ADVANCED TREATMENTS

Therapeutic options for those with fluctuating symptoms in Parkinson's Disease

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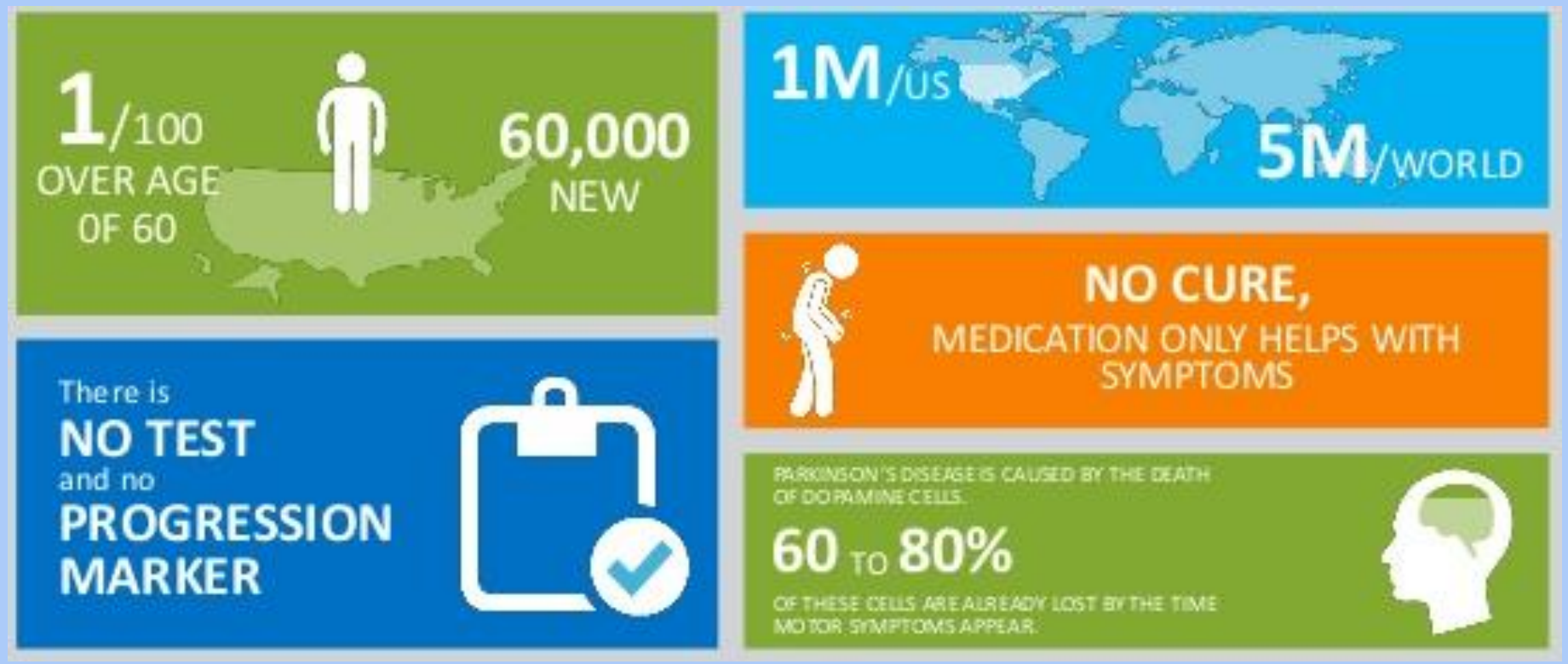
Co-Director

INOVA®

Movement Disorders Program

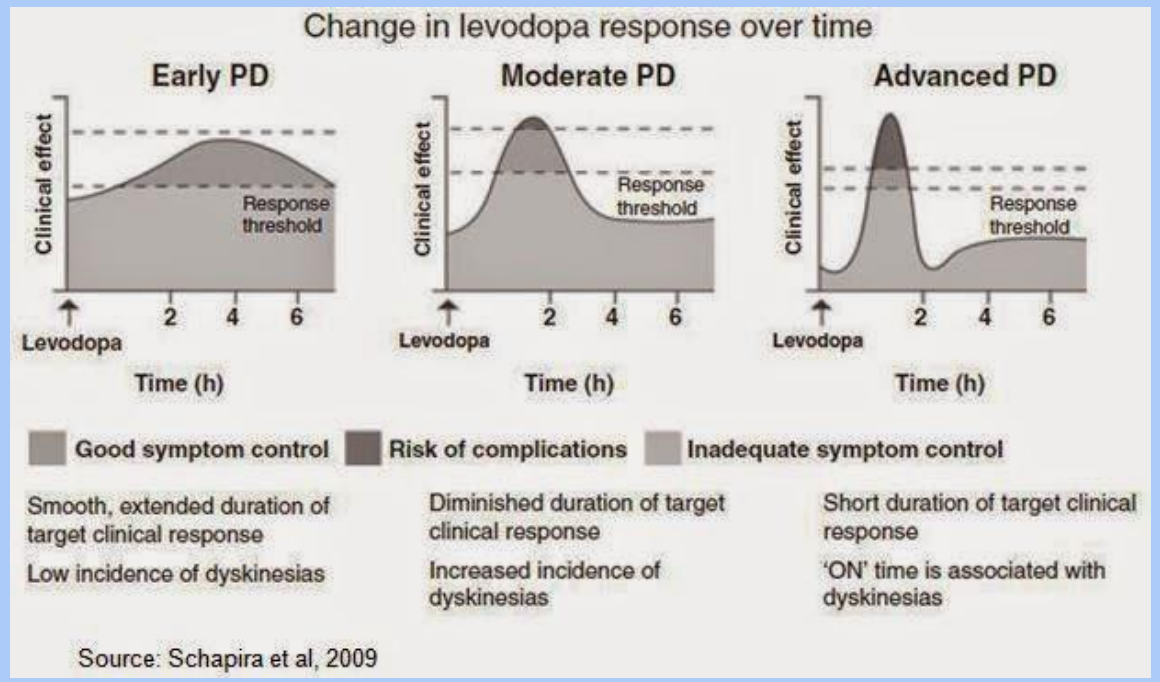
WHY DOES PARKINSON'S DISEASE ADVANCE?

