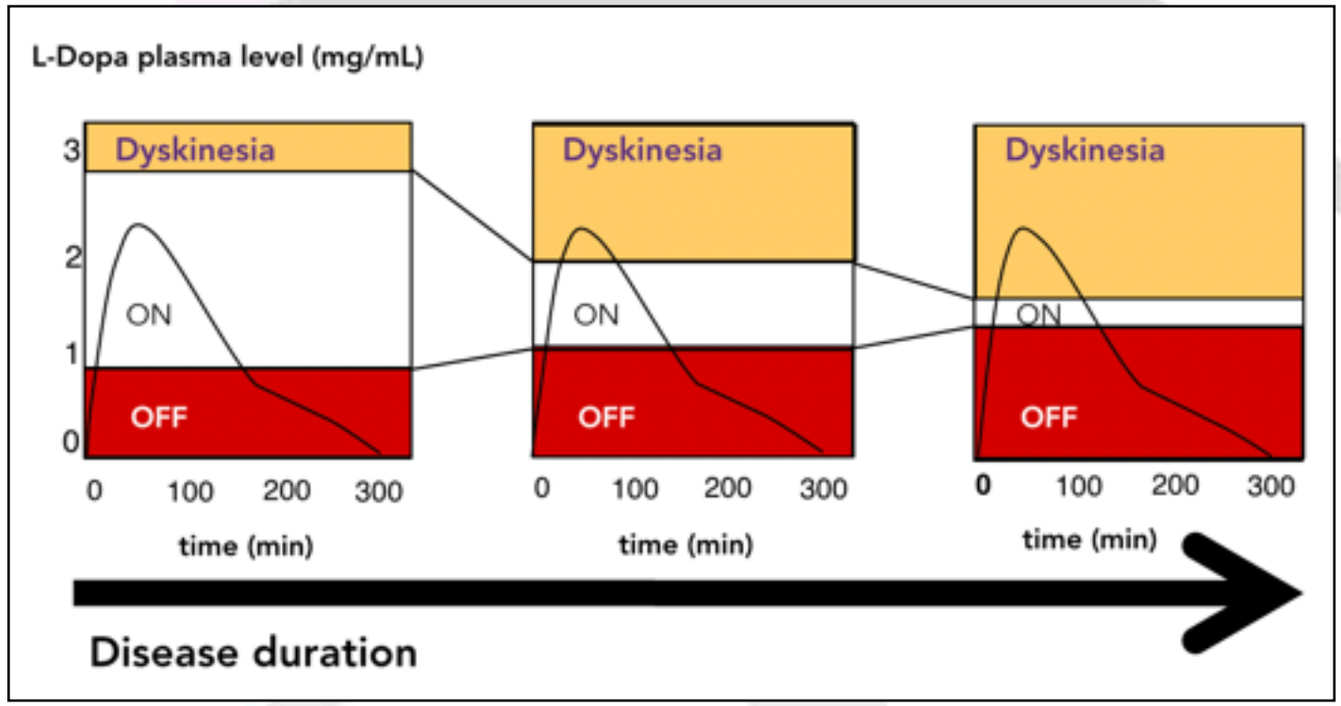
Pulsatile stimulation of striatal dopamine receptors

↓

Destabilization of the basal ganglia network

↓

Development of LD related motor complications



Change to "narrow therapeutic window"

Calabresi P, et al. Mov Disord 2008;23:S570-9.
Olanow C, et al. Nat Clin Pract Neurol 2006;2:382-92.
Stocchi F, et al. Mov Disord 2008;23:S599-S612.
Antonini A. J Mov Disord 2009;2:4-9.

Proposed infusion strategy for managing motor complications

Development of LD related motor complications

Providing more continuous dopaminergic stimulation (CDS)

Reduction in LD related motor complications

"Widening of Therapeutic Window"

Constant levodopa levels with continuous drug delivery (CDD) system of **infusion therapy (APO & LCIG)** (avoids peak and trough levels)

Additional potential benefits of CDS include

- Alleviating nocturnal disturbances
- Avoiding priming for motor fluctuations and dyskinesia
- Minimizing daytime sleepiness
- Preventing the development of GI dysfunction
- Reducing the risk of developing psychosis or behavioral disturbances

Wolters E, et al. CNS Sperrt 2008;suppl 7:1-14.
Olanow C, et al. Lancet Neurol 2006;5: 677-87.
Stocchi F, et al. Neurology 2004;62:S56-63.
Antonini A. J Mov Disord 2009;2:4-9.

Central mechanism for development of motor complications (2)

Loss of dopamine in SNc

↓

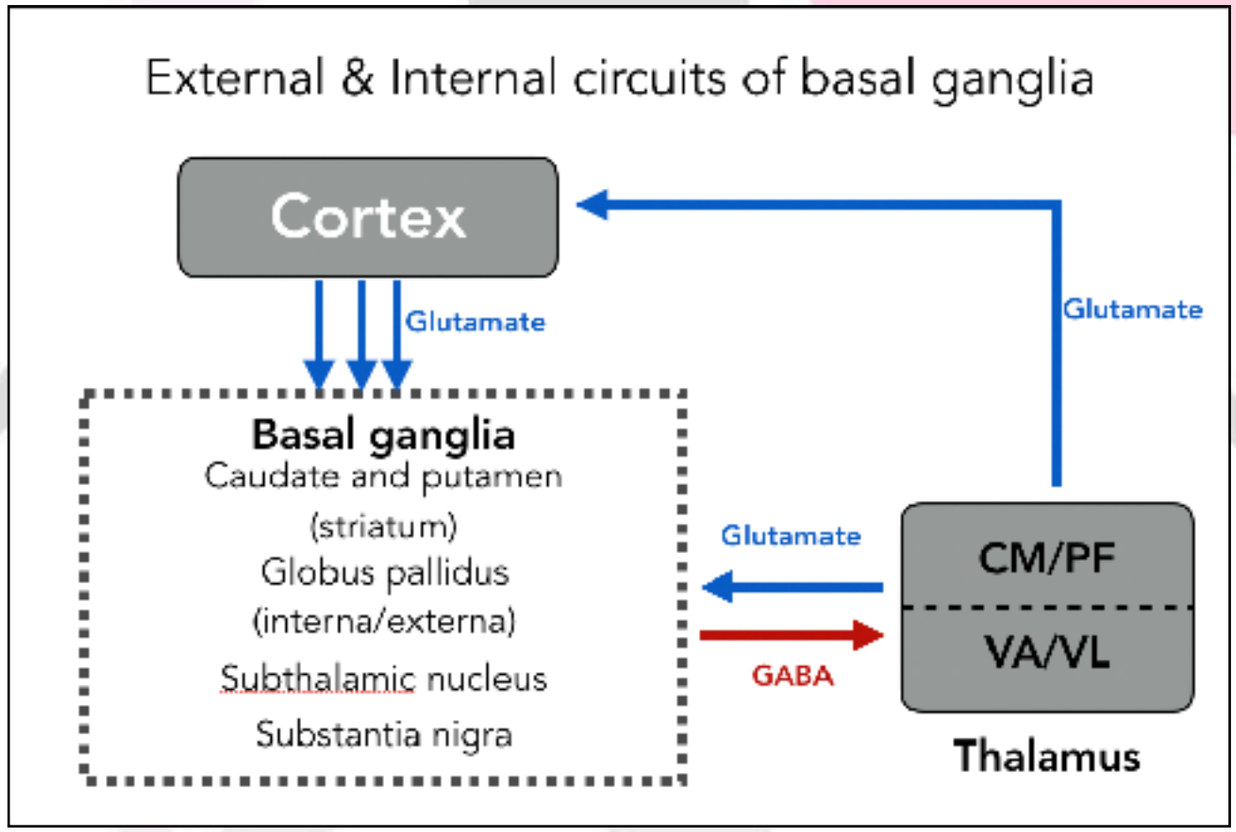
Increased activity in the output nuclei of basal ganglia (STN, GPi, Thalamus)

↓

Hypokinetic and Hyperkinetic symptoms

↓

Development of LD related motor complications



Direct and indirect pathways

Delong MR. Trends Neurosci 1990;13:281-5.
Lang A, et al. N Eng J Med 1998;339:1044-53.
Lang A, et al. N Eng J Med 1998;339:1030-43.
Obeso J, et al. Adv Neurol 1997;74:3-18.
Obeso J, et al. JNNP 1997;62:2-8.

Proposed surgical strategy for managing motor complications

Development of LD related motor complications

Lesion of the basal ganglia nuclei (STN, GPi, Thalamus, etc.)

