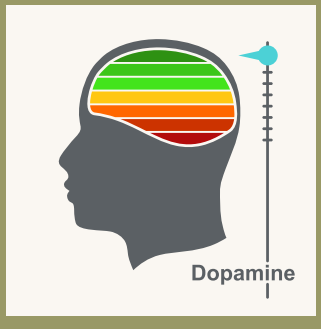
Optimizing Motor Function in PD: Strategies for Effective Symptom Management



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Fraser Health Movement Disorder Clinic

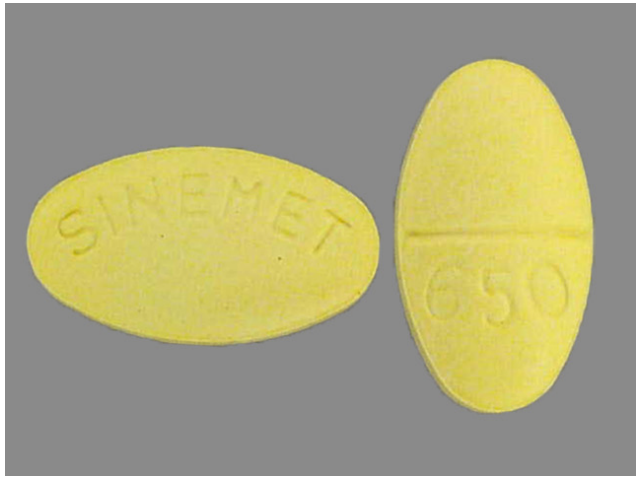
Disclosures and acknowledgements

- I have served as a consultant on Advisory Boards for Sunovion Pharmaceuticals, Paladin Labs, Abbvie, and Merz, for which I have received compensation for my involvement.

- I am not a patent holder, shareholder or financially invested in any of the pharmaceutical products discussed in this presentation, and I am not receiving financial support in the form of research grants from any industry or commercial supporters.

Outline

- General discussion of how Parkinson's medications work, and why they stop working adequately (aka "motor fluctuations")
- Options for making Levodopa work better
  - How dose do these options work
  - Advantages and disadvantages
- Options for "filling in the gaps"
- Brief discussion on Advanced Therapies
  - Duodopa
  - DBS
- New therapies – *Coming Soon*
- Specific treatments for resting tremor, freezing and dyskinesia



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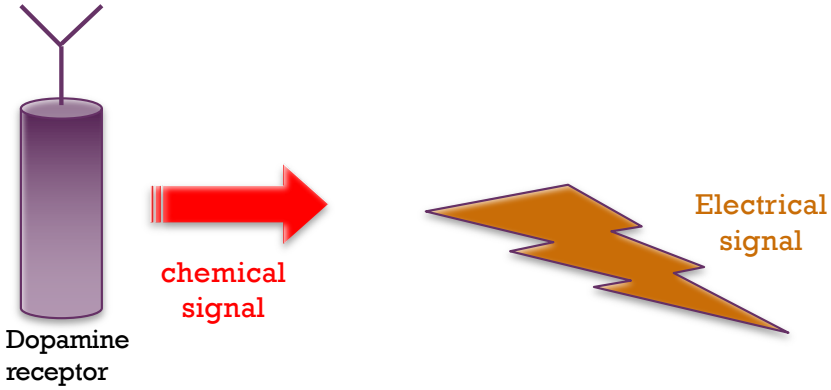
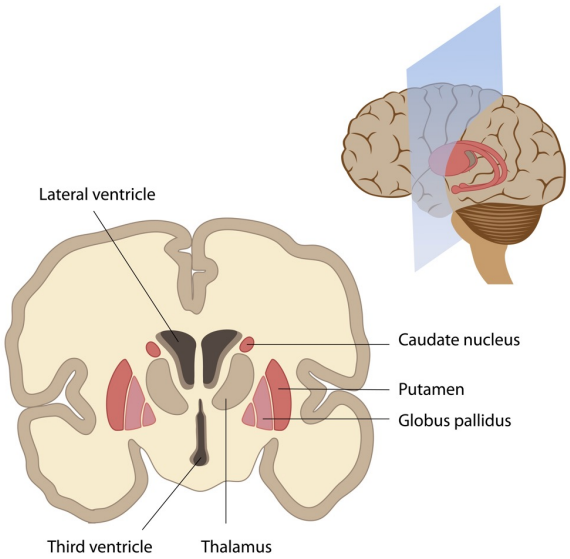
In the early stages, Parkinson's motor symptoms are due to low dopamine

Parkinson's motor symptoms

- Dopamine is a chemical in the brain that is important for the proper function of the basal ganglia
- Dopamine acts by binding to dopamine receptors in the basal ganglia





Parkinson's motor symptoms

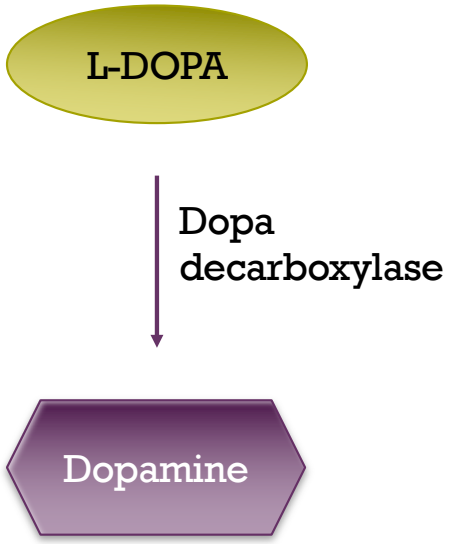
- Low dopamine leads to:
  - Slowness
  - Stiffness
  - Shuffling
  - Loss of dexterity
  - Reduced spontaneity of movement
  - Tremor at rest

- Need to increase dopamine levels/signaling in the brain to move more normally

Levodopa/carbidopa

- **L(eva)-dopa** = chemical building block of dopamine
  - Requires absorption in small intestine – starts working within 30-90 minutes
    - Protein - reduces absorption
    - Diarrhea/constipation – reduces absorption
    - Carbonated beverages - increases absorption speed