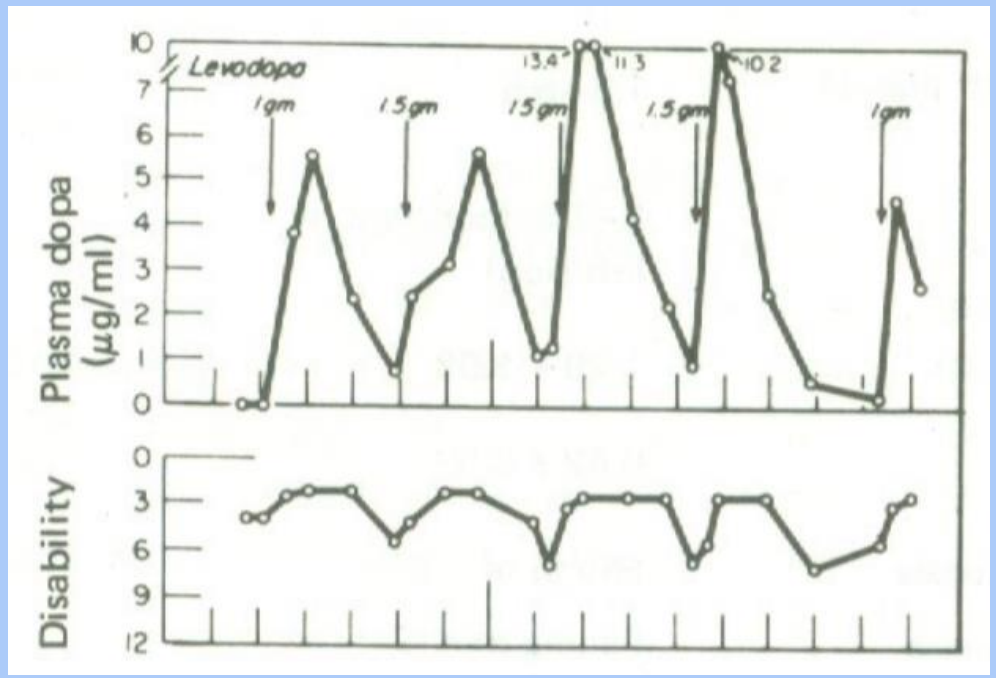
1. The disease itself



WHY DOES PARKINSON'S DISEASE ADVANCE?

2. Medications used





WHY DOES PARKINSON'S DISEASE ADVANCE?

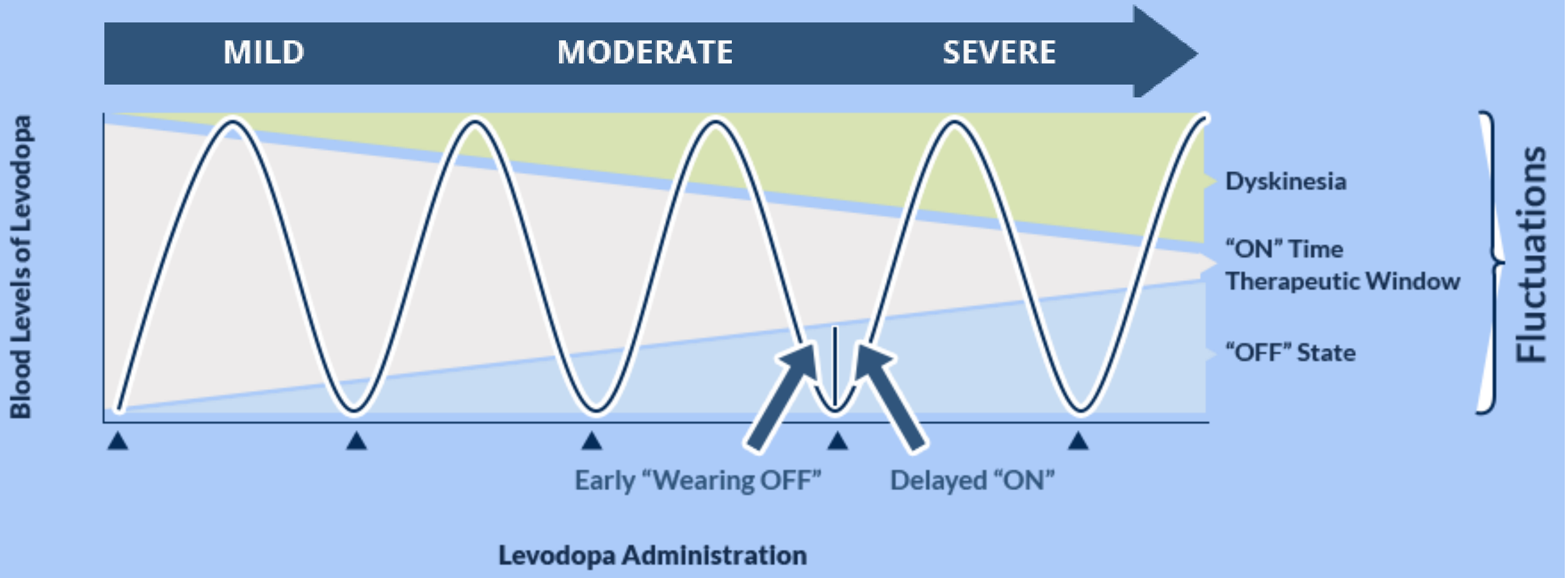
2. Medications used

- ELLDOPA trial 16.5% of patients randomized to **600 mg** of LD daily developed dyskinesias after only 9 months of treatment versus 2.3% among those on 300 mg (2004)
- Worsening motor complications with doses ≥ **600mg** per day at 6 months and 6 years (2005)
- Increased motor fluctuations and dyskinesia ≥ **500mg** per day at 6 years (2013)

Combination of disease progression and pulsatile medication dosing impacts the number of dopamine receptors present among other things.