Reduction in LD related motor complications

Surgery itself does not act directly on dopaminergic neuron, but compensate for the secondary effects of dopamine loss

Ablative surgery

Deep Brain Stimulation

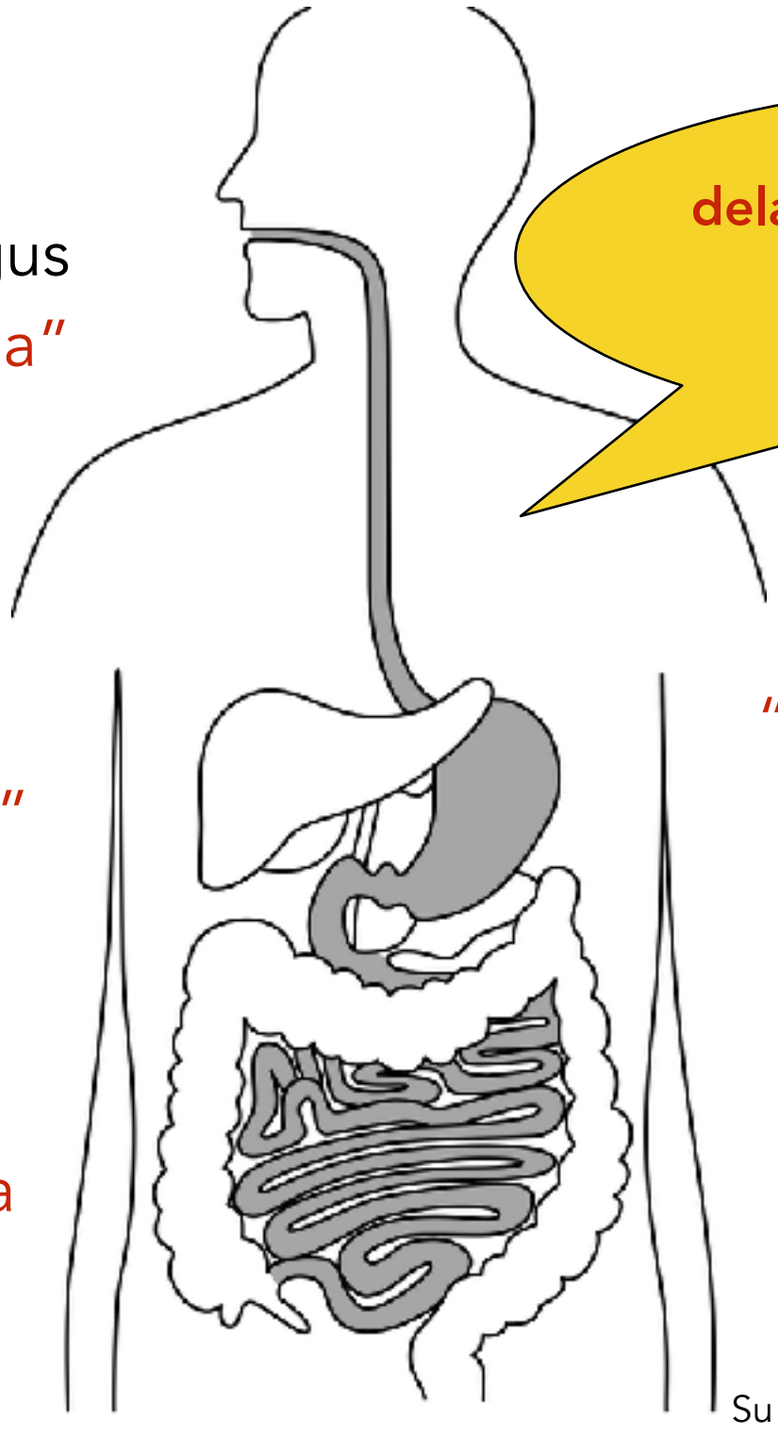
High-frequency stimulation(>100 Hz) = therapeutic effects of ablative surgery

Azis TZ, et al. Mov Disord 1991;6:288-92.
Bergman H, et al. Science 1990;249:1436-8.
Benabid A, et al. Appl. Neurophysiology 1987;30: 344-346.

Peripheral mechanism for development of motor complications

GI dysfunctions are common in PD and usually related to motor fluctuations

Oropharynx & Esophagus
"Sialorrhea & Dysphagia"



Stomach
"Gastroparesis & H.pyroli"

Small bowel
"Bacterial overgrowth"

Anorectum
"Defecatory dyssynergia
& Fecal incontinence"

Colon
"Constipation"

Su A, et al. Parkinsonism Relat Disord 2017;39:17-26.
Fasano A, et al. Lancet Neurol 2015;14:625-39.

Bypass GI strategies with device-aided therapies may be useful to overcome these problems.

Getting to know on each treatment methods

2

In-depth understanding of Apomorphine treatment

Timelines of apomorphine

1869
Apomorphine first synthesis by Matthiessen and Wright

1951
Apomorphine first used in PD

1967
Apomorphine shared structure similarity to dopamine

1979
The successful use of subcutaneous apomorphine in combination with domperidone reported

1993
Apomorphine recieves first European marketing license

1860 → 1870-1950 → 1960 → 1970 → 1980 → 1990 → 2000 → 2010

1870
Observations on apomorphine were reported in terms of benefits on involuntary movements

1970
Apomorphine confirmed as a potential treatment

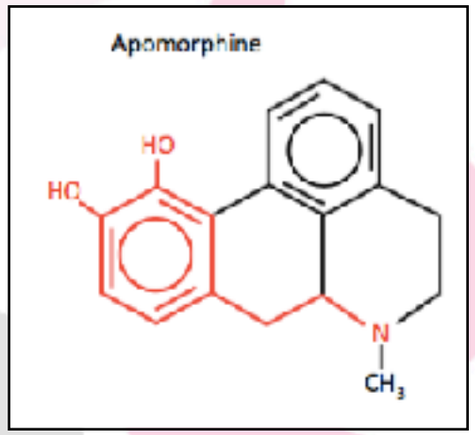
1988
Efficacy of apomorphine confirmed with 50% reduction in OFF periods up to 5 years later

2000's
Additional European and non-European marketing licences granted

Djamshidian A, et al. Parkinsonism Related Disord 2016 ;Suppl 1:S9-S12.

Apomorphine

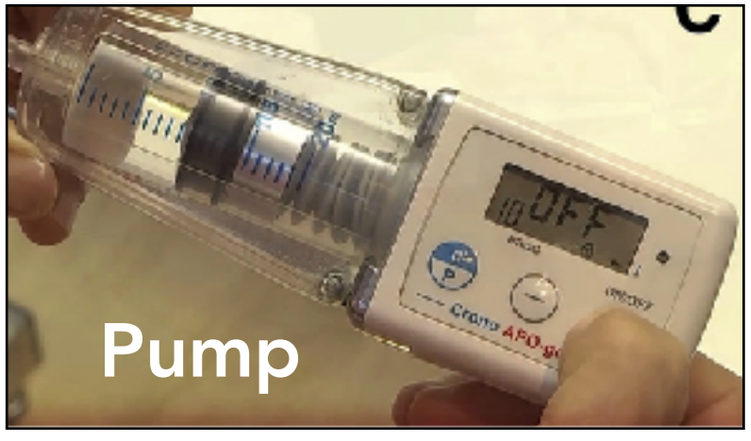
(Aporphine derivatives)



- Potent dopamine agonist (D2>D1), affinity D4>D3>D2. Highly affinity to dopaminergic, serotoninergic and adrenergic receptor.
- Powerful emetic
- Highly lipophilic and slightly water soluble, rapid transport across BBB. Rapidly absorbed, high first pass hepatic metabolism: not suitable for oral administration.
- **Subcutaneous injection*** : intermittent injection or continuous infusion
  - Peak levels achieves within 5-15 minutes, elimination half-life is 33 minutes, and a mean duration of action is lasted for 45- 60 minutes.

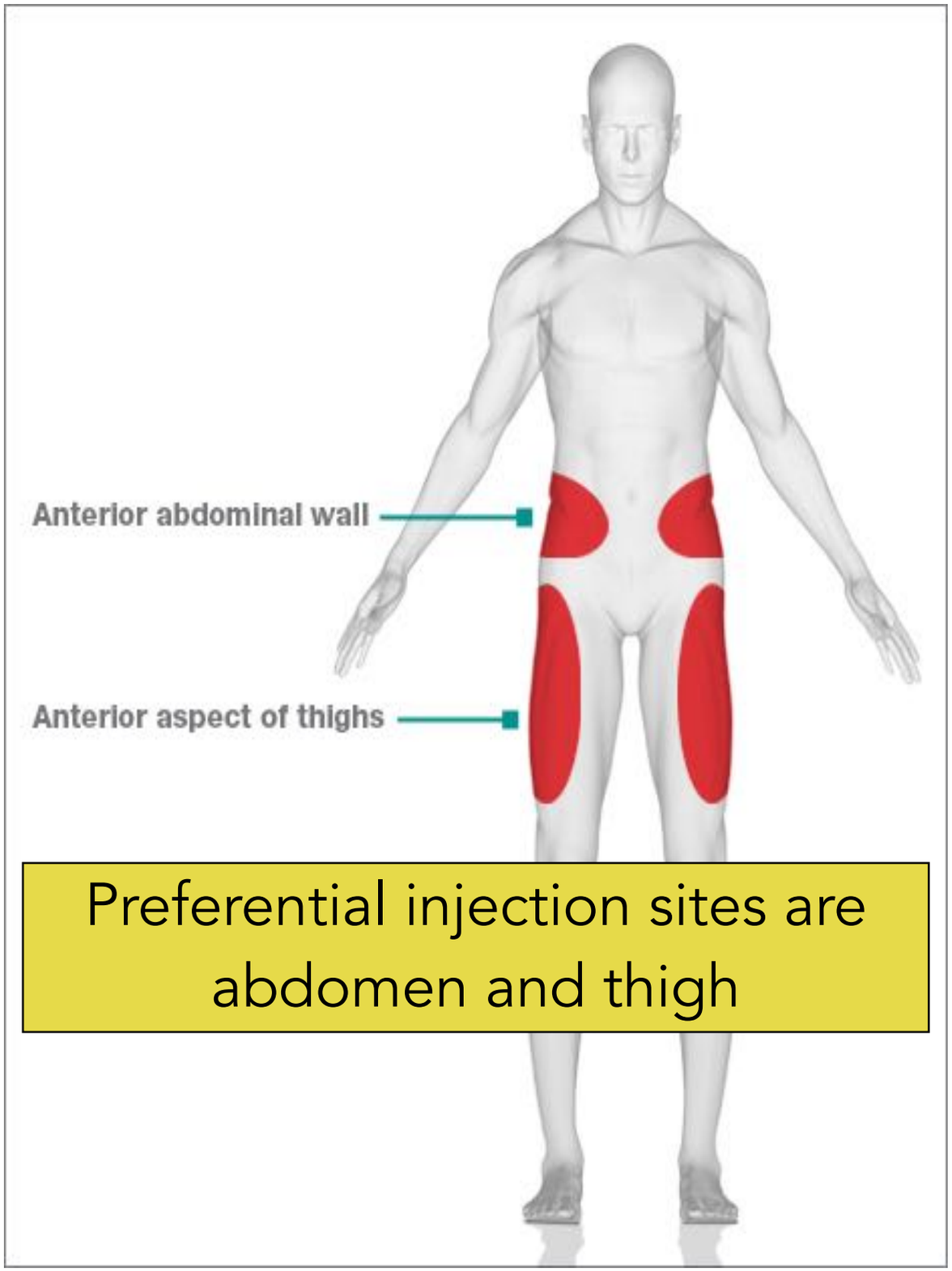
Jenner P, et al. Parkinsonism Relat Disord 2016;Suppl1:S13-S21.