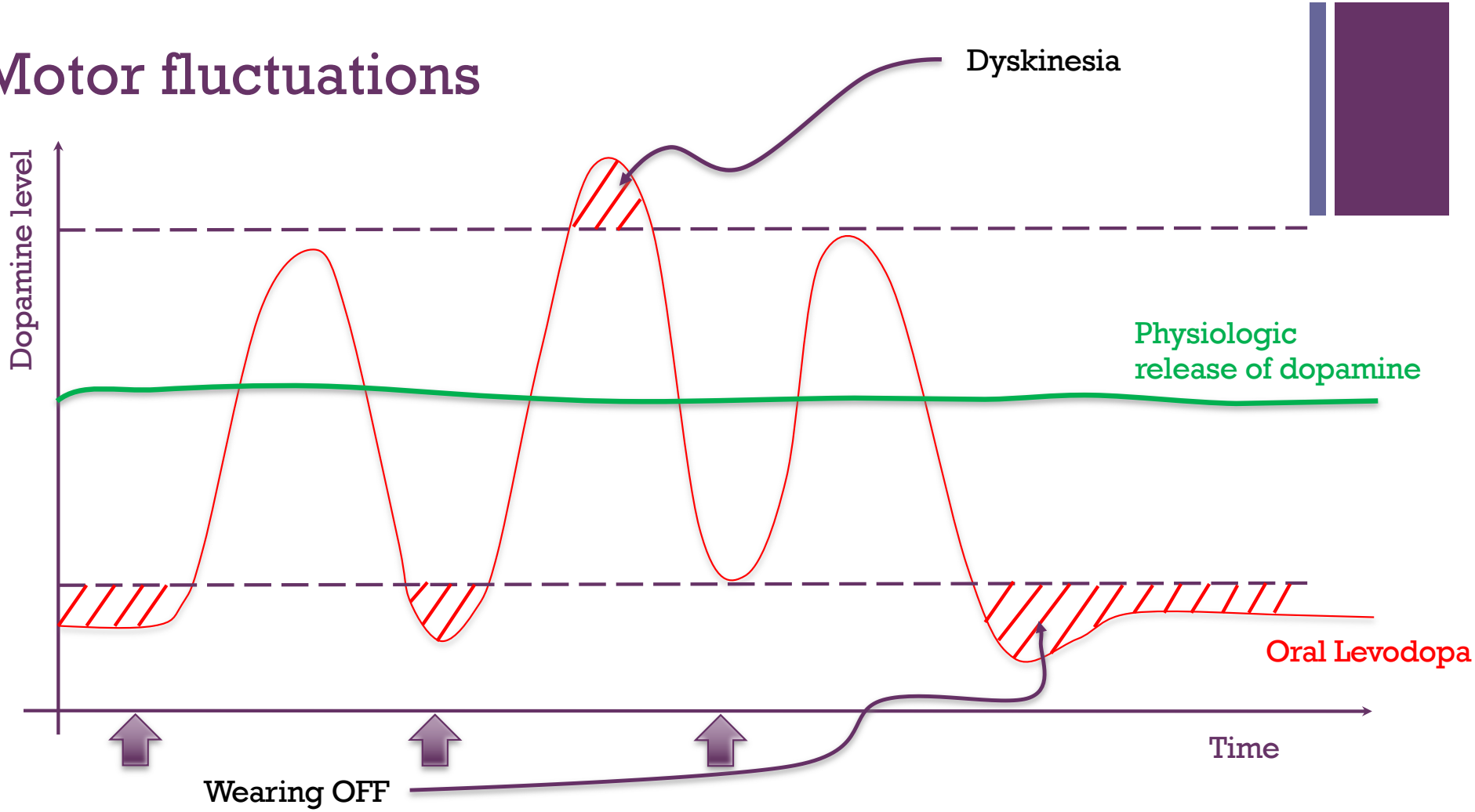
- **Carbidopa** = Dopa decarboxylase inhibitor
  - Prevents peripheral conversion of levodopa → dopamine
    - Reduces systemic side effects
  - Increases the amount of levodopa transported to the brain
    - Improves duration of levodopa action by 1.5 hours



Levodopa comes in different formulations

- **Sinemet®** = Merck-branded levodopa/carbidopa (no longer being manufactured)
- Immediate release (IR) vs controlled-release (CR)
  - CR formulation provides more sustained ON time than IR formulation
  - But ....
    - CR has slower and less complete absorption rate → delayed time to clinical benefit compared with IR
    - And a less consistent clinical response versus the IR formulation
- **Prolopa®** = levodopa + benserazide
- **Stalevo®** = levodopa/carbidopa + entacapone

Motor fluctuations



Wearing OFF

- **In the early stages** …. a low dose of Levodopa effectively tops up the dopamine levels in the brain, such that most people get consistent symptom control with 3 doses per day

- **As the disease progresses** …. the loss of more dopamine-producing brain cells, makes it harder for each dose of Levodopa to prevent symptoms from re-emerging and people experience the phenomenon of **"wearing OFF"**
  - **The effects of Levodopa diminish before it is time for the next dose** … experience a return of slowness/stiffness/tremor (motor symptoms) and other non-motor symptoms between doses of Levodopa

Types of OFF episodes

- **Wearing OFF between doses of Levodopa**
  - May occur between every dose or only following certain doses
- **Morning OFF** – when a person awakens in the morning in an OFF state prior to taking their first dose of Levodopa
- **Late afternoon wearing OFF**
- **Delayed ON** - a delay in symptom improvement after dose of Levodopa is taken
- **Partial or Failed ON** – less than optimal symptom improvement after taking a dose of Levodopa, by comparison to a person's normal response to Levodopa
- **Unpredictable OFF** – abrupt and random changes from an ON state to a OFF state over seconds to minutes

Impact of OFF episodes

- Reduced quality of life from:
  - Impaired mobility (e.g. using the bathroom, unable to be active in the morning, unable to maintain active lifestyle)
  - Re-emergence of tremor → affects dexterity (e.g. difficulty with meals, performing house chores or work tasks)
  - Pain from rigidity (e.g. difficulty rolling in bed, frozen shoulder) and/or dystonia (e.g. twisting of feet, curling of toes)
  - Anxiety and depression

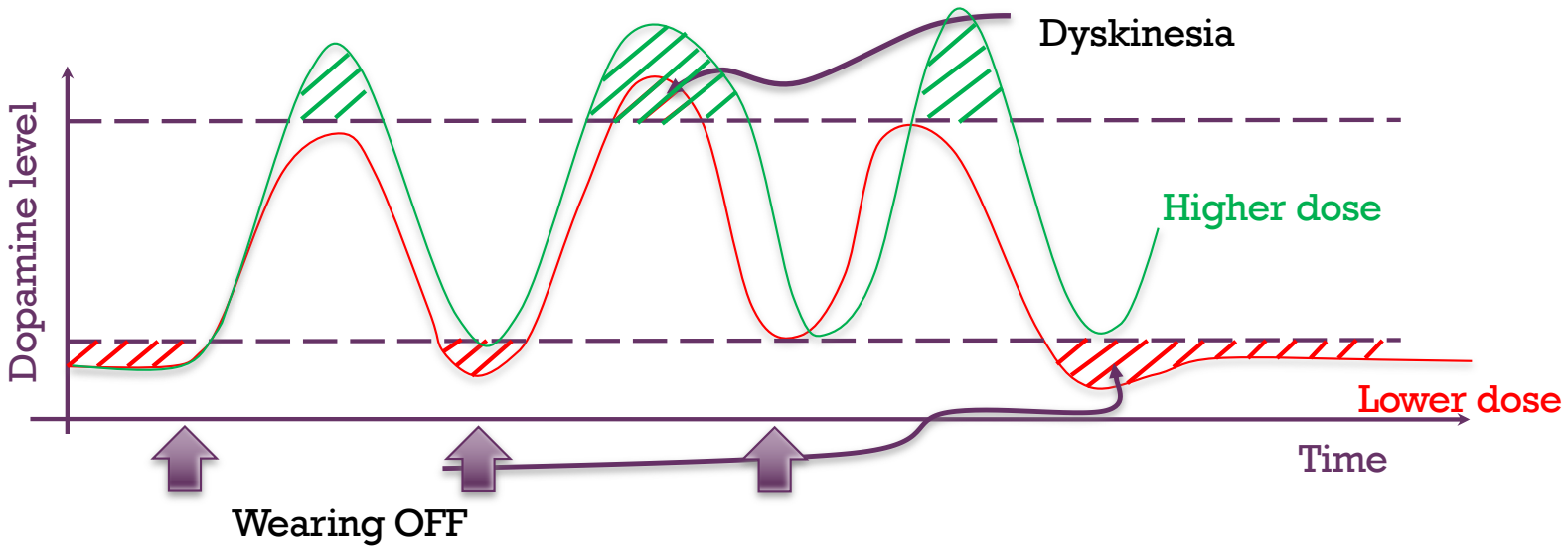
- Increased number of ER visits, hospitalizations, and ICU admissions [Thach et al., J Med Econ, 2021]
  - Translates into higher rates of nursing home placement and a higher economic burden on health care systems

