Advanced therapies for Parkinson disease: Duodopa

Nov 18 2020

Tara Rastin, MD, FRCPC
Movement Disorders Specialist
University of British Columbia & Vancouver Coastal Health Authority
Djavad Mowafaghian Centre for Brain Health
Pacific Parkinson Research Institute

Faculty/Presenter Disclosure

I have nothing to disclose.

Webinar Outline

- What is Parkinson disease & what are its symptoms?
- How is Parkinson disease treated?
- When are advanced therapies for Parkinson disease indicated?
- What is levodopa continuous intestinal gel (LCIG)/Duodopa? How does it work?
- Is LCIG right for me?

- Q & A

What is Parkinson disease?

- Parkinson disease is a neurodegenerative condition, with loss of dopamine-producing cells and accumulation of specific protein within brain cells (called Lewy bodies)
  - neuro-: brain disorder
  - degenerative: progressive (slowly, over years and decades)
  - loss of dopamine
  - accumulation of a protein called alpha-synuclein

- Parkinson disease is the second most common neurodegenerative disorder, after Alzheimer disease
- ~100,000 Canadians living with Parkinson disease (0.3% of population)
- ~10,000 newly diagnosed Canadians per yer

What are the symptoms of Parkinson disease?

- Symptoms are very variable!
  - There are many symptoms possible, but one individual does not necessarily develop/experience all the symptoms
  - Symptoms within one individual also change over time
- Motor symptoms:
  - Slowness of movement, stiffness, resting tremor, change in sense of balance
  - Slowness of movement can manifest in various ways: decreased arm swing or stride when walking, running or playing sports, smaller/cramped handwriting, decreased dexterity with manual hobbies or tasks (e.g., drawing, knitting, applying makeup, chopping/cooking, building models, mechanical work…), reduced facial expression, changes in speech, changes in swallowing, drooling
- Non-motor symptoms:
  - Common, and likely under-recognized (more on the next page)

What are the symptoms of Parkinson disease?

Possible Non-motor symptoms

- Constipation
- Sleep disorders (including REM-behaviour sleep disorder)
- Poor sense of smell
- Fatigue, low energy levels
- Mood disorders
- Pain
- Changes in bladder control
- Drop in blood pressure when standing, lightheadedness/fainting
- Cognitive changes
- Hallucinations
- Impulse control disorders

How is Parkinson disease treated?

- Cures or disease-modifying/halting therapies do not exist, yet
- However, many symptoms can be controlled with a combination of:
  - medications (typically aiming to "replace" dopamine)
  - regular exercise (very important, but not the focus of this webinar)

- Note:
  Some non-motor symptoms respond to dopamine-related therapy but many do not and should be treated separately, for example:
  - Constipation
  - Mood disorders
  - Disruptive sleep disorders
  - Low blood pressure
  - Bladder symptoms (especially when in combination with enlarged prostate)
  - Hallucinations, other cognitive changes

Levodopa/carbidopa treats symptoms by ‘replacing’ dopamine

- Levodopa/carbidopa was a major breakthrough in symptomatic treatment of Parkinson disease in the 1960s
- Levodopa is converted to dopamine in the brain (carbidopa prevents conversion to dopamine outside the brain, to reduce side effects such as nausea and low blood pressure)
- Levodopa remains the most effective/potent medication available
- Everyone with Parkinson disease eventually requires levodopa, but very early in disease symptoms may be controlled with other agents alone