Apomorphine specifications and contents

Types of injection	Continuous infusion pump	Intermittent injection pen
Indications	Motor complications despite optimized oral medications	Rescue therapy for OFF period
Contents	10 mg/ml solution 5 ml per ampule 1:1 NSS Dilution 1mg = 0.2 ml	10 mg/ml solution Each 3 ml pen = 30 mg apomorphine hydrochloride " 1 click = 1 mg " (expire time of 48 h)
Doses	Usually 4-8 mg/h Maximum 16 h per day	Start with 1-2 mg 1-10 injections per day
Equipments	 **Pump**	 **Pen**

Bhidayasiri R, et al. Parkinsonism Relat Disord 2016;33:S42-S48.

Preferential injection sites



Preferential injection sites are abdomen and thigh

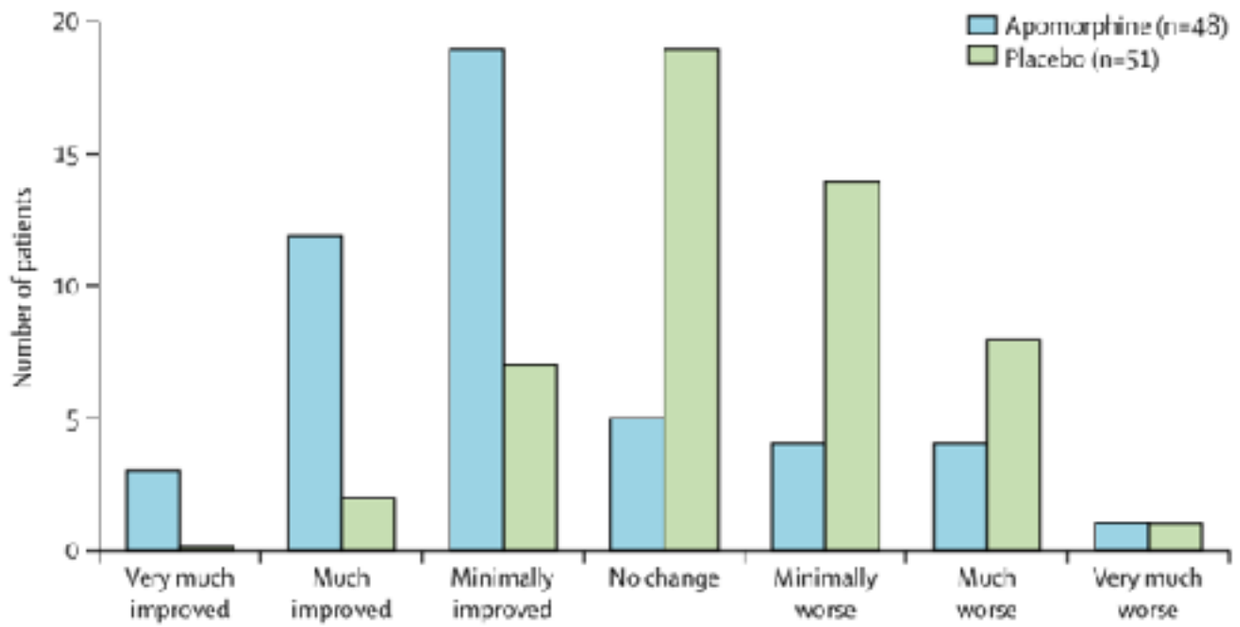
Apomorphine subcutaneous infusion in patients with Parkinson's disease with persistent motor fluctuations (TOLEDO): a multicentre, double-blind, randomised, placebo-controlled trial

Regina Katzenschlager, Werner Poewe, Olivier Rascol, Claudia Trenkwalder, Günther Deuschl, K Ray Chaudhuri, Tove Henriksen, Teus van Laar, Kevin Spivey, Senthil Vel, Harry Staines, Andrew Lees

12-week double-blind phase and the 52-week open-label phase (Apomorphine vs. Placebo)

Significant improvement in following parameters

- Reduced off time (hour per day)
- Increased on time (hour per day)
- Reduced levodopa equivalent dose (mg)
- Improved Patient Global Impression
- No any unexpected safety signals



Patient Global Impression of Change from baseline to week 12

Continuous Apomorphine infusion provide short-term benefits for PD-related symptoms

Katzenschlager R, et al. Lancet Neurol 2018;17:749-59.

Continuous Apomorphine infusion also provide long-term benefits for PD-related symptoms

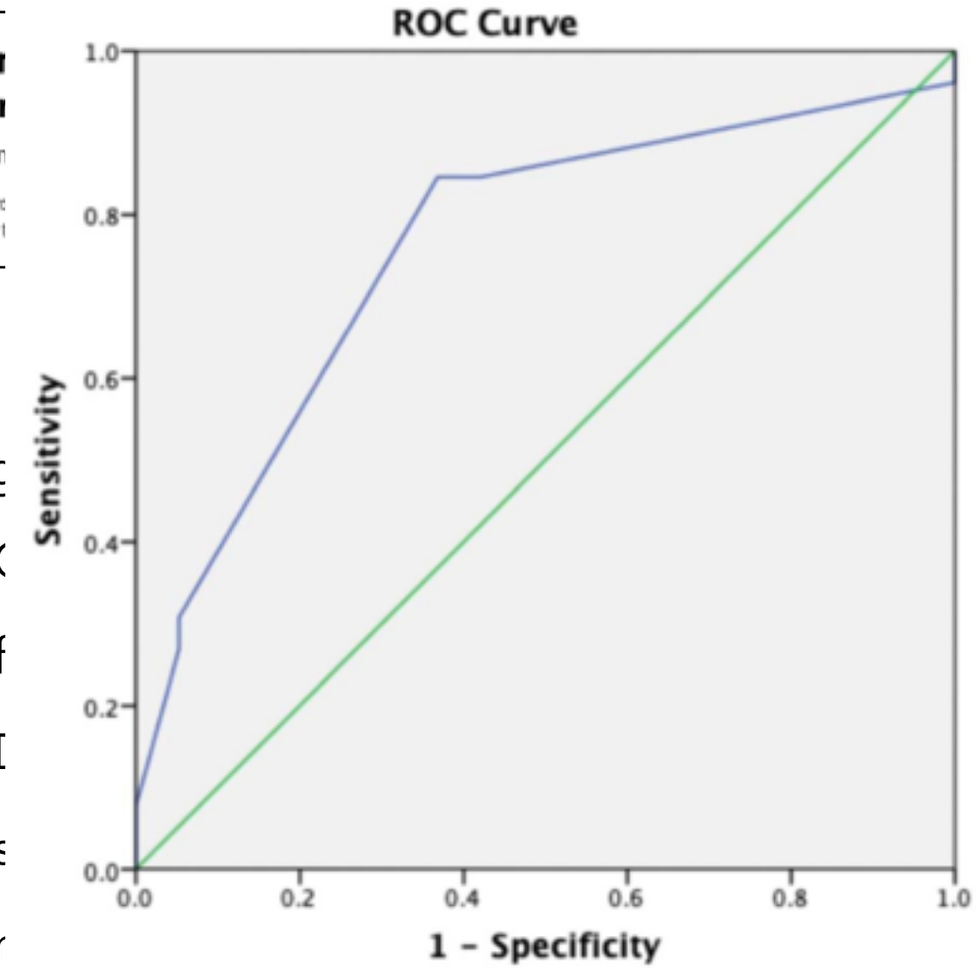
Long-term Apomorphine Infusion Users Versus Short-term Users: An International Dual-center Analysis of the Reasons for Discontinuing Therapy

Roongroj Bhidayasiri, MD, FRCP, Oranong Phokaewvarangkul, MD, PhD,* Kamoiwan Boonpang, RN,* Thanutai Boonrungkol, MD,* Yuwadee Thongchuen, MD,* Natnan Kantachadvanich, RN,* and Pedro J. Garcia Ruiz, MD†*

Thai cohort vs. Spanish cohort

Significant improvement in following parameters

- Reduced off time (hour per day)
- Reduced UPDRS motor section
- Discontinuation rate up to 60% (due to unmet satisfaction, neuropsychiatric side effects, skin nodules, dyskinesia, etc.)
- Daily off hours after APO therapy was found to be a significant predictive factor for APO discontinuation with an odd ration of 5.952*



The cutoff point that determined APO discontinuation was calculated to be 1.75 or more off hours (sensitivity, 84.6%; specificity, 63.2%).