Result = Worsening on-off fluctuations throughout the day

CARBIDOPA – LEVODOPA



APPROACH TO THERAPY

Classic	vs	Contemporary
▪ Pulsatile and frequent ▪ Higher and higher doses		▪ Predictable and long acting ▪ Low doses, multiple targets ▪ “Rational polypharmacy” ▪ Employ technology earlier
▪ Fluctuations ▪ Early side effects ▪ Treatment horizon		▪ Smoother ▪ Reduced side effects ▪ More evergreen

EXPANDED TOOLBOX UP UNTIL 3 YEARS AGO

- Dopamine Agonist

Neupro® (Rotigotine Transdermal System)

REQUIP ropinirole HCl

Mirapex® pramipexole dihydrochloride tablets

- Carbidopa/Levodopa formulation

PARCOPA® (carbidopa and levodopa orally disintegrating tablets)

- MAOB inhibitor

Once-Daily AZILECT® (rasagiline tablets)

- COMT inhibitor

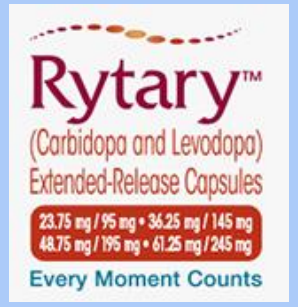
Stalevo® (levodopa, carbidopa and entacapone) tablets

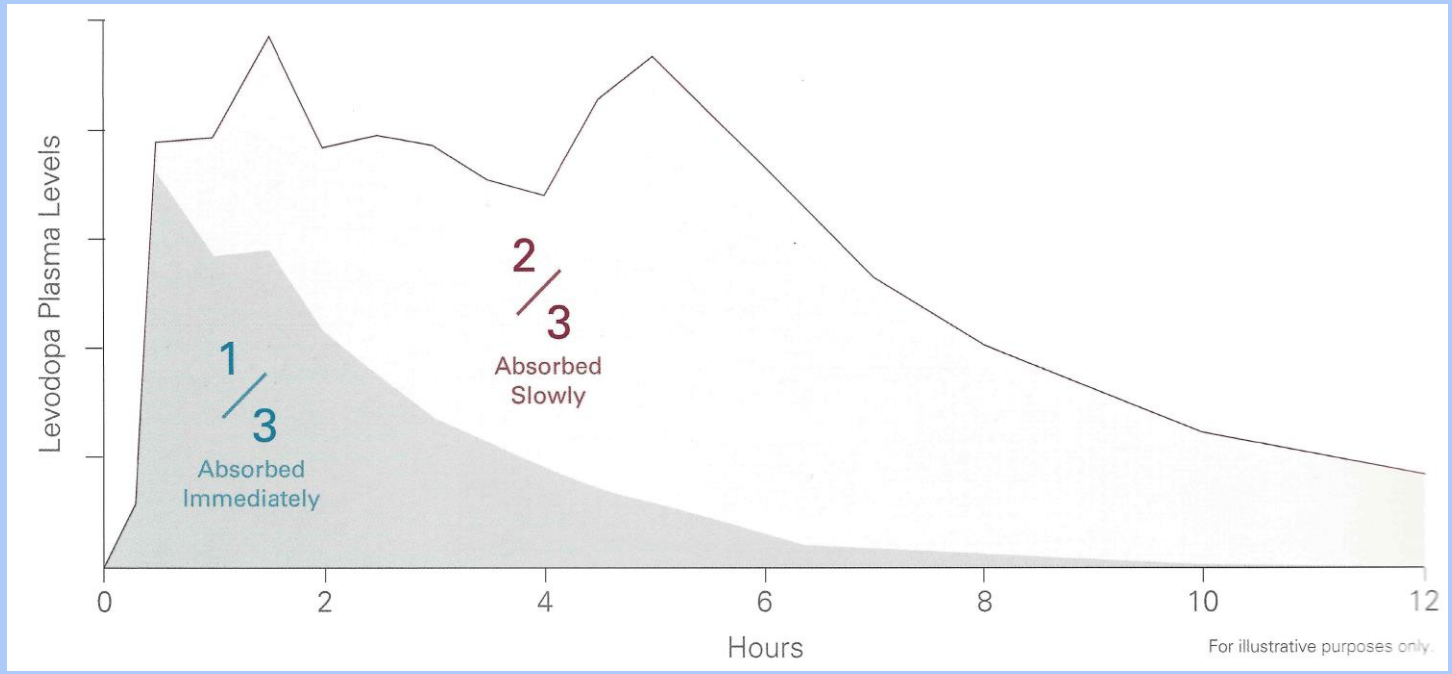
COMTan® (entacapone) tablets

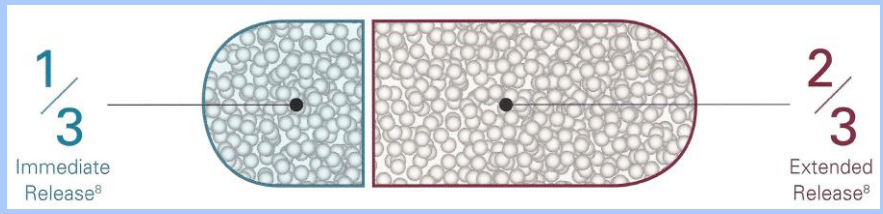
NEW FORMULATION

Rytary™

- New formulation to deliver Carbidopa-Levodopa.
- Can last from 5 to 8 hours compared to 2 to 3 hours for Sinemet.
  - 1 to 2 hours less off time, 2 hours more on time







Pahwa et al: APEX-PD Investigators. Randomized trial of IPX066, carbidopa/levodopa extended release, in early Parkinson's disease. Parkinsonism Relat Disord. 2014 Feb;20(2):142-8.

Hauser et al: ADVANCE-PD investigators. Extended-release carbidopa-levodopa (IPX066) compared with immediate-release carbidopa-levodopa in patients with Parkinson's disease and motor fluctuations: a phase 3 randomised, double-blind trial. Lancet Neurol. 2013 Apr;12(4):346-56.