- In an online survey of 3000 people with PD conducted by the Michael J Fox Foundation, 64% reported between 2-4 hours of OFF time per day

How can we make Levodopa work better?

Strategies to reduce/alleviate OFF time

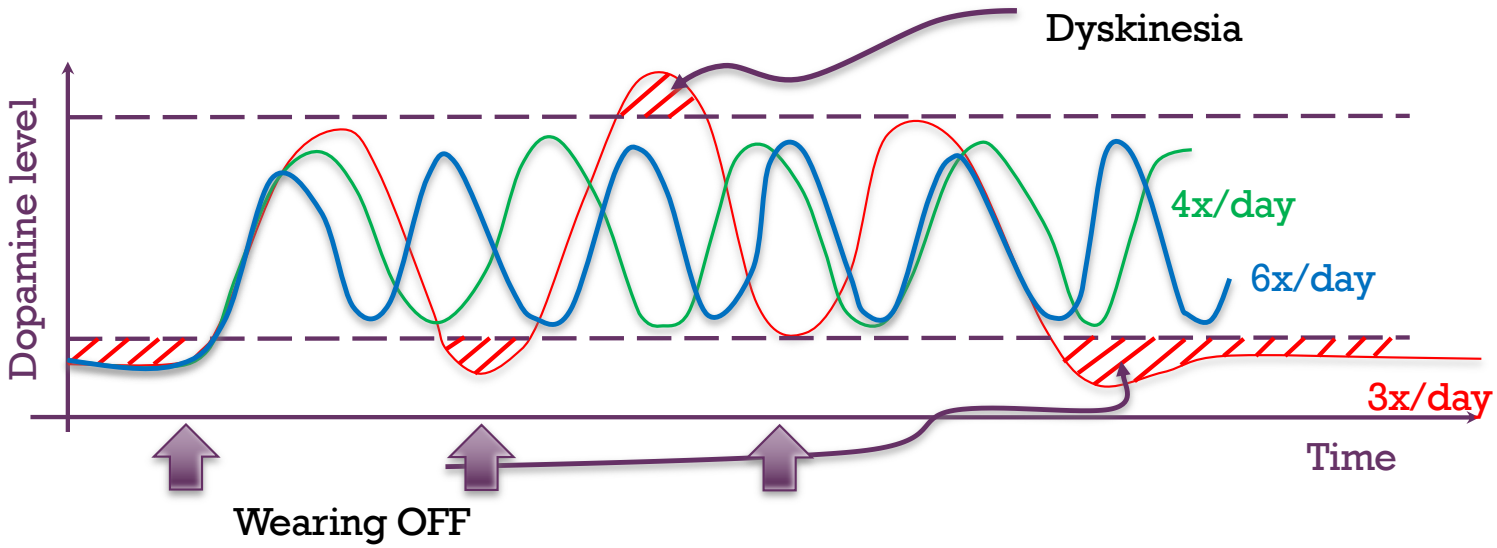
- Increase dose of Levodopa ….



….. but can lead to toxicity (e.g. peak-dose dyskinesia) and side effects

Strategies to reduce/alleviate OFF time

- Decrease time between doses of Levodopa (e.g. smaller doses more often) …



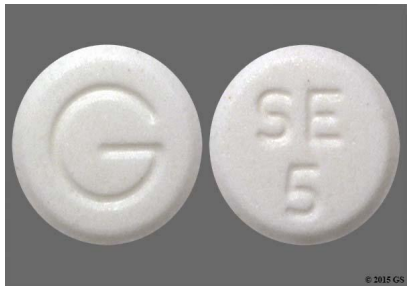
… but can lead to greater inconvenience (e.g. timing of protein-containing meals becomes more difficult to schedule)

Strategies to reduce/alleviate OFF time

- Increase time that Levodopa is active in brain … by blocking the enzymes which breakdown dopamine

  - COMT inhibitors – entacapone (Comtan®), opicapone, tolcapone
    - Needs to be taken with every dose of Levodopa
    - Increases ON time by 30 minutes
    - Large pill
    - Can increase dyskinesia
    - Can cause diarrhea

  - MAO B inhibitors - selegiline, rasagiline (Azilect ®), safinamide
    - Taken 1-2x/day
    - Increases ON time by 30 minutes
    - Can increase dyskinesia
    - Can elevate mood excessively = mania



- These adjunctive therapies are used to reduce the overall OFF time …. BUT some people with Parkinson's will continue to experience OFF episodes no matter how aggressive we are with these therapies.