More about levodopa…

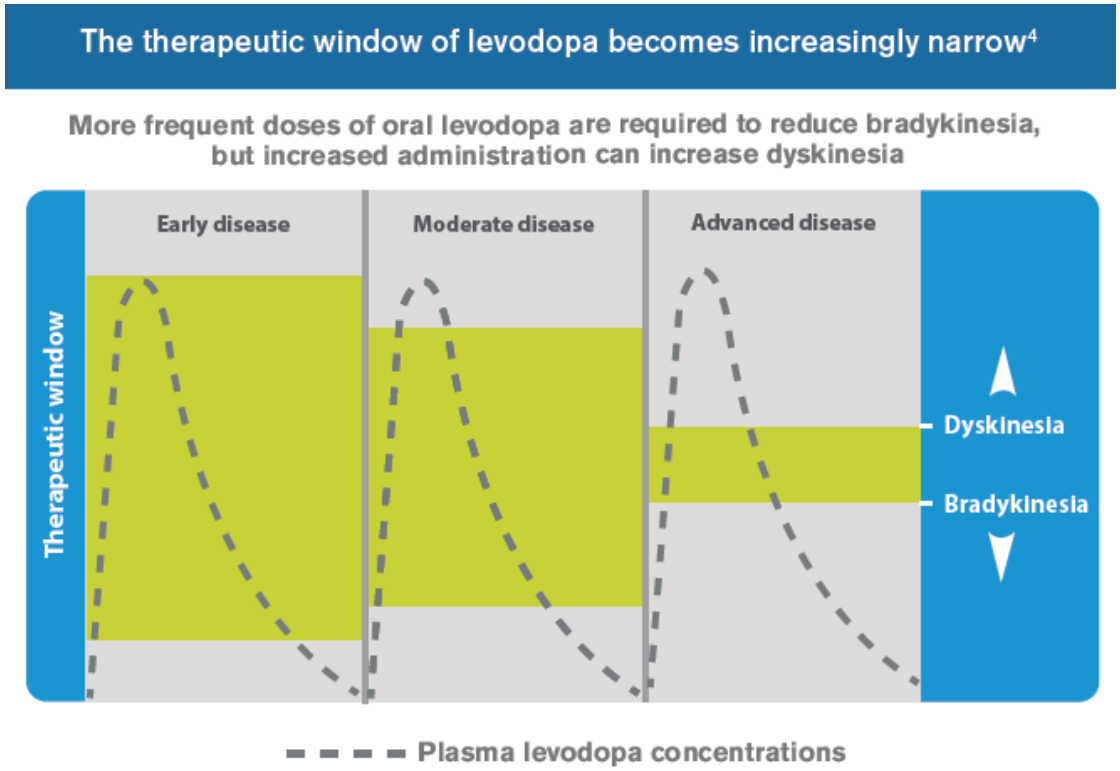
- Symptoms that improve with levodopa are called levodopa-responsive
  - These are often motor symptoms such as stiffness, slowness, tremor, but sometimes non-motor symptoms too such as soreness/pain, sweating, episodic anxiety, bladder urgency, etc.
- Initially, there is a long-duration effect
  - Overall improvement noted after days/weeks of treatment, no worsening noted if the odd dose is missed, but clear worsening if medication stopped or reduced after days/weeks
- With disease progression, patients become more aware of a dose-dependent response
  - symptoms improving and returning with each dose of medication every few hours
  - "off" periods are times when medication effects have "worn off" and symptoms return
  - motor fluctuations refer to frequent cycling between "on" and "off" periods, and/or presence of bothersome dyskinesias (more on the next slide)

More about levodopa and dyskinesia

- With increased duration of disease, patients can experience dyskinesia:
  periods of excess rocking/writhing movements correlating in time with doses of levodopa
  - https://www.youtube.com/watch?v=_XXLbGT_DfU
- Our current understanding is that dyskinesia correlate best with longer disease duration and higher individual doses of levodopa, rather than cumulated levodopa exposure

- With advanced disease, “off” periods and severe dyskinesia can alternate as levodopa blood levels rise and fall

Therapeutic window narrows as PD advances



Reprinted by permission from Macmillan Publishers Ltd: *Nat Clin Pract Neurol*. Drug insight: continuous dopaminergic stimulation in the treatment of Parkinson's disease. Olanow CW, Obeso JA, Stocchi F. Vol. 2(7) copyright 2006.