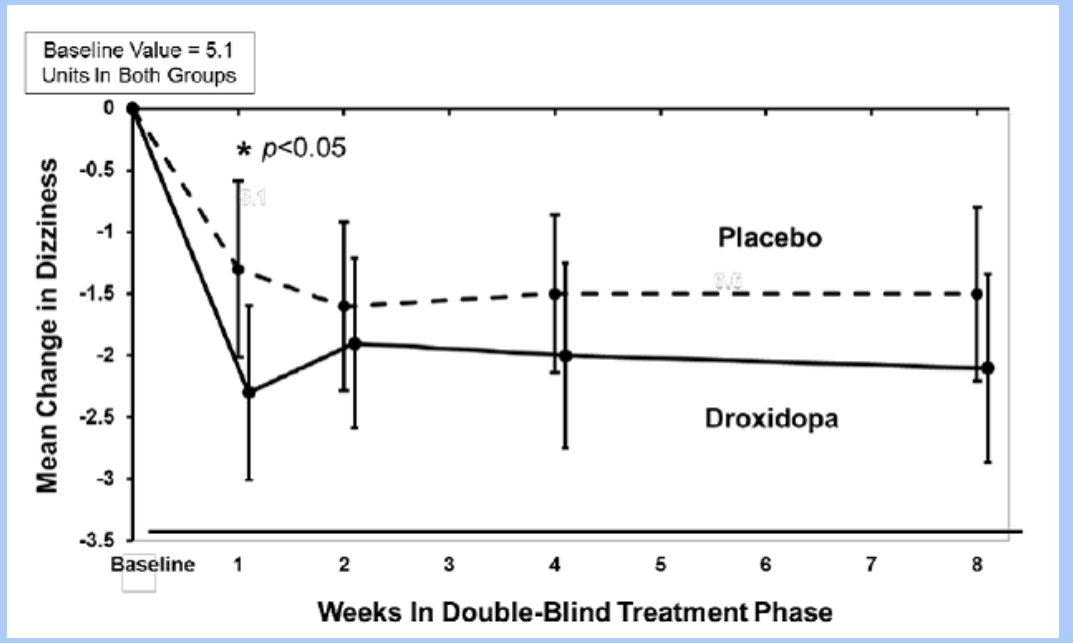
ORTHOSTATIC HYPOTENSION

Northera™

- OH is common symptom of Parkinson's Disease
- Can be worsened by dopamine supplementation

- Prodrug for Norepinephrine, crosses BBB
- Peripheral Nervous system – increased BP, improved Neurogenic Orthostatic Hypotension
- Central Nervous system – attention? Gait? Falls?

Northera™
(droxidopa) Capsules
100 mg · 200 mg · 300 mg



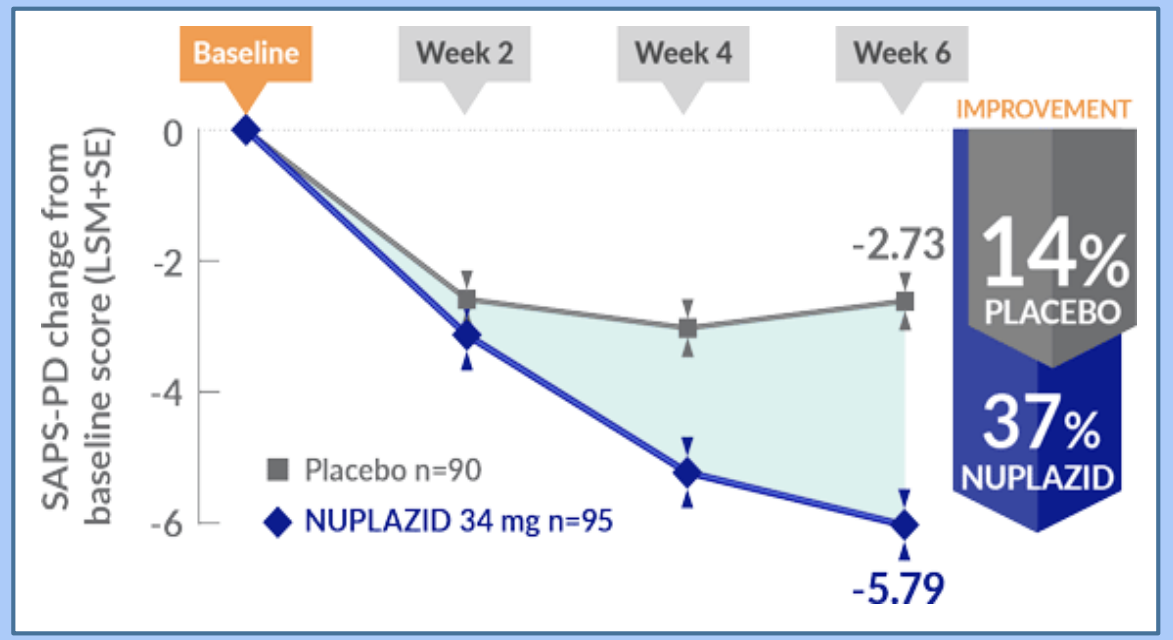
Kaufmann et al. Droxidopa for neurogenic orthostatic hypotension: a randomized, placebo-controlled, phase 3 trial. Neurology. 2014 Jul 22;83(4):328-35.

HALLUCINATIONS AND PSYCHOSIS

Nuplazid (Pimavanserin)™

- First antipsychotic medication specifically designed for hallucinations and ‘psychosis’ associated with Parkinson’s Dementia and Lewy Body Dementia.
- Serotonin Agonist with no impact on dopamine receptors
- Novel drug status
- + SAPS-PD improvement with no change in UPDRS