Medications which also stimulate dopamine receptors

Dopamine Agonists

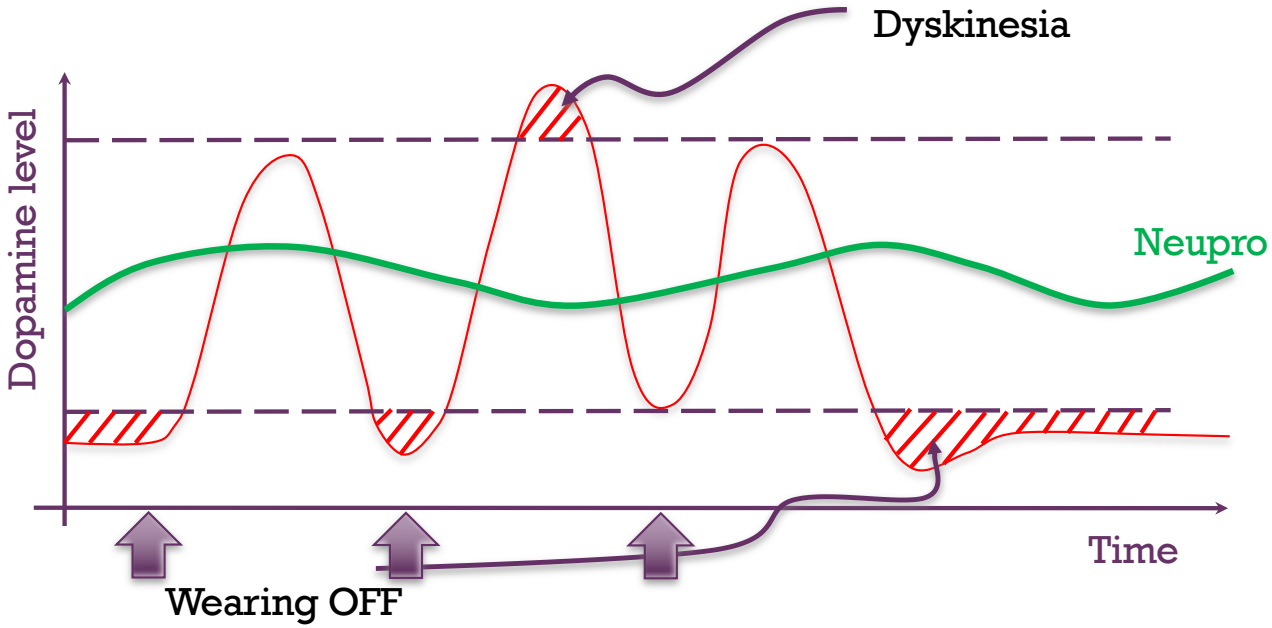
- Pramipexole (Mirapex®), Ropinirole (Requip®)
  - Do not activate the dopamine receptors as well as Levodopa
  - Need to be taken multiple times per day
  - Can cause problems with **impulse control disorders**

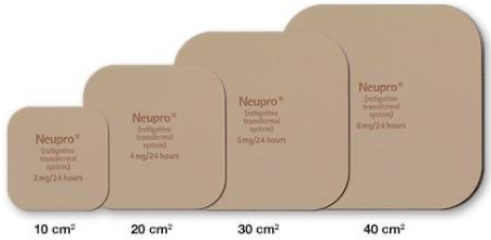
Bromocriptine

- Do not activate the dopamine receptors as well as Levodopa
- Need to be taken multiple times per day
- Can cause pulmonary and cardiac fibrosis → requires regular monitoring with lung and heart imaging

Strategies to reduce/alleviate OFF time

- More consistent/continuous delivery of dopamine-stimulating medication
  - **Transdermal Neupro™ (rotigotine) patch**





- Does not replace need for Levodopa … but can help to reduce amount of Levodopa required
  - Less OFF time, less dyskinesia
- But … medical glue can cause rash

Strategies to reduce/alleviate OFF time

- **On-demand therapies with rapid onset**
  - Movapo™ - subcutaneous apomorphine injection
  - Kynmobi™ - sublingual apomorphine film
  - Inbrija™ - levodopa inhalation powder

Apomorphine

- Advantages
  - Rapid onset of action with 10-15 minutes
  - Tolerance does not develop over time → personal dose remains the same regardless of progression of disease
  - Robust and reliable effect

Medications which also stimulate dopamine receptors

Apomorphine

- Disadvantages
  - Short duration of effect 60-90 minutes → not meant to replace Levodopa (but could potentially allow for lower daily amounts of Levodopa to be used)
- Not a one-size fits all treatment
  - Not ideal if individual OFF periods are longer than 90 minutes
  - Did not 'prevent' wearing OFF episodes from occurring or worsening
  - For people with advanced Parkinson's disease who need assistance for medication administration – need to have highly engaged caregiver present to administer apomorphine in a timely manner
- Apomorphine was briefly available in Canada between 2021 to October 2023
  - **Fraser Health Movement Disorder Clinic** – over 40 patients successfully using apomorphine to treat their OFF episodes
  - But withdrawn from the Canadian market due to a lack of profitability

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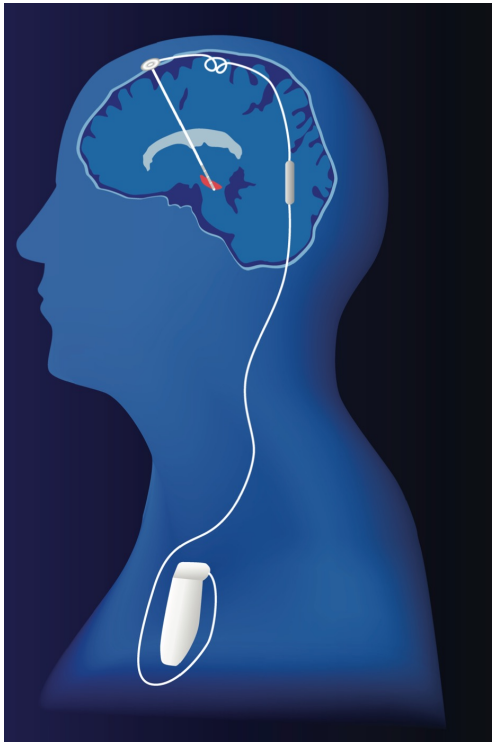
Advanced Therapies

Consistent/continuous stimulation of the dopamine-sensitive brain networks

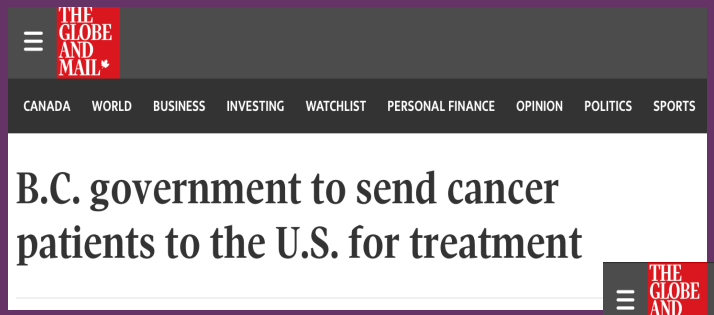
Deep Brain Stimulation (DBS)

- A "pacemaker for the brain"
- Replaces the chemical stimulation of dopamine pathways by Levodopa, with direct electrical stimulation
  - **The best response to DBS is equivalent to the best response that a patient has to Levodopa**
- Indicated in PD patients who:
  - Continue to experience a robust response to Levodopa
  - Have developed complications from being on too much Levodopa (e.g. disabling dyskinesia)
  - Are healthy enough to undergo the procedure
  - Have not developed significant cognitive decline
- **Not a disease modifying therapy** … but can give a person with PD more years with good quality of life (less OFF time, less dyskinesia)
  - 0.5% risk of brain hemorrhage during the procedure
  - Risk of hardware failure and infection



There is a 3-4 year waiting list for DBS in BC

The number of surgeries that can be done per year is largely restricted by Provincial funding