Bhidayasiri R, et al. Clin Neuropharm 2019;42:172-8.
Kimber T, et al. Intern Med J 2017; 47:570-3.

Apomorphine adverse events

Common

- Administration site reactions
- Nausea and vomiting
- Yawning
- Sedation and somnolence
- Dizziness
- Neuropsychiatric disturbances

Uncommon

- Hemolytic anemia
- Postural hypotension
- Penile erection
- Sudden onset of sleep
- Eosinophilic syndrome
- Peripheral edema

Bhidayasiri R, et al. Parkinsonism Relat Disord. 2016.
Bhidayasiri R, et al. Clin Neuropharm. 2015.
Antonini A, et al. Parkinsonism Relat Disord. 2009.

3

In-depth understanding of Levodopa-carbidopa intestinal gel treatment

Timelines of LCIG

1961

Observations on levodopa injection were reported in terms of benefits in PD movements.

1975

The firstI investigation of levodopa IV infusion

1986

The first intraduodenal levodopa infusion used in PD

1967

Observations on oral levodopa were reported in terms of benefits in PD movements.

1994

A Company with Uppsala University become as one share-holder, was founded in 1994.

Aquilonius SM, et al. Upsala J Med Sci 2017;122:71-7.

Levodopa/carbidopa intestinal gel

- Overcome pharmacokinetic problems with gastric emptying interfering with standard oral levodopa absorption.
- Similar principles to apomorphine infusion, including: daytime monotherapy and usually initiation as an inpatient
- In comparison to standard oral LC, LCIG significantly reduced off the and increased on time without troublesome dyskinesia in advanced PD.

A 100 ml cassette contains 2000 mg of L-dopa and 500 mg of carbidopa

kurgan R, et al. Ann Neurol 1988;23: 589-95
Olanow C, et al. Lancet Neurol 2015;13:141-9
Slevin j, et al. J Parkinson Dis 2015; 5:165-74

Medication specification and content

LCIG (Duodopa) contains the following:

- Levodopa (L-dopa) 20 mg/ml
- Carbidopa 5 mg/ml
- Thickening agent (Carmellose sodium)

A 100 ml cassette contains 2000 mg of L-dopa and 500 mg of carbidopa (1 ml contains 20 mg L-dopa and 5 mg carbidopa)

Shelf-life

LCIG has the following shelf-life: 15 weeks in refrigerator

Once out of the refrigerator LCIG must be used immediately within the first 24 hours. After this period of time, the active ingredients suffer natural degradation. A typical signal of degradation is an altered color of the LCIG gel.

How to administer the LCIG?

Calculate daily consumption

Daily consumption is the sum of the following

- Morning dose (ml)
- Continuous maintenance dose/infusion rate (ml/hour) multiplied by the time in hours.
- Extra doses (ml)

Each Drug Cassette is for single use.
Should not be used longer than 16 hours

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

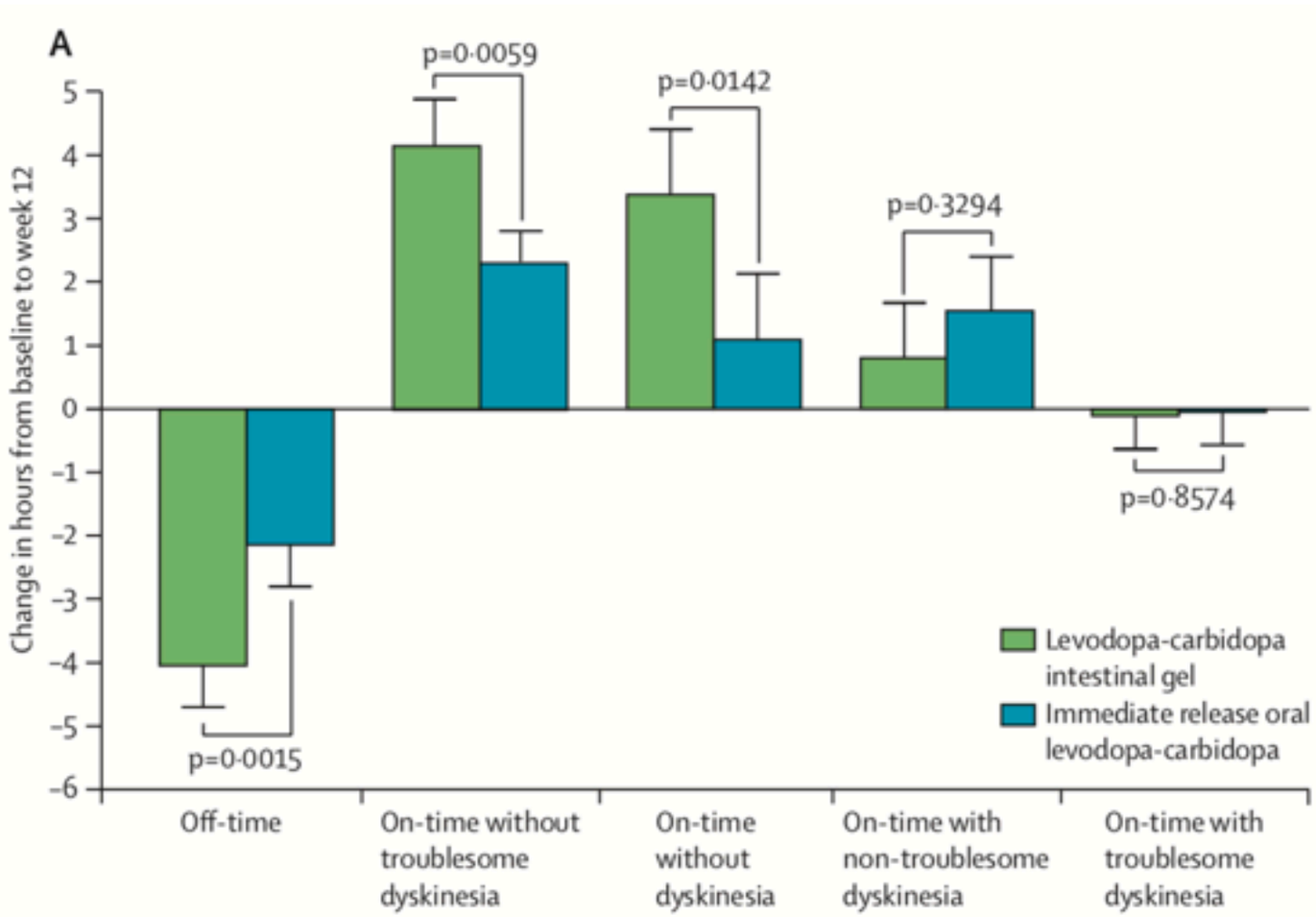
C Warren Olanow, Karl Kieburtz, Per Odin, Alberto J Espay, David G Standaert, Hubert H Fernandez, Arvydas Vanagunas, Ahmed A Othman, Katherine L Widnell, Weining Z Robieson, Yili Pritchett, Krai Chatamra, Janet Benesh, Robert A Lenz, Angelo Antonini, for the LCIG Horizon Study Group

12-week double-blind study (Oral LD +LCIG vs. Oral LD + Placebo gel)

Significant improvement

- Reduced off time (hour per day)
- Increased on time (hour per day)
- Improved PDQ-39 (QOL)
- Improved clinical global impression-improvement (CGI-I)

63 (89%) of patients had device-related complications



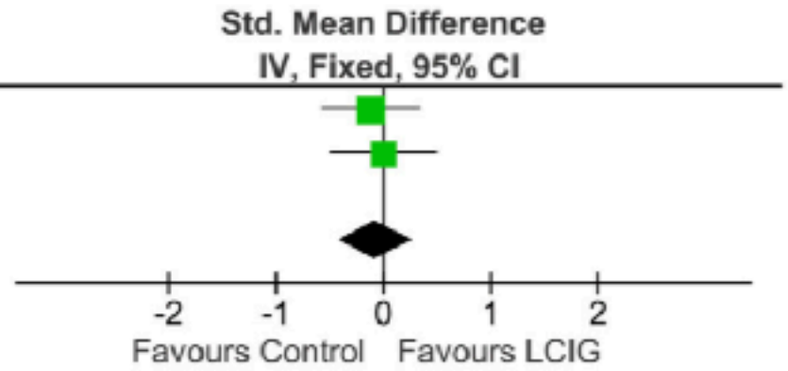
Olanow C, et al. Lancet Neurol 2014;13:141-9.