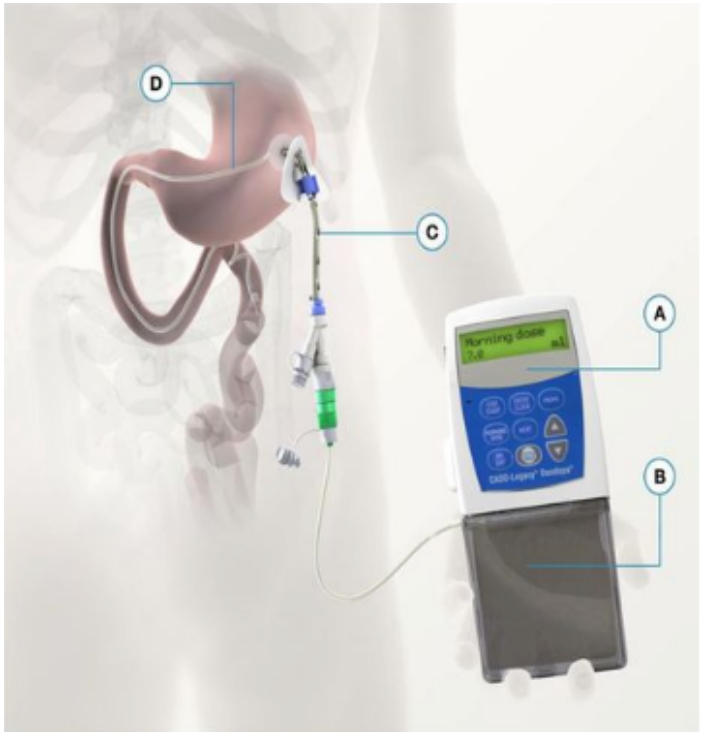
Therapies for advanced Parkinson disease (summary slide)

- When severe dyskinesias and/or frequent “off” periods occur, the following advanced therapies may be helpful:
  - Levodopa continuous gel intestinal (LCIG)/Duodopa
    - Works for symptoms that respond well to levodopa (i.e., levodopa-responsive symptoms)
    - Used when frequent wearing-off and/or severe dyskinesia are interfering with quality of life
    - Cognitive impairment is less of a concern than in deep brain stimulation
    - Presence of a care partner is important
  - Deep brain stimulation (not the focus of this webinar)
    - Pacemaker connected to electrodes implanted in the brain, delivering a small electrical current to specific brain regions
    - Symptoms that respond well to DBS are symptoms that are levodopa-responsive! (i.e., DBS is not for everyone and does not fix all problems)
    - Poor overall health, more advanced age, cognitive impairment, psychiatric symptoms, and certain midline motor symptoms such as freezing of gait and soft speech can be reasons to avoid DBS

Levodopa/carbidopa intestinal gel (LCIG) - Duodopa

LCIG or Duodopa is used in the treatment of advanced Parkinson disease, where frequent "off" periods or motor fluctuations *in spite of maximal/optimized oral therapies*.

Good levodopa response is necessary: Levodopa-unresponsive symptoms will not improve with LCIG



A. Pump; B. Cassette; C. PEG; D. J-tube

How does LCIG work?

- A tube (called a PEG-J tube) is placed through the stomach wall, with its tip lying in the small intestine
- Pump is attached to the tube
- Cassettes containing levodopa gel are connect to the pump, and levodopa is pumped at a set constant rate into the small intestine

Benefits continuous intestinal infusion may provide

- Stabilize levodopa concentrations in the bloodstream, to stay within the therapeutic window
  - More “ON” time/less “OFF” time
  - Reducing bothersome dyskinesia
- Bypasses the stomach to avoid the effects of slowed or delayed gastric emptying