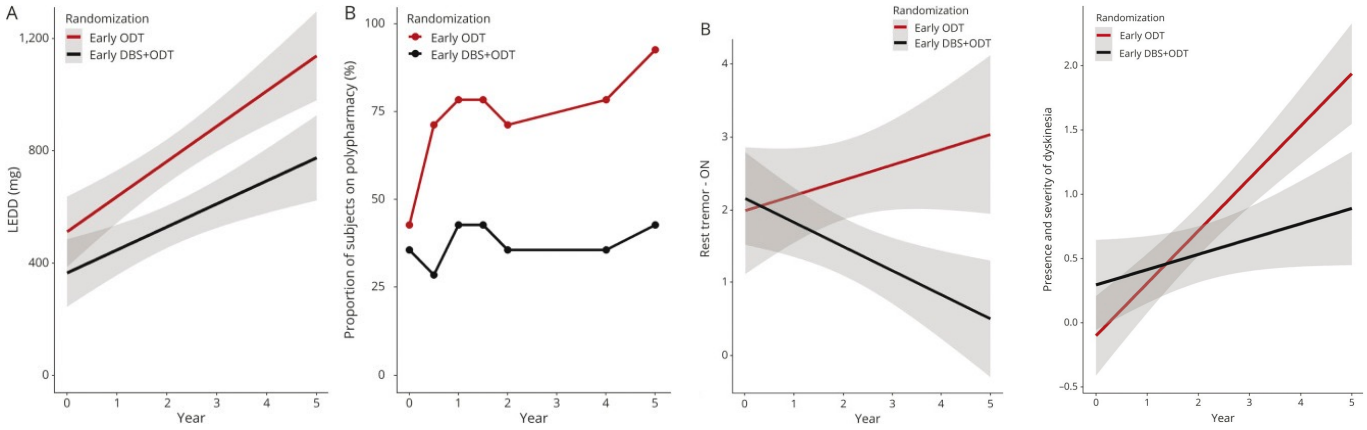
Earlier DBS implantation may lead to better outcomes

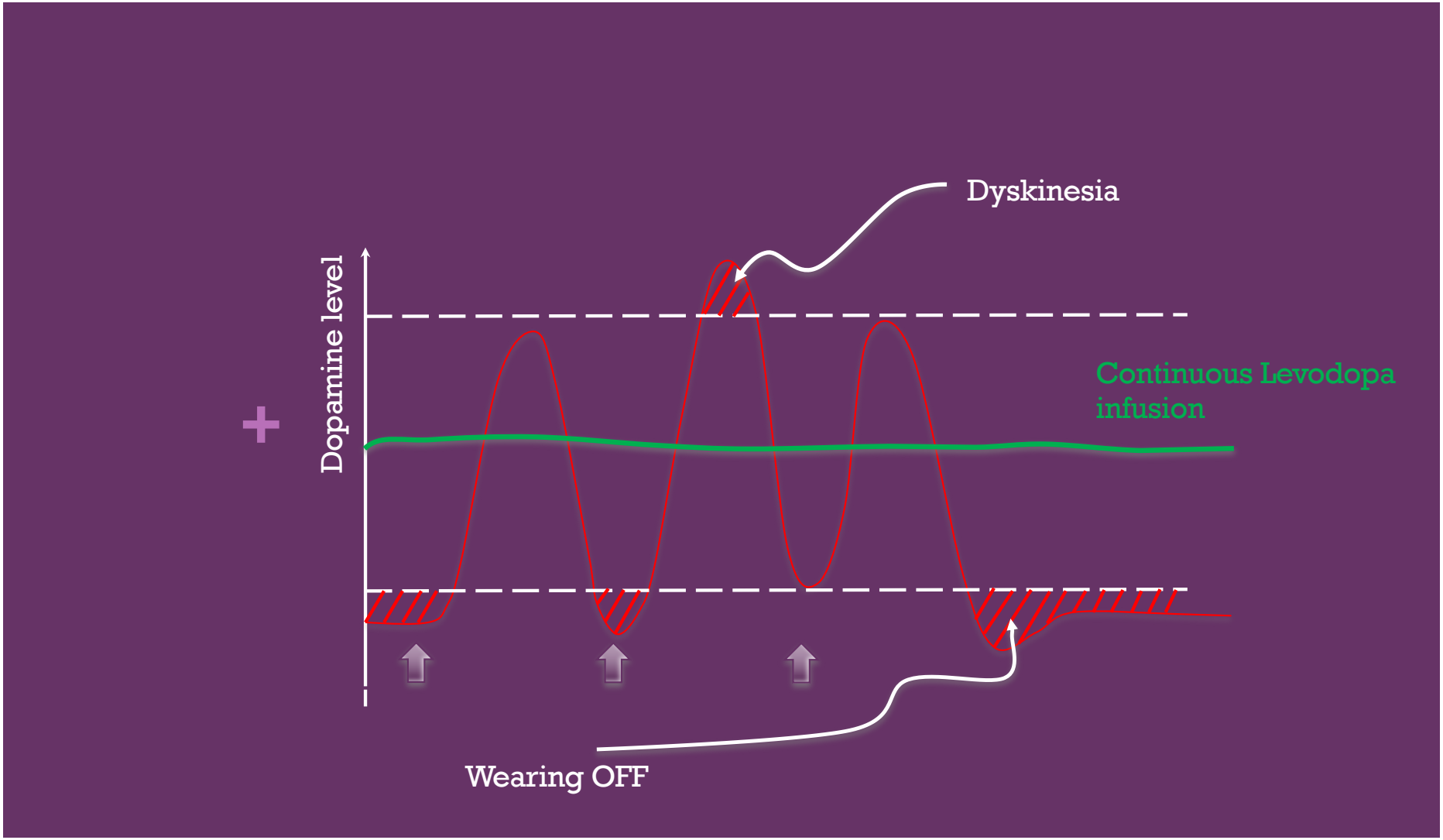
Neurology. 2020 Jul 28; 95(4): e393–e401.
doi: 10.1212/WNL.0000000000009946
PMCID: PMC7455319
PMID: 32601120

Deep brain stimulation in early-stage Parkinson disease

Five-year outcomes
Hacker et al.