Levodopa-Carbidopa Intestinal Gel in Parkinson's Disease: A Systematic Review and Meta-Analysis

A

On time with troublesome dyskinesia	LCIG Mean	LCIG SD	LCIG Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Olanow et al. 2014	1	1.6	37	1.2	1.7	34	53.4%	-0.12 [-0.59, 0.35]	2014
Slevin et al. 2015	1.06	2.04	33	1.06	1.73	29	46.6%	0.00 [-0.50, 0.50]	2015
Total (95% CI)			**70**			**63**	**100.0%**	**-0.06 [-0.40, 0.28]**	

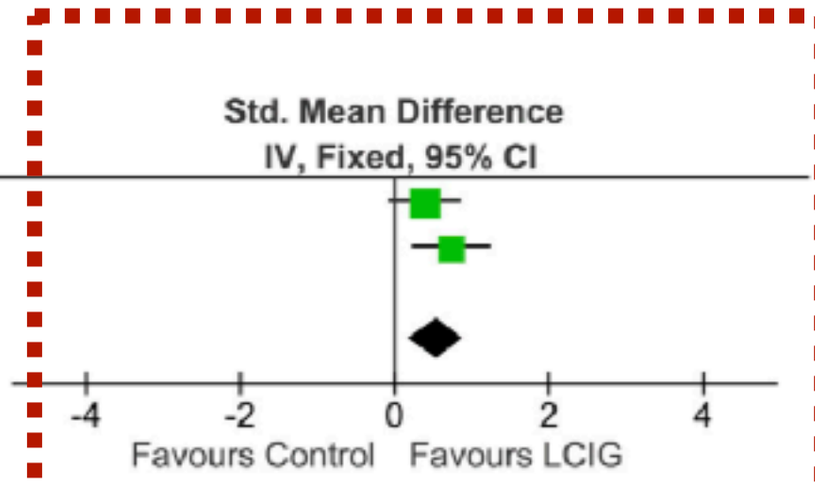
Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)



B

On time without troublesome dyskinesia	LCIG Mean	LCIG SD	LCIG Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Olanow et al. 2014	8.7	2	37	7.8	2.5	34	54.7%	0.40 [-0.08, 0.87]
Slevin et al. 2015	11.83	2.68	33	9.86	2.61	29	45.3%	0.73 [0.22, 1.25]
Total (95% CI)			**70**			**63**	**100.0%**	**0.55 [0.20, 0.90]**

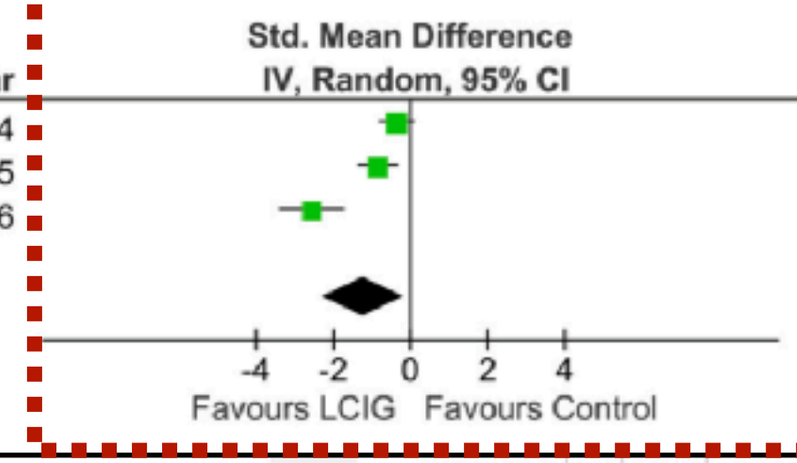
Heterogeneity: Chi² = 0.91, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 3.09 (P = 0.002)



C

Off time	LCIG Mean	LCIG SD	LCIG Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Olanow et al. 2014	6.3	1.8	37	7	2.1	34	35.1%	-0.36 [-0.82, 0.11]	2014
Slevin et al. 2015	3.11	2.56	33	5.08	2.03	29	34.6%	-0.84 [-1.36, -0.31]	2015
Merola et al. 2016	0.8	0.7	20	2.5	0.6	20	30.3%	-2.56 [-3.41, -1.70]	2016
Total (95% CI)			**90**			**83**	**100.0%**	**-1.19 [-2.25, -0.12]**	

Heterogeneity: Tau² = 0.78; Chi² = 19.54, df = 2 (P < 0.0001); I² = 90%
Test for overall effect: Z = 2.19 (P = 0.03)



Wang L, et al. Front Neurol 2018

LCIG adverse events

Reported Adverse Reactions for Naso-Jejunal Tube (NJ)

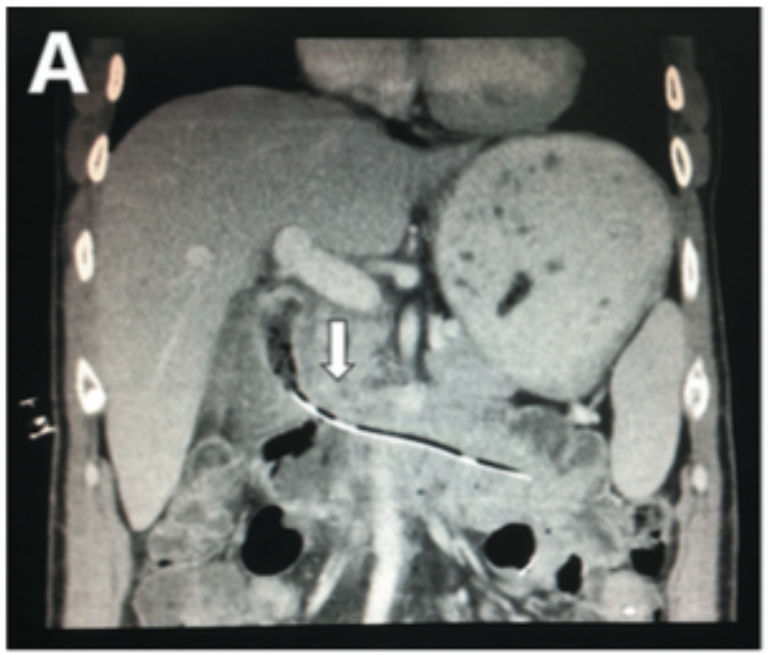
- Oropharyngeal pain
- Abdominal distention, abdominal pain, abdominal discomfort, pain, throat irritation
- Gastrointestinal injury, esophageal hemorrhage
- Anxiety, dysphagia, and vomiting

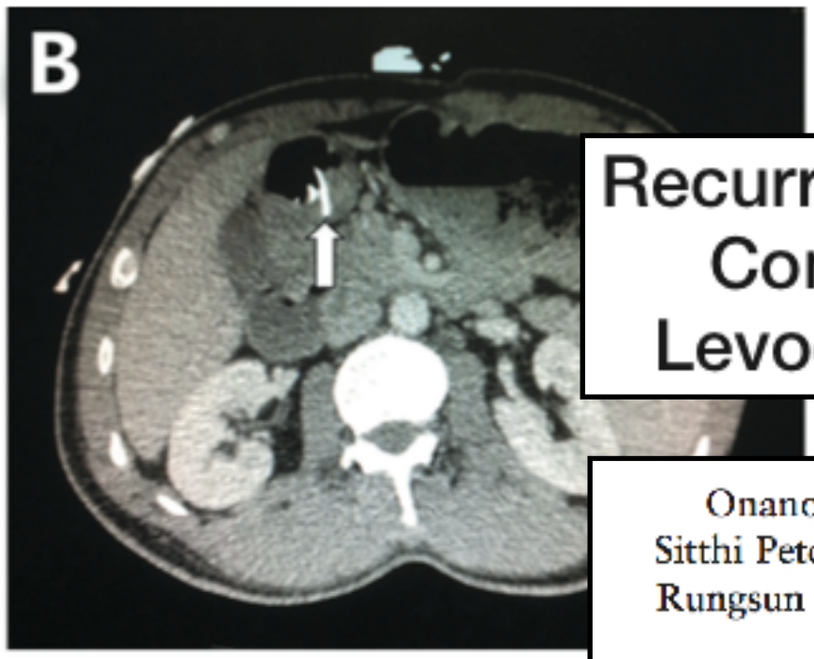
Reported Adverse Reactions for PEG/J

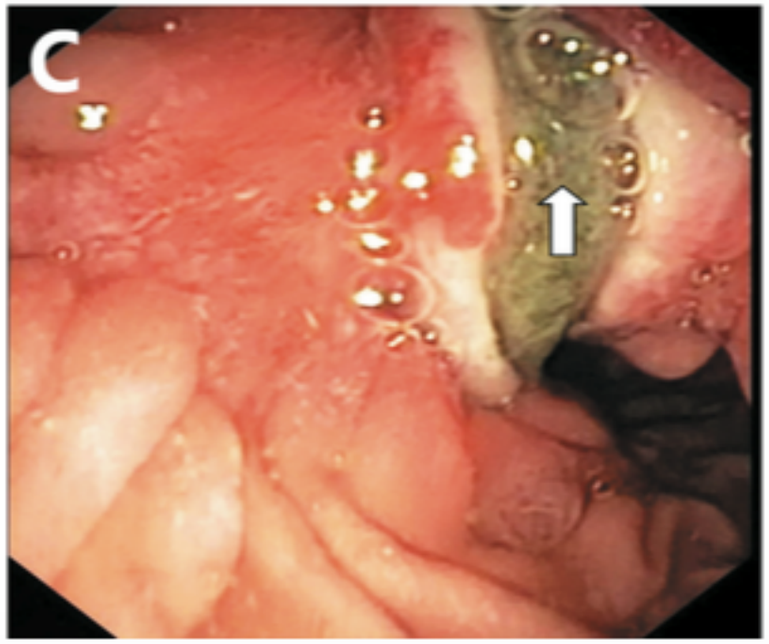
- Abdominal pain, abdominal discomfort, abdominal distension, flatulence, or pneumoperitoneum.
- Dislocation of the intestinal tube backward into the stomach or obstruction in the device leads to reappearance of motor fluctuations