NUPLAZID™
(pimavanserin) tablets



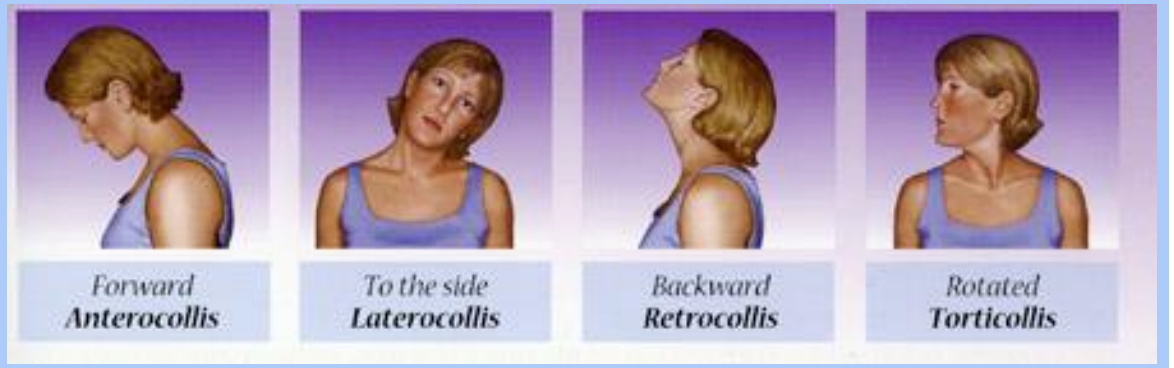
Hacksell, Uli et al. “On the Discovery and Development of Pimavanserin: A Novel Drug Candidate for Parkinson’s Psychosis.” *Neurochemical Research*39.10 (2014): 2008–2017. *PMC*. Web. 4 June 2015.

BOTULINUM TOXIN INJECTIONS

- 2015 Systematic review - “strong evidence” (Level 1) that instrument guidance with EMG and ultrasound was more effective in toxin placement.[1]

- EMG guided – pain and/or muscle spasm
  - Cervical dystonia
  - Segmental dystonia of arms/legs/neck/trunk
  - Writer’s cramp
  - Blepharospasm, hemifacial spasm
  - Tremor

- Excessive drooling (sialorrhea)



1) Grigoriu et al. “Impact of injection-guiding techniques on the effectiveness of botulinum toxin for the treatment of focal spasticity and dystonia: a systematic review.” Arch Phys Med Rehabil. 2015 May 13.

TECHNOLOGY

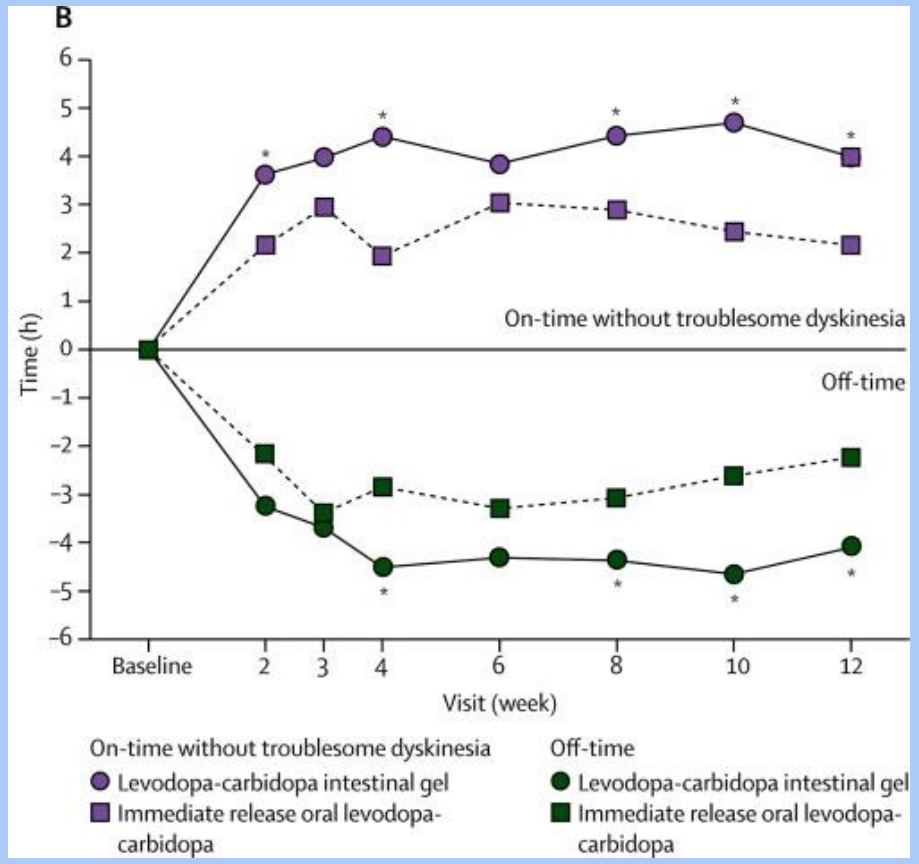
- DUOPA Intestinal Gel
- Focused Ultrasound
- Deep Brain Stimulation

CONSTANT DELIVERY OF LEVODOPA

Duopa™

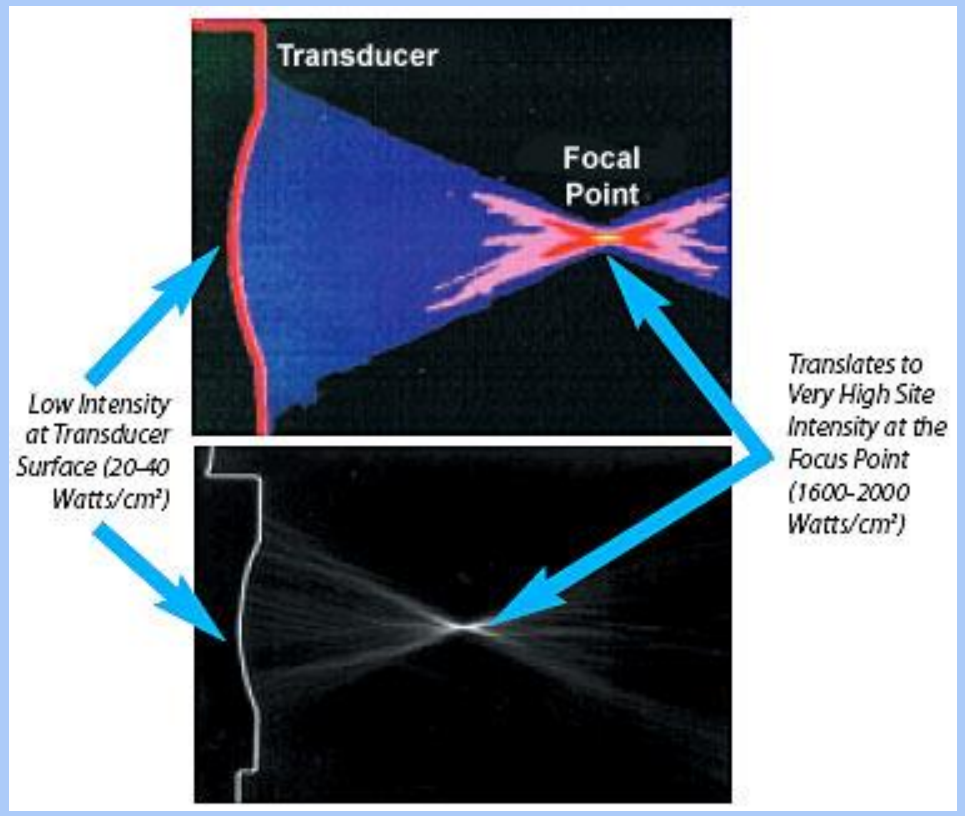
- Dopamine gel continuously administered via intra-intestinal pump
- Provides steady delivery of levodopa without the fluctuations of oral medication
- Off time decreased by 4h and on time increased by 4h[1]