- Prospective, single-blind clinical trial
  - Enrolled 28 patients who were taking PD medications for 6 months to 4 years (at an early stage of their disease)
  - Randomized 1:1 to either (1) early subthalamic (STN) DBS + optimal drug therapy, or (2) optimal drug therapy alone
  - Results reported after 5 years suggest that patients who receive early DBS can have:
    - Sustained benefit
    - Require less Levodopa
    - Experience less polypharmacy
    - Have better control of resting tremor
    - Less likely to develop dyskinesia




Dyskinesia
Dopamine level
+
Continuous Levodopa infusion
Wearing OFF

Levodopa continuous intestinal gel (Duodopa® - Abbvie)

- LCIG is levodopa delivered at a constant rate from an external pump connected to a tube that goes from outside to the body directly into the small intestine

- Indicated in patients with significant OFF time and/or dyskinesia despite all possible efforts to optimize oral therapy
  - The ultimate way of taking smaller, more frequent doses
    - PEG-J tube placed into the small intestine
    - Pump is connected to the tube and cassette containing Levodopa gel is attached
    - Pump runs automatically throughout the day delivery Levodopa in regular frequent intervals to stay in optimal range
    - Can deliver extra doses as needed

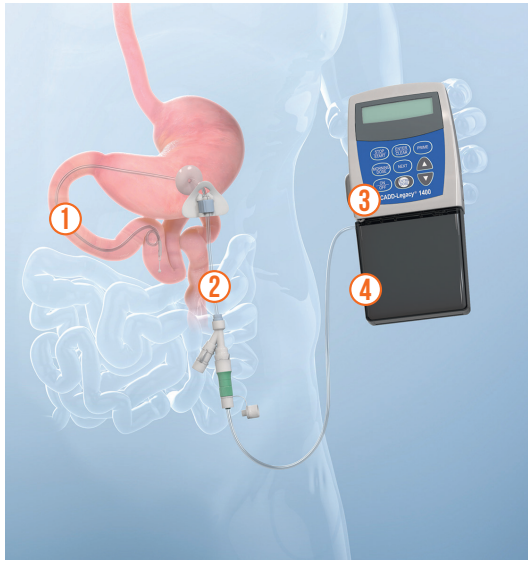


Image courtesy of Abbvie

Levodopa continuous intestinal gel (Duodopa® - Abbvie)

- Ideal for patients who:
  - Continue to experience a robust response to Levodopa
  - Taking very frequent smaller doses to avoid OFF time and/or reduce dyskinesia
  - Are able to manage the pump independently and/or have good caregiver support
- Infection and leakage of stomach fluid are serious potential complications
- The tube can get displaced, blocked or break → needs to be well-cared for and replaced approximately every 18 months

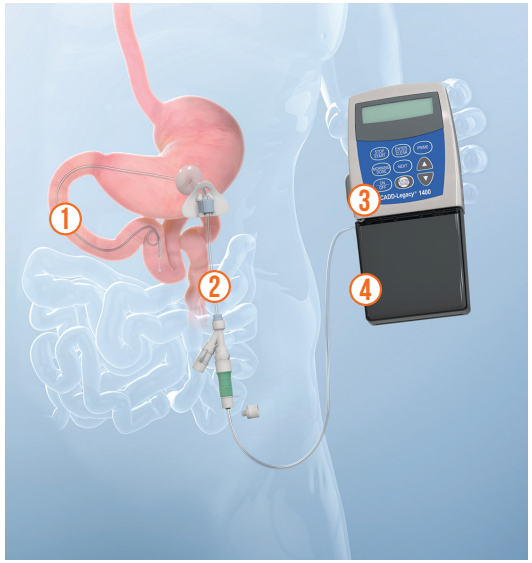


Image courtesy of Abbvie

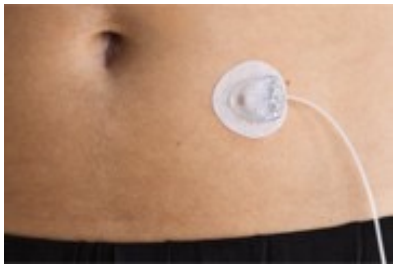
… to a Movement Disorder Clinic near you

Continuous Subcutaneous Levodopa Infusion Pump

Vyalev™ by Abbvie – levodopa/carbidopa delivered at a constant rate from an external pump connected to a tube that goes from outside to the body directly into a small canula placed under the skin

- **foslevodopa/foscarbidopa** formulation - improve absorption and tolerability

Pr VYALEV™
240 mg/mL+12 mg/mL solution for infusion
foslevodopa/foscarbidopa



www.neria.com

Continuous Subcutaneous Levodopa Infusion Pump

Vyalev™ by Abbvie

- 12 week double-blind, multi-centre randomized controlled trial
- 141 patients assigned 1:1 to either (1) subcutaneous Levodopa infusion or (2) oral Levodopa
- Increased ON time without dyskinesia increased an average of **1.75 hours/day** and reduced OFF time by an average of 1.79 hours/day

Continuous Subcutaneous Levodopa Infusion Pump

Vyalev™ by Abbvie

Home › Neurology and Therapy › Article

Continuous Subcutaneous Foslevodopa/Foscarbidopa in Parkinson's Disease: Safety and Efficacy Results From a 12-Month, Single-Arm, Open-Label, Phase 3 Study

ORIGINAL RESEARCH | Open access | Published: 26 August 2023 | (2023)

- 52 week, phase 3, open-label, single arm, multi-centre trial
  - 223 PD patients enrolled with disease duration ~ 10 years; 39% drop-out rate
- At week 26 …
  - OFF time reduced from average of 36% of the day to 17% of the day
  - ON time without dyskinesia increased from 40% of the day to 69%
  - OFF time upon awakening decreased from 77% to 20%

Pr VYALEV™
240 mg/mL+12 mg/mL solution for infusion
foslevodopa/foscarbidopa

Continuous Subcutaneous Levodopa Infusion Pump

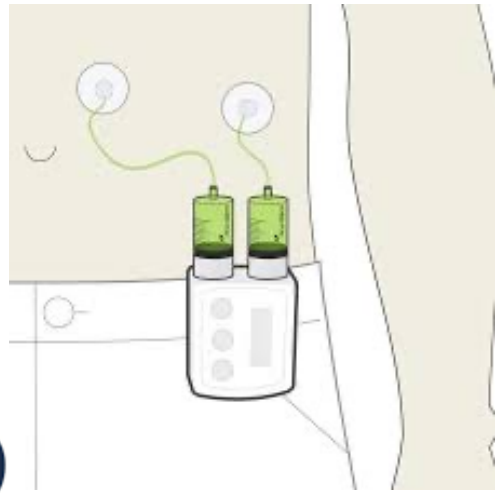
Vyalev™ by Abbvie

- CADTH (Summer 2023) – recommended reimbursement by public drug plans, based on input from multiple stakeholders, including Parkinson BC and BC Movement Disorder Neurologist Group
- Not yet covered under BC Pharmacare
- Advantages
  - Less invasive than Duodopa with similar efficacy – **does not require a surgical procedure**
  - Less risk of major infection and eliminates tube-related complications of Duodopa
- Disadvantages
  - Skin and subcutaneous fat reactions → note: just because the study participants had adverse skin effects, did it mean that they all discontinued? **No, in fact, many of the patients who had these side effects ended up continuing in the study**

Continuous Subcutaneous Levodopa Infusion Pump

ND0612

- Phase 2 (BeyoND) trial to assess safety:
  - Enrolled 214 patients with advance PD, all of whom were treated with ND0612
  - 1 year duration with active extension trial in 114 patients
  - 73% of patients reported at least 1 adverse event … vast majority were infusion site reactions
    - Subcutaneous nodules, pain, bad bruising (hematoma), or d… scab-like skin (eschar)
    - Nausea
    - No serious or irreversible side effects