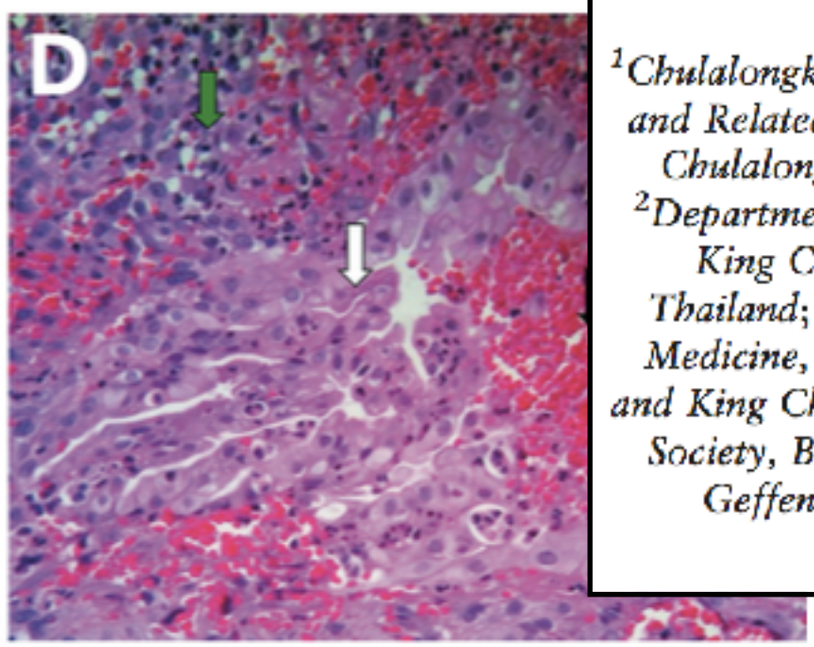
Olanow C, et al. Lancet Neurol 2015;13:141-9
Slevin j, et al. J Parkinson Dis 2015; 5:165-74
Abbvie drug information

PEG-J tube related complication









Recurrent Pancreatitis as a Rare Complication of Duodenal Levodopa Infusion Treatment

Onanong Jitkritsadakul, MD,[1] Priya Jagota, MD[1]
Sitthi Petchrutchatachart, MD,[1] Lalana Sansopha, MD[2]
Rungsun Rerknimitr, MD,[3] Roongroj Bhidayasiri, MD, FRCP, FRCPI[1,4,*]

[1]Chulalongkorn Center of Excellence on Parkinson's Disease and Related Disorders Chulalongkorn University and King Chulalongkorn Memorial Hospital Bangkok, Thailand; [2]Department of Pathology, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand; [3]Division of Gastroenterology, Department of Medicine, Faculty of Medicine Chulalongkorn University and King Chulalongkorn Memorial Hospital Thai Red Cross Society, Bangkok, Thailand; [4]Department of Neurology, Geffen School of Medicine at UCLA Los Angeles, California, USA

Jitkritsadakul O, et al. Mov Disord 2013;28:1308-10.

4

In-depth understanding of functional neurosurgery

Development of functional neurosurgery

Cortex → Basal ganglia

Ablative surgery → DBS surgery

"Brain pacemaker"

Early neurostimulation → Advanced neurostimulation

Current treatment on Functional Neurosurgery

	Ablative surgery	Deep Brain Stimulation	
Locations	• Thalamotomy • Pallidotomy • Subthalamotomy	• Thalamus • Globus pallidus • Subthalamic nucleus	• Etc.
Methods	• Radiofrequency • Cryosurgery • Gamma knife • MRgFUS	• Lead : Conventional Quadripolar • IPG: SC, PC, RC • Programming: Monopolar, Bipolar, Interleaving, etc. • Stimulation: Open-loop vs Closed-loop	

DBS is now considered the preferred surgical treatment for disabling movement and psychiatric disorders.

Indications for DBS	FDA approval (USA)	CE marks (European)	Health Canada License	TGA (Australia)
Parkinson's disease	Yes	Yes	Yes	Yes
Essential tremor	Yes	Yes	Yes	Yes
Primary dystonia	Yes (HDE)	Yes	Yes	Yes
Obsessive-compulsive disorders	Yes (HDE)	Yes	Yes	Yes
Refractory epilepsy	Yes	Yes	Yes	Yes
Tourette's syndrome	No	No	No	No
Major depression	No	No	No	No
Dementia (Alzheimer's disease)	No	No	No	No
Pain	No	No	No	No
Other indications	No	No	No	No

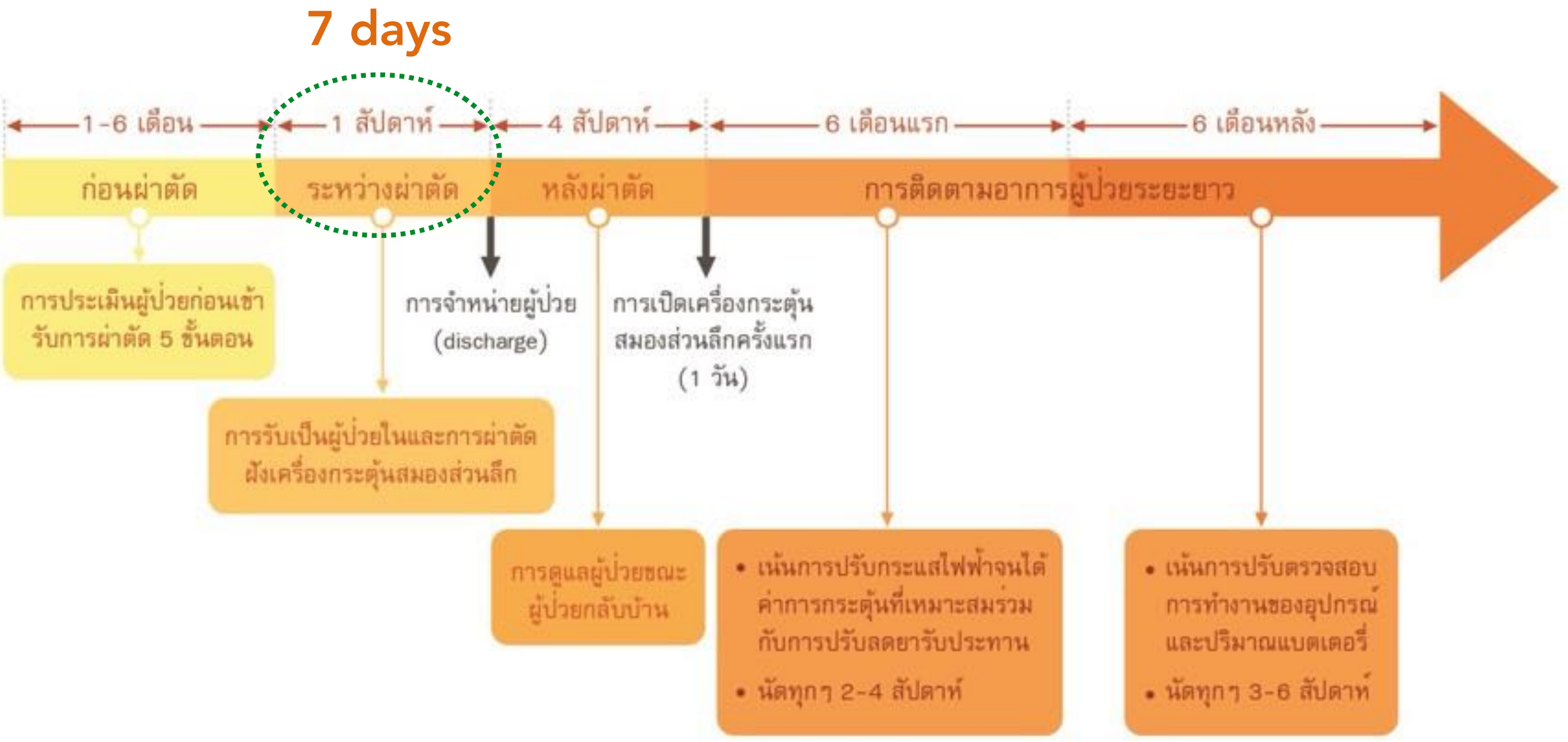
HDE; Humanitarian Device Exemption, FDA; Federal, Health Canada License, TGA: Therapeutic Goods Administration. Indication for Parkinson's disease; Both advanced PD and early motor fluctuations. Indication for epilepsy; As adjunctive treatment for partial-onset seizures in adults with medically-refractory epilepsy, Other indications; Mood disorders, tremor in multiple sclerosis, cluster headache, hypertension, minimally conscious state, obesity, memory impairment, aggressiveness, drug addiction, and other

DBS eligibility criteria for PD

- Age < 75 years*
- Parkinson's disease for at least 4 years
- Presence of bothersome disease-related symptoms (motor fluctuations, dyskinesias, persisting tremor) and/or side effects related to anti-parkinsonian medications
- Motor improvement with dopaminergic medication or presence of medically refractory tremor
- Absence of medical conditions preventing surgery
- Absence of ongoing severe, medically resistant neuropsychiatric diseases (e.g., severe depression, severe cognitive impairment)

Moro E, et al. J Neurol 2016;265:112-9

Timelines of DBS procedures



Long-term results of a multicenter study on subthalamic and pallidal stimulation in Parkinson's disease

- The main aim of this study was to evaluate the effects of bilateral STN- and GPi-DBS in patients with advanced PD followed for a minimum of five and a maximum of 6 years.
- Primary outcome: UPDRS motor score
- Secondary outcome: medications, ADL, dyskinesias
- These results confirm the long-term efficacy of STN and GPi DBS in advanced PD.