Duopa
carbidopa/levodopa
enteral suspension
4.63 mg/20 mg per mL



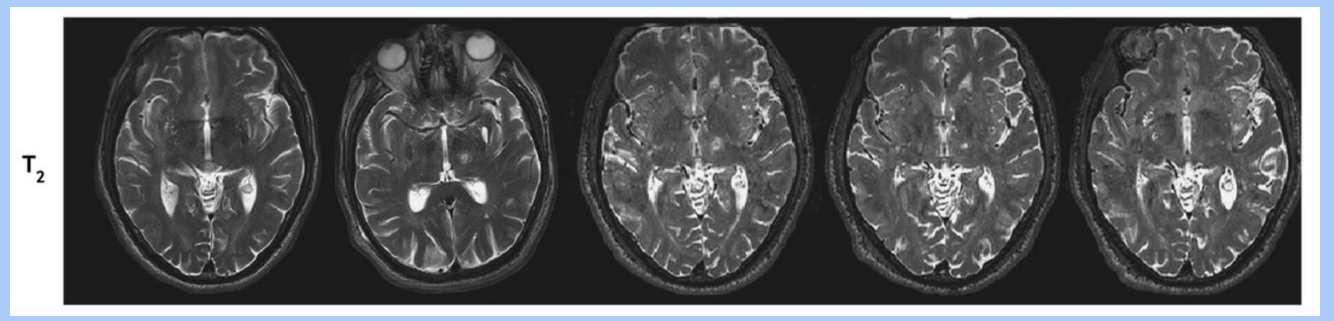
Olanow et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. Lancet Neurol. 2014 Feb;13(2):141-9.
http://www.parkinson-italia.it/

FOCUSED ULTRASOUND



- 1,000 ultrasound beams
- Non-invasive
- Creates focal lesion at target
- Still in research

- New approach to an old technique?
- Too early for long-term results?



"So far, the jury is out. We are, after all, burning a hole in the brain."

DEEP BRAIN STIMULATION (DBS)

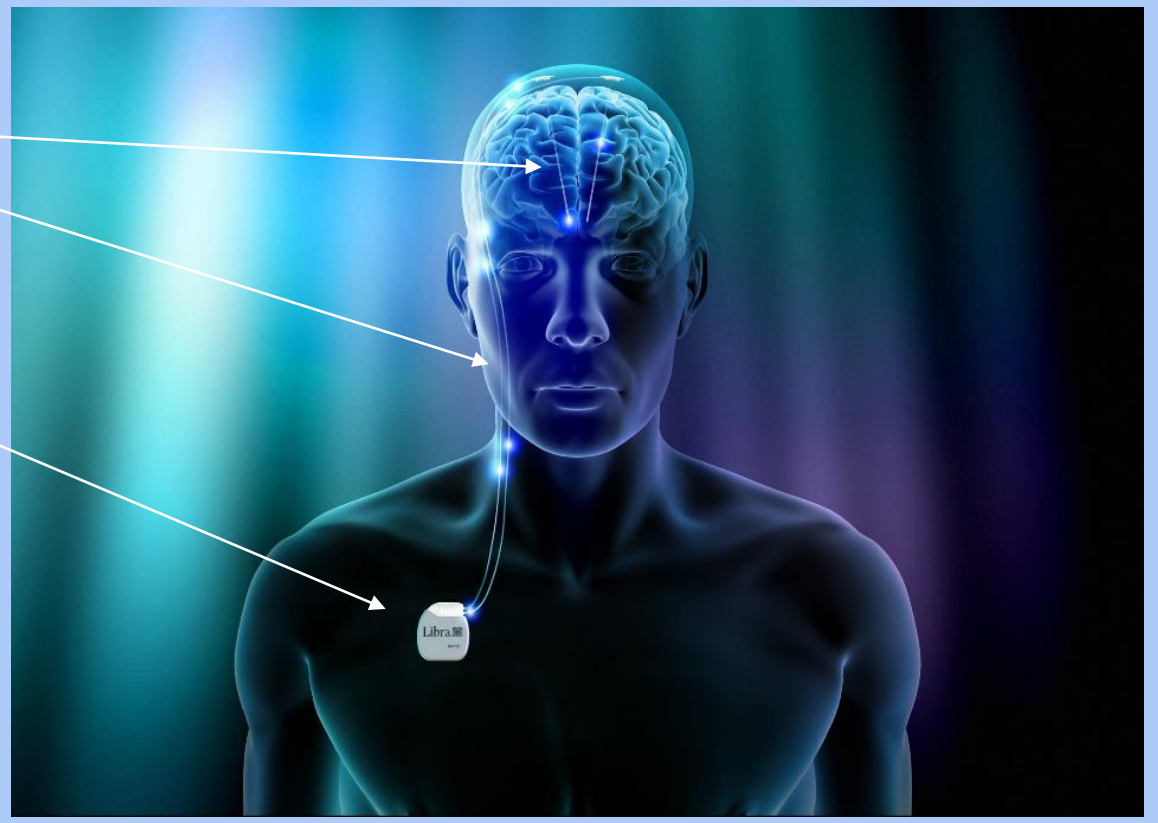
1990s – DBS emerged as safer treatment with significantly longer duration of action compared to lesioning; no 'burnout'.