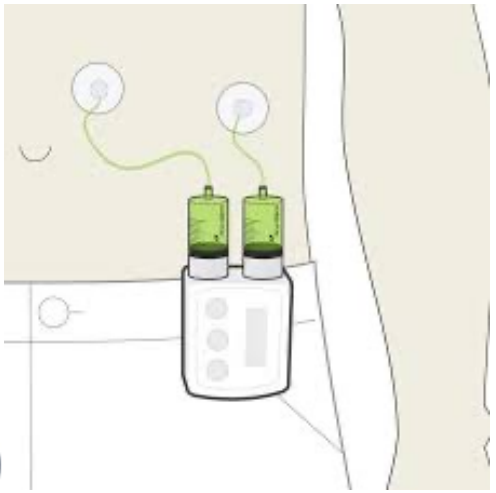


NeuroDerm™
A Mitsubishi Tanabe Pharma Group Company

Continuous Subcutaneous Levodopa Infusion Pump

ND0612

- Phase 3 (BouNDless) Trial to assess efficacy:
  - Randomized double blind, double dummy, control trial
  - 381 PD patients enrolled were randomized 1:1 and followed for 3 months
  - ON time without dyskinesia increased by an average of **1.73 hours/day**
  - **Comparable proportions of people in both groups left the trial** — 6.3% with ND0612 and 6.1% with oral LD/CD. Among those who did so due to side effects, the proportions were 5.5% with ND0612 and 3.1% with oral LD/CD



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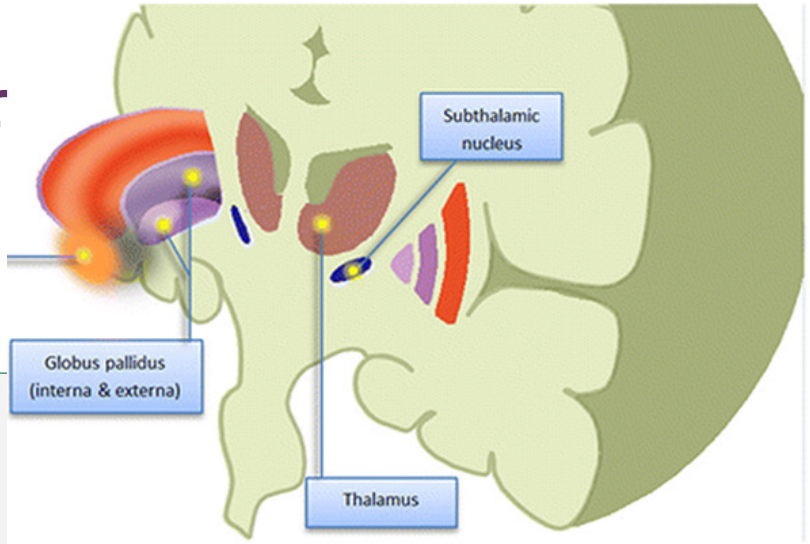
Tremor

Treatments for Tremor

- Levodopa
  - 1/3 of patients will experience very good tremor suppression
  - 1/3 of patients will experience partial suppression of tremor
  - 1/3 of patients will not experience any tremor suppression

- Anticholinergic medications – reduce acetylcholine signaling in the brain (and everywhere else throughout the body)
  - In order of potency: Benztropine (Cogentin®), Trihexyphenidyl (Artane®), procyclidine (Kemadrin®), Ethopropazine (Parsitan®)
  - Robust tremor control … but side effects can be intolerable:
    - Common side effects: dry eyes, dry mouth, constipation, nausea, lightheadedness
    - Serious side effects: disorientation, delusional thoughts and hallucinations

Advanced therapies for Tremor



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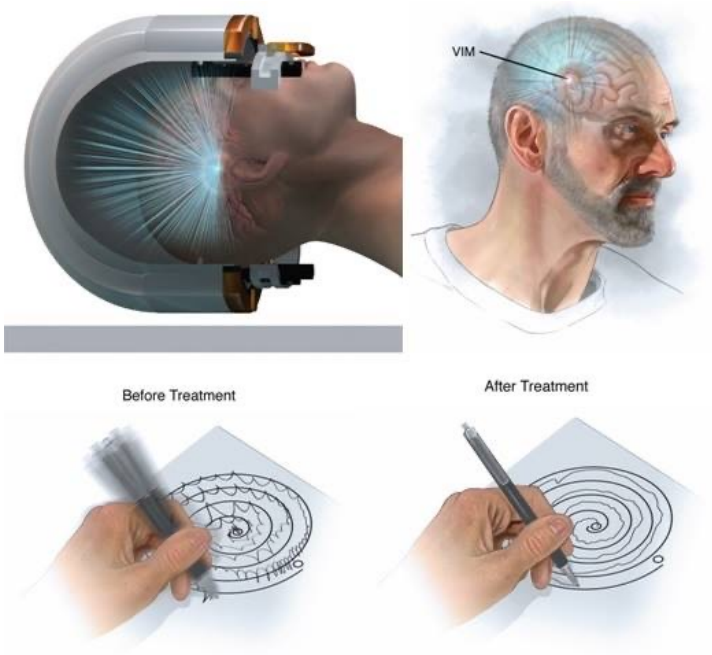
September 26, 2017; 89 (13) ARTICLE

Thalamic deep brain stimulation for tremor in Parkinson disease, essential tremor, and dystonia

Rubens Gisbert Cury, Valerie Fraix, Anna Castrioto, Maricely Ambar Pérez Fernández, Paul Krack, Stephan Chabardes, Eric Seigneuret, Eduardo Joaquim Lopes Alho, Alim-Louis Benabid, Elena Moro

- Thalamic (VIM) DBS
  - Sustained suppression of resting tremor in 70% of patients after 1 year and 63% after 10 years
  - But invasive therapy caries risk of serious side effects (brain hemorrhage and infection) – 2%

Advanced therapies for Tremor



https://seattleneurosciences.com

Movement Disorders
Official Journal of the International Parkinson and Movement Disorder Society

BRIEF REPORT

Focused Ultrasound Thalamotomy for Tremor in Parkinson's Disease: Outcomes in a Large, Prospective Cohort

Melissa M.J. Chua MD, Sarah E. Blitz BS, BA, Patrick R. Ng MD, David J. Segar MD, Nathan J. McDannold PhD, P. Jason White PhD, Sarah Christie PA-C, Michael T. Hayes MD, John D. Rolston MD, PhD, G. Rees Cosgrove MD, FRCSC ... See fewer authors

First published: 04 August 2023 | https://doi.org/10.1002/mds.29569

- 48 patients with medically refractory resting tremor
- Significant tremor control was achieved in all patients, but there was significant drop-out at 1 year (n = 22) and 3 years (n = 2 patients remaining in the study)