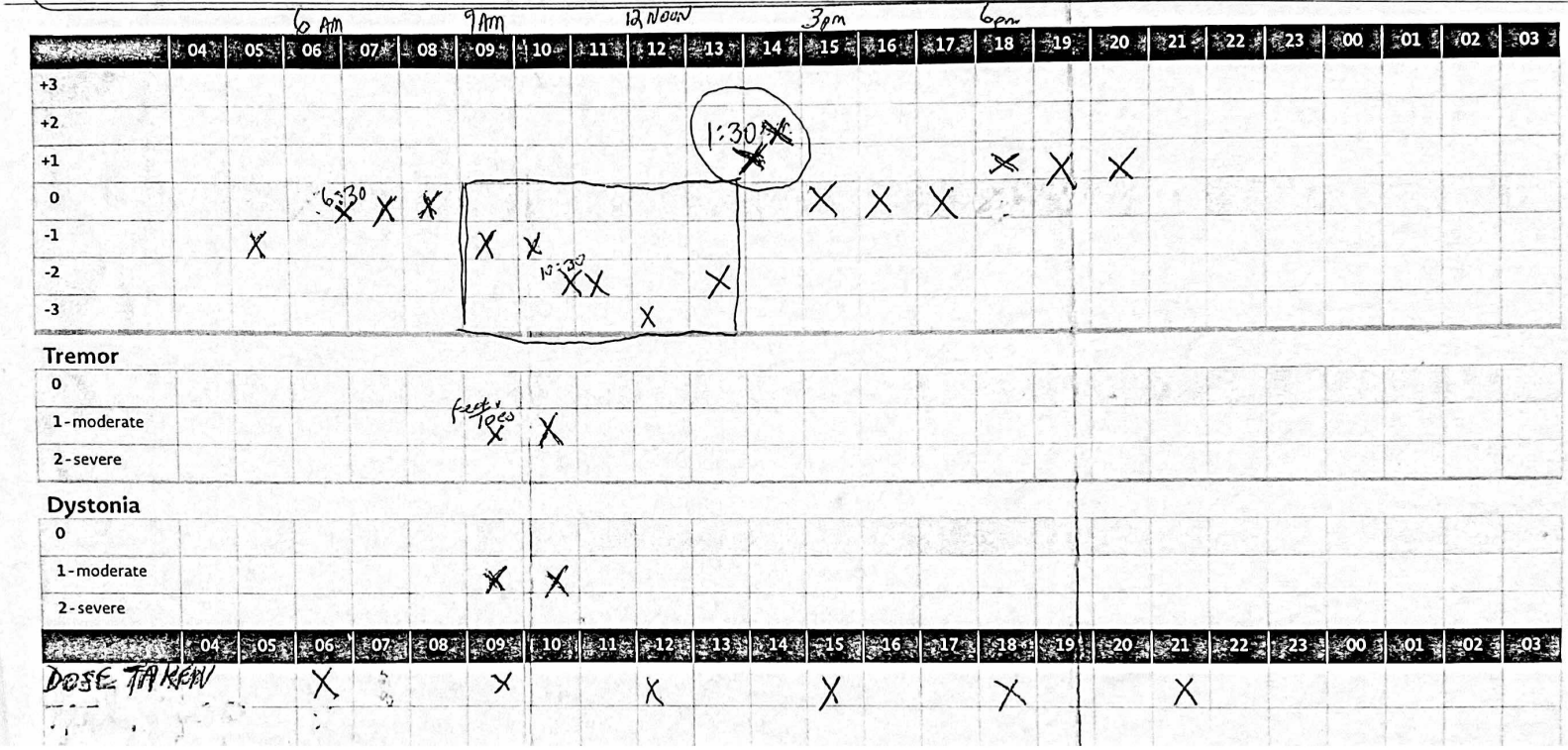
Is LCIG right for me?

- Are there levodopa-responsive symptoms, but too much wearing off and/or bothersome dyskinesia in spite of optimizing oral medications?
  - LCIG does not improve symptoms that do not respond to levodopa
  - Need to be able to reliably report "off" periods and dyskinetic periods
    - symptom diaries (example on the next slide)
- Are there reasons that make it impossible or unsafe to place a PEG-J tube? (e.g., psychosis/severe agitation, previous abdominal surgery or intra-abdominal infections, etc.)
- Patient preference: PEG-J tube appearance & care, need for a pump, etc.
- Other practical considerations:
  - Engaged care partner
  - Local HCP willing & able to provide assessment, basic stoma care, physically make pump adjustments; ability to travel for assessments & titration
  - Local GI care

Mobility

+3 Extra movement may interfere with voluntary movement
+2 Clear extra movement / moving continuously even in rest
+1 Visible small extra movements / can be intermittent
0 On without symptoms (on without dyskinesia)

-1 Patient feels rigidity / slow movement / no arm swinging
-2 Remarkable slowness / may need assistance when arising or walking
-3 Can't arise or walk / may move some extremities but with remarkable slowness



The basic process to starting LCIG

- Evaluation by a movement disorders specialist at a centre offering LCIG titration
- If eligible:
  - Referral to Abbvie community resource nurse for pump related education
  - Referral to GI specialist for PEG-J tube placement
  - Slightly different approaches to initial titration exist; at our centre:
    - 2-4 weeks after PEG-J placement, outpatient titration over 3-4 days
    - Approximately 8-9am – 430pm at our centre with a nurse, 3-4 days in a row
    - Care partner in attendance, for education, support, and to help with travel to & from
    - Physician in close communication with nursing to find appropriate rate of infusion
    - Further education re: pump, stoma care, etc

Questions & Discussion

Thank you for your attention