- Surgically implanted device to deliver a controlled stimulation of electricity to a specific region of the brain.
- Implanted in 2 step procedure, then programmed as outpatient.
- Unlike previous surgeries for PD (pallidotomy or thalamotomy), DBS does not damage healthy brain tissue by destroying nerve cells.
- Removable, if necessary, with little to no tissue damage.*

* Haberler et al. No tissue damage by chronic deep brain stimulation in Parkinson's disease. Ann Neurol. 2000 Sep; 48(3):372-6

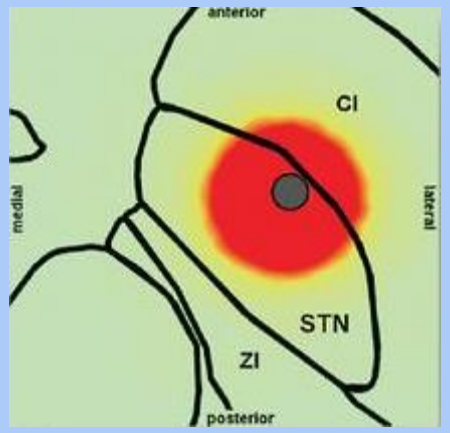
DEEP BRAIN STIMULATION (DBS)

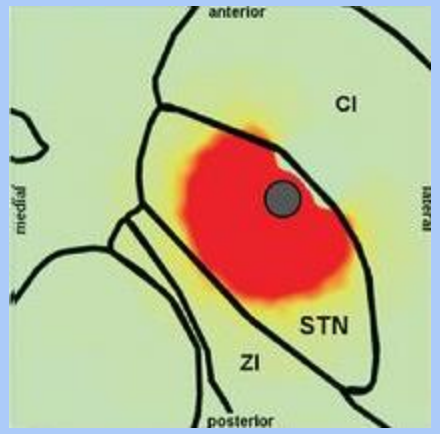
- The DBS system consists of three components:
  - Intracranial Lead
  - Extension connecting lead and generator
  - Implanted pulse generator (neurostimulator)
- Unilateral or bilateral leads
- Proper patient selection is key



AN EXPANDING FIELD

- Directional stimulation
- Improved technology
- Smaller technology, thinner
- Longer battery life





Medtronic

ST. JUDE MEDICAL

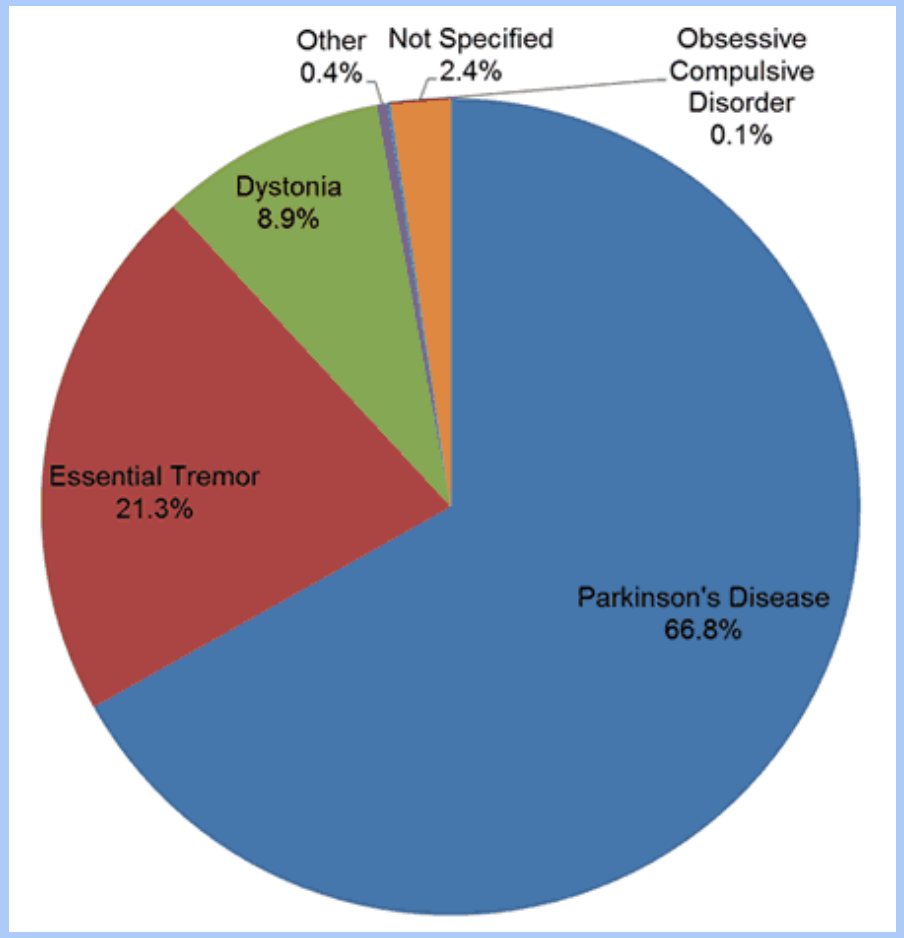
Boston Scientific

DBS INDICATIONS

- DBS is an FDA indicated surgical procedure for the treatment of movement disorders, such as:
  - Parkinson's Disease
  - Essential Tremor
  - Dystonia

- FDA approved:
  - Essential tremor in 1997
  - Parkinson's disease in 2002
  - Dystonia in 2003

Covered by all insurance providers.