Advantages

- Robust tremor suppression
- Non-invasive

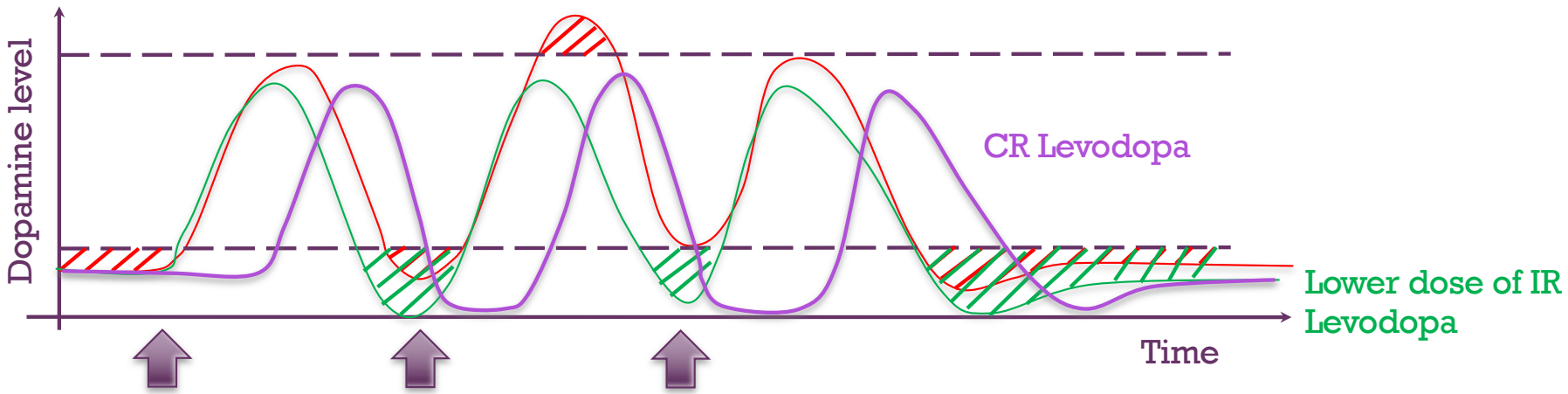
Disadvantages

- Side effects can occur and persist > 1 year (e.g. gait imbalance, sensory loss, motor weakness, loss of taste, speech difficulties)
- Not available in BC → Sunnybrook Hospital (Toronto)

Dyskinesia

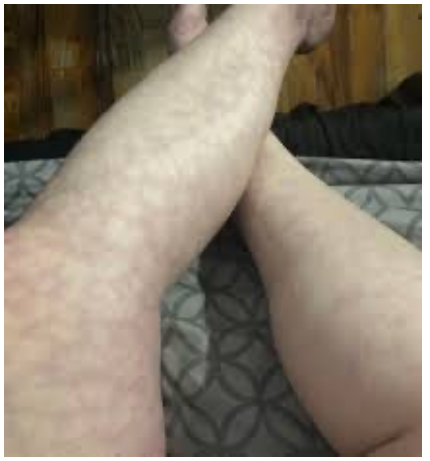
Treatments for Dyskinesia

- 1st step is to optimize your Levodopa/carbidopa regimen
  - Smaller more frequent doses
  - Combination of Immediate-Release and Controlled-Release levodopa/carbidopa formulations



Treatments for Dyskinesia

- As the disease progresses … the brain loses the ability to *buffer* the pulse of dopamine that occurs with each dose of Levodopa
- At this point, it may become necessary to start **Amantadine** 100 mg 2x/day
  - An NMDA receptor antagonist
  - Side effects include:
    - Common: drowsiness, lightheadedness, leg edema, dry mouth, constipation, **livedo reticularis**
    - Serious: cognitive impairment, delusional thinking and hallucinations
- Pallidal (GPi) DBS – reduces dyskinesia so that a person with PD can better tolerate Levodopa
  - Unlike STN DBS, this does not reduce reliance on Levodopa



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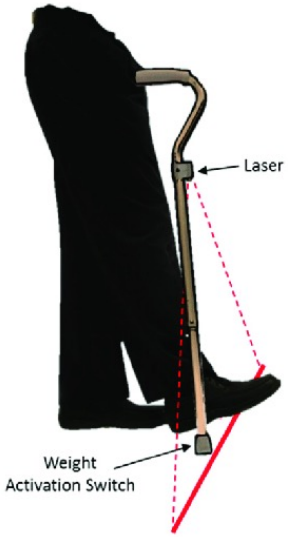
Freezing

Treatments for Freezing

- 1st step is to optimize your Levodopa/carbidopa regimen
- Next step: amantadine 100 mg 2x/day – also for freezing!
- **U-step Walker (~ $1000 USD, Laser Cane ($230 USD) and Laser Cue ($200 USD)**



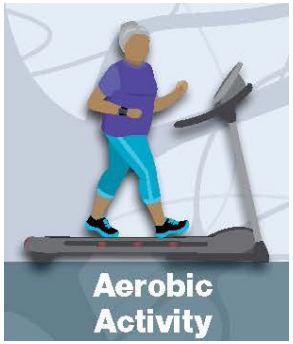
www.ustep.com

The medications for Parkinson's do not slow the progression of the disease. They help you move better, but then the rest is up to you …

… exercise is the only thing known to slow down the progression of Parkinson's disease.

Parkinson-specific exercise programs

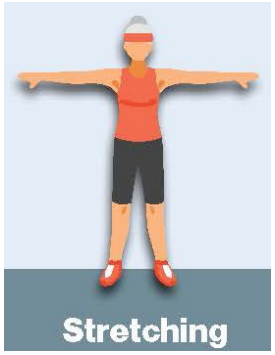
Current recommendations:



- Aerobic exercise at a minimum of:
  - 3x/week
  - 30-40 minute main exercise set (don't forget to do warm up and cool down stretches)
  - Get heart rate to within 70-85% of max

Along with …

- Strength training 2-3 days/week
  - 8 to 15 repetitions for major muscle groups or arms and legs
  - Weight machines, resistance bands or light handheld weights
- Balance and agility training, together with stretching 2-3 days/week



Prior to starting any exercise program, you should consult with your healthcare team (family doctor or Neurologist) to ensure that you can safely engage and complete any exercise intervention

Adapted from the Parkinson's Foundation
www.parkinson.org

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Take home messages …

Take home messages

- The building block of all Parkinson's medication treatment regimen is Levodopa
  - There are many "flavors" of Parkinson's disease … so treatment regimens need to be individualized for every individual with Parkinson's disease
- Advanced therapies are used to better optimize motor symptoms
  - But the best response to these therapies is equivalent to your best response to Levodopa
- Access to Advanced Therapies is limited in BC
  - There is a need to improve funding and access to DBS, Focused Ultrasound (FUS) and Duodopa
- New therapies are emerging which hold the promise of improving the quality of life of people with Parkinson's disease
  - Vyalev
- Medications alone are not enough … to live your best possible life, you have to stay active!

Fraser Health Movement Disorder Clinic at Jim Pattison Centre in Central Surrey

- Dr. Anish Kanungo: Coastal Clinics (South Surrey)
- Dr. David Rydz (New West)
- Dr. Claire Hinnell (Langley)

Vancouver Coastal Health Movement Disorder Clinic at UBC in Vancouver

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