TABLE 4. *Unresolved AEs present at 5-year follow-up in both STN and GPi patients*

	STN (n = 35)	GPi (n = 16)
No of patients with AEs	26	8
Total no of AEs	47	11
Cognitive decline	8	2
Depression/anxiety	7	2
Hypersexuality	1	2
Speech difficulties	10	2
Balance disturbances	5	1
Gait disorders	9	1
Motor fluctuations	3	
Sleep disorders	4	

Moro et al. Mov Disord 2010;25:578-586

DBS-related adverse events

- Surgical-related
- Stimulation-related
- Hardware-related

Long-term follow-up and Electromagnetic interference

- Battery replacement
- Leisures and exercises
- Carefully consider on particular medical procedures

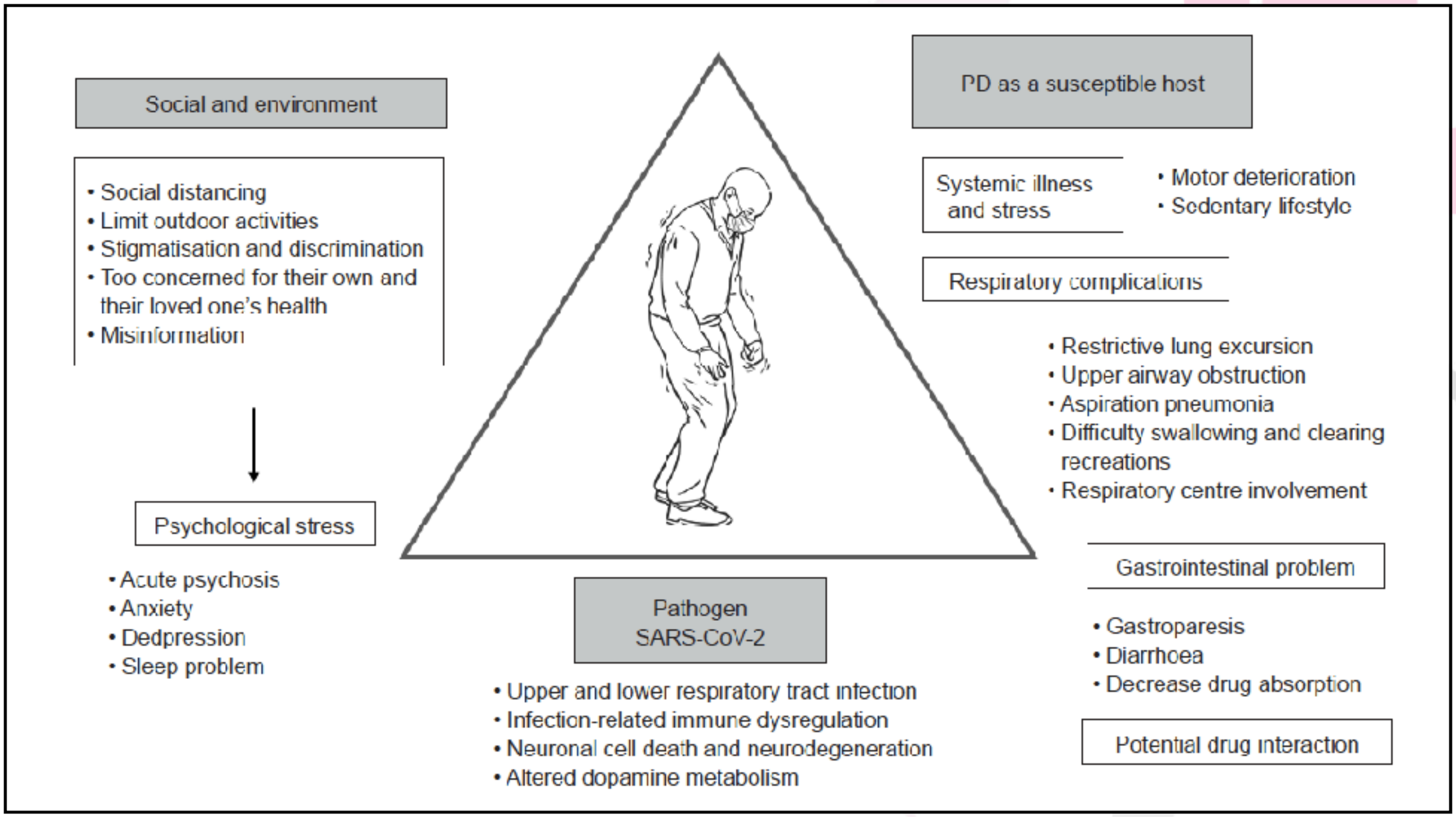
DO	DON'T
X-ray	MRI*
Mammogram	Diathermy
Diagnostic ultrasound	Deep heat treatment
CT/PET scan	Therapeutic ultrasound diathermy

**: MRI 1.5 T only and complete checklists*

5

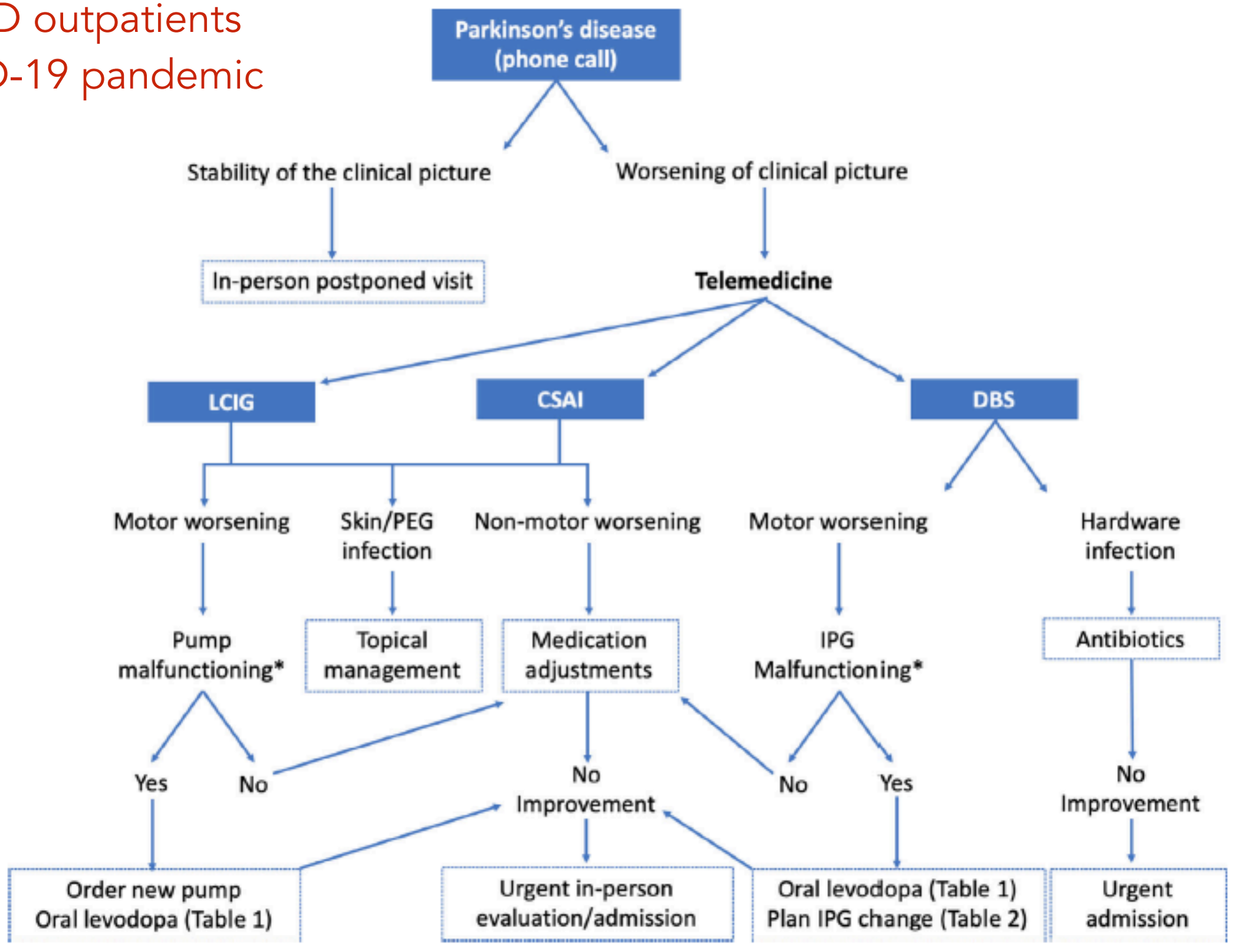
The impact of COVID-19 pandemic and device-aided therapy patients

Impact of COVID-19 on PD patients



Bhidayasiri R, et al. J Mov Disord 2020;13(2):105-114.