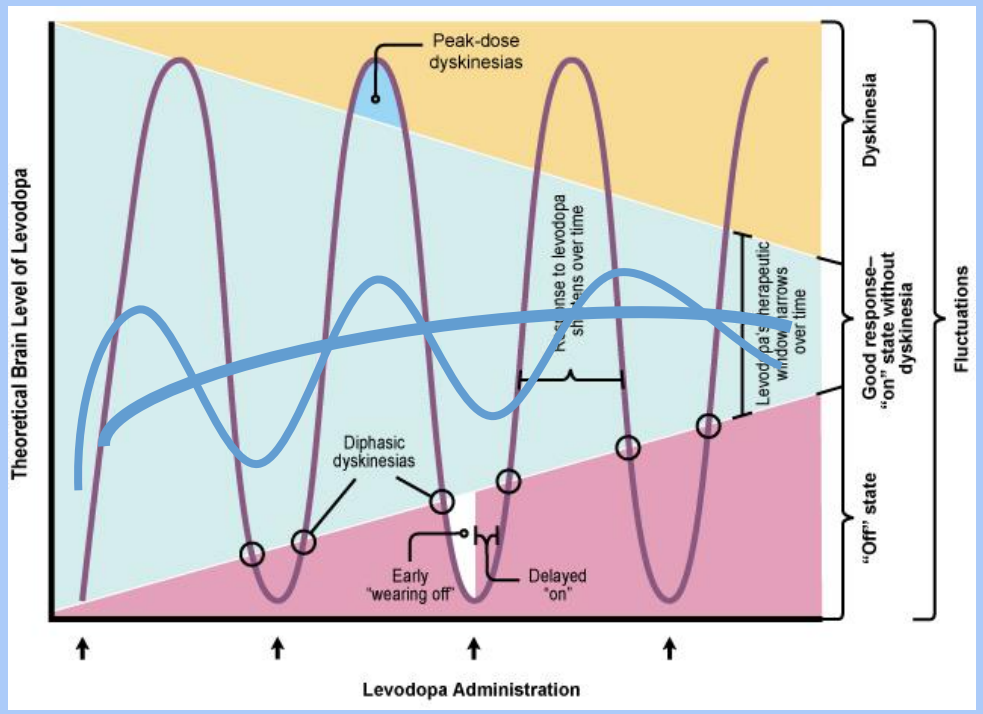
Iplantable Systems Performance Registry (ISPR) for deep brain stimulation systems. July 2009 -July 31, 2013.

BENEFIT FOR OUR PATIENTS

Parkinson's Disease:

- **80-90%** of patients note improvement
- **60%** reduction in medications
- **60%** reduction in dyskinesias
- **80%** improvement in "off" periods
- **10%** improvement in "on" periods

- Reduction in medications leads to decrease in the following:
  - Cost
  - Side effects (nausea, orthostasis, cognitive change, and downstream dyskinesia risk)



Krack et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med. 2003 Nov 13; 349(20):1925-34.

WHO IS A CANDIDATE

- A good candidate for DBS per our center:

1. Parkinson's Disease at least 3 yrs (FDA indication)
2. Experiencing a response to medication
3. Experiencing the on-off fluctuation of medication
4. Able to participate in care
5. Good surgical candidate
6. No diagnosed dementia or severe psychiatric disorder

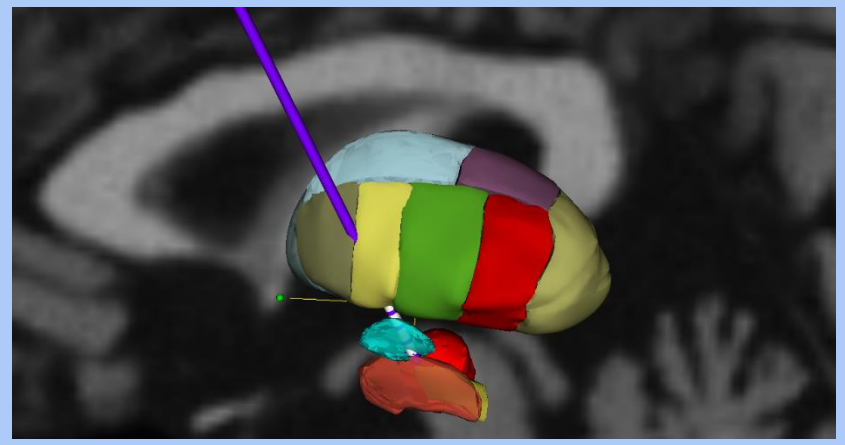
MULTIDISCIPLINARY APPROACH

A team approach is key to a successful outcome.

- Cognitive evaluation
  - Full Neuropsychiatric testing
- Psychiatric evaluation, if necessary
- Physical therapy, occupational therapy and speech therapy
- Neurosurgical evaluation
  - Work together for pre-surgical planning
    - GPI vs STN, Unilateral vs Bilateral
  - Intra-operative cooperation
- Movement Disorders Specialist

www.Smithsonianmag.com

PARKINSON'S DISEASE



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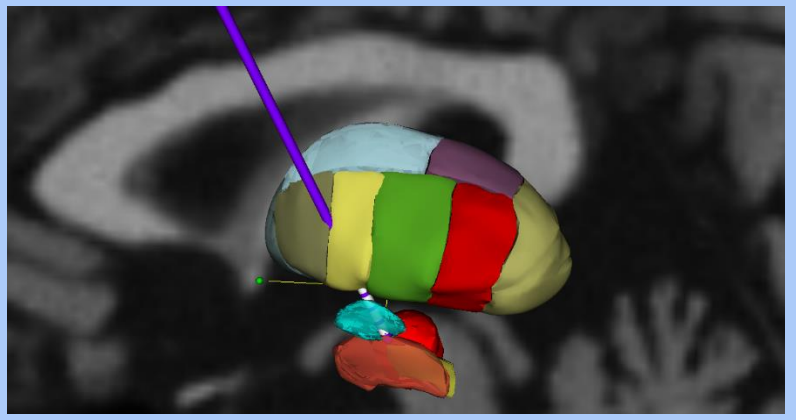

TO THE FUTURE

- Longer-acting levodopa formulations (10 hours or greater)
- New MAO-B and COMT inhibitors
- Inhaled or sublingual formulations
- Improved technology
- Targeted protein therapy
- Cure

All of this equals

HOPE

THANK YOU

INOVA®

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