Proposed triaging system for Advanced PD outpatients during COVID-19 pandemic



Fasano A, et al. Mov Disord Clin Prac 2020;7(4):361-72.

Telemedicine can help physicians provide necessary care to PD patients during this COVID-19 situation

Care of patients with device-aided therapies in times of COVID-19

- All measures of social distancing must be strictly and carefully practiced.
- Patients should avoid or postpone in-patient hospital stay for nonemergency reasons. In addition, elective DBS surgeries may need to be postponed (except for battery replacement surgery**).
- Outpatient visits can be substituted by the available tools of telemedicine.
- If patients require in-patient or ICU admission, the continuous of device-aided therapy is recommended.
- The physician must ensure the maintenance of previous PD medications, especially the adequate dosages of L- dopa/DDCI, as recommended.
- In case of sudden system failure, patients shall use their oral emergency medication.

Papa S, et al. Mov Disord 2020;35:711-5.
Fasano A, et al. Mov Disord Clin Prac 2020;7(4):361-72.

6

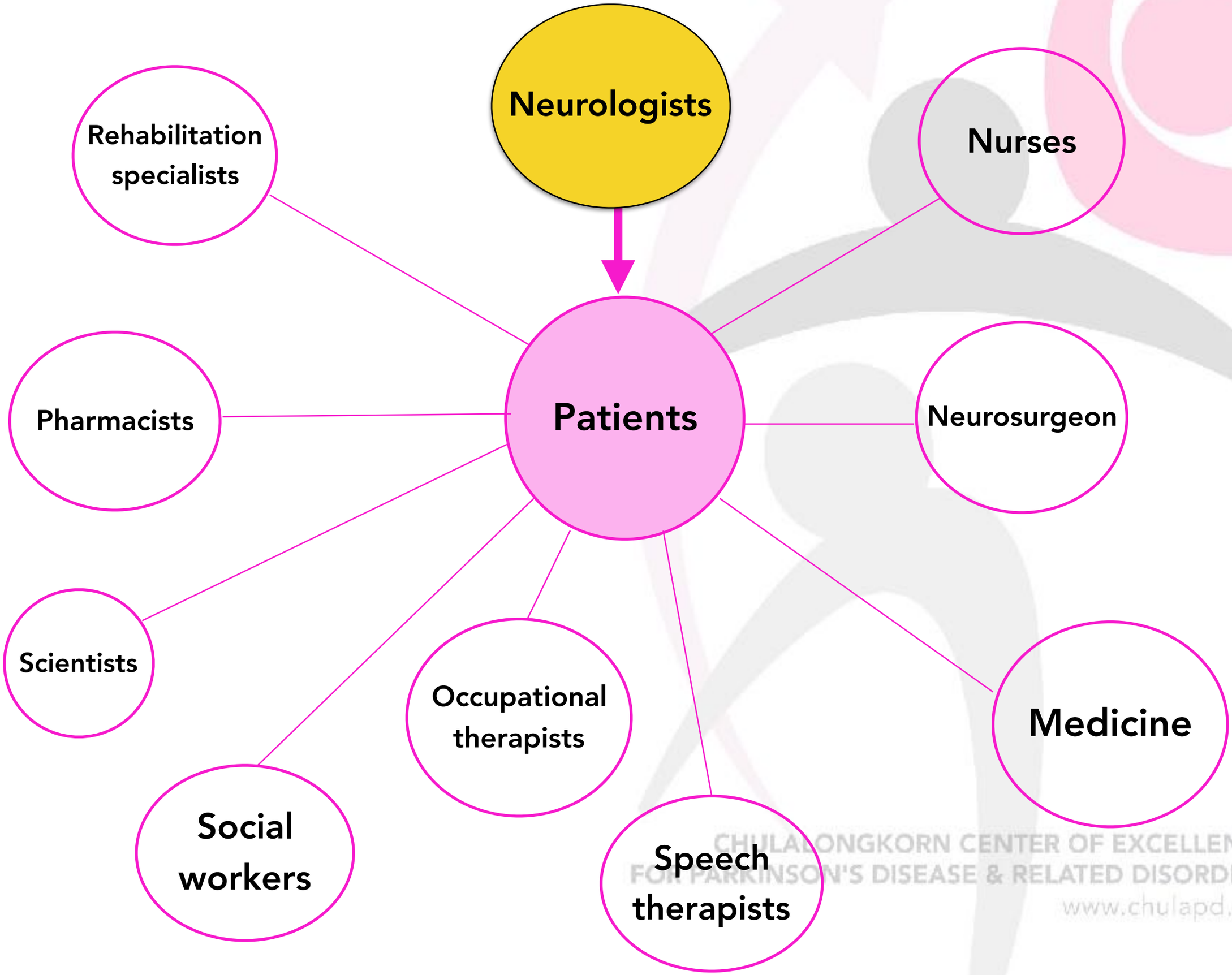
How to implement device-aided therapy in your clinical practices

How different between conventional oral medications and device-aided therapy

Items	Oral therapy	Device-aided therapy
Suitable for severe motor complications	No	Yes
Invasive procedures	No	Yes
Dosing titration location	OPD (Patient's home)	IPD or daycare*
Device complexity	No	Yes
Carrying device	No	Yes
Certain limitation on some procedures and interventions*	No	Yes
Price	Less expensive	More expensive
Reimbursement	Yes	Yes (Government officer*)

**: MRI 1.5 T only and complete checklists, deep heat therapy, diathermy*

Multidisciplinary care team for device-aided therapy

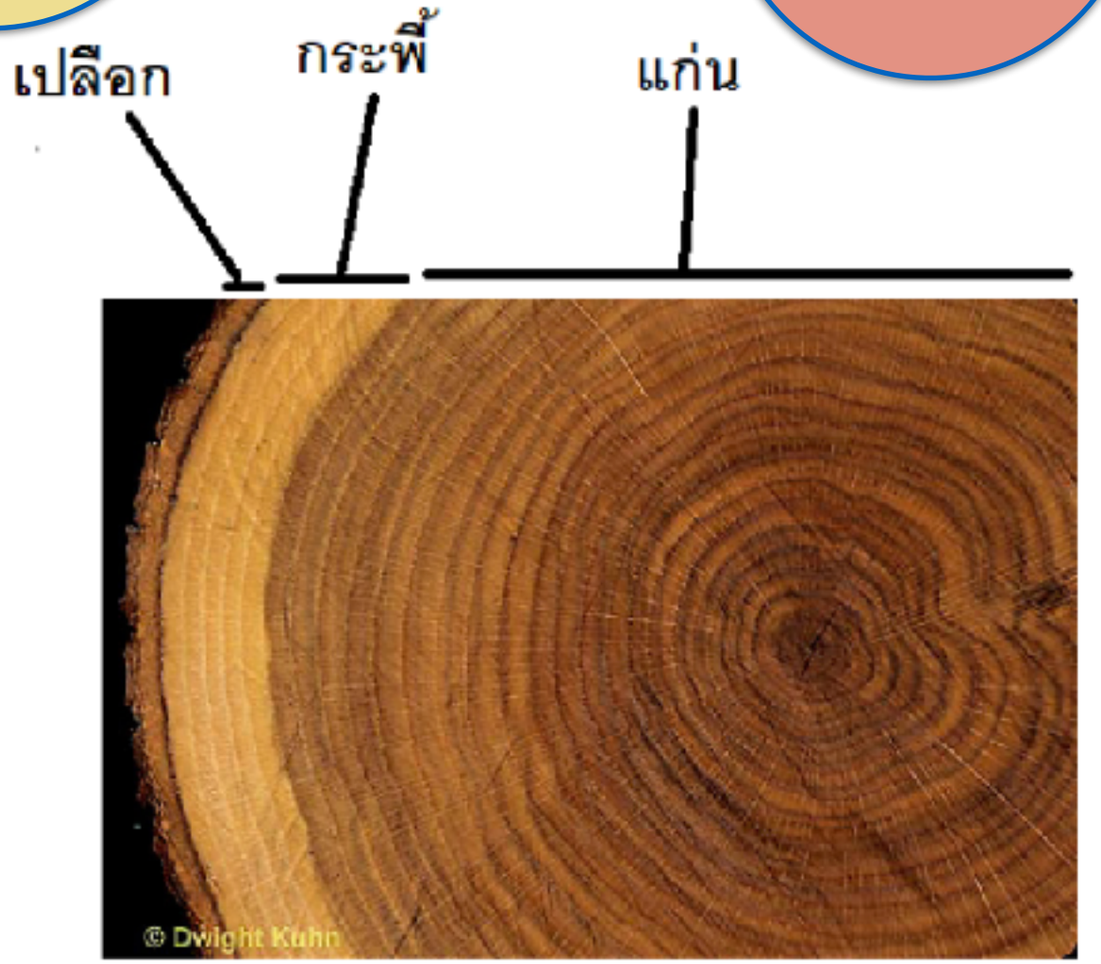


Take Home Message

Subcutaneous Apomorphine

LCIG

Ablative Sx DBS



Three effective therapeutic options for motor complications

- Similar aims
- Different adverse effects
- Different logistic issues

Understanding the Advanced Treatments in Parkinson's Disease

Onanong Phokaewvarangkul, MD, PhD.

Assistant Professor of Neurology, Chulalongkorn Centre of Excellence for Parkinson's Disease and Movement Disorders, Chulalongkorn University and King Chulalongkorn Memorial Hospital