ADVANCEMENTS IN THE TREATMENT OF PARKINSON'S DISEASE

Neurorestoration and Beyond

INOVA®
Movement Disorders Center

INOVA MOVEMENT DISORDERS CENTER

INOVA®
Movement Disorders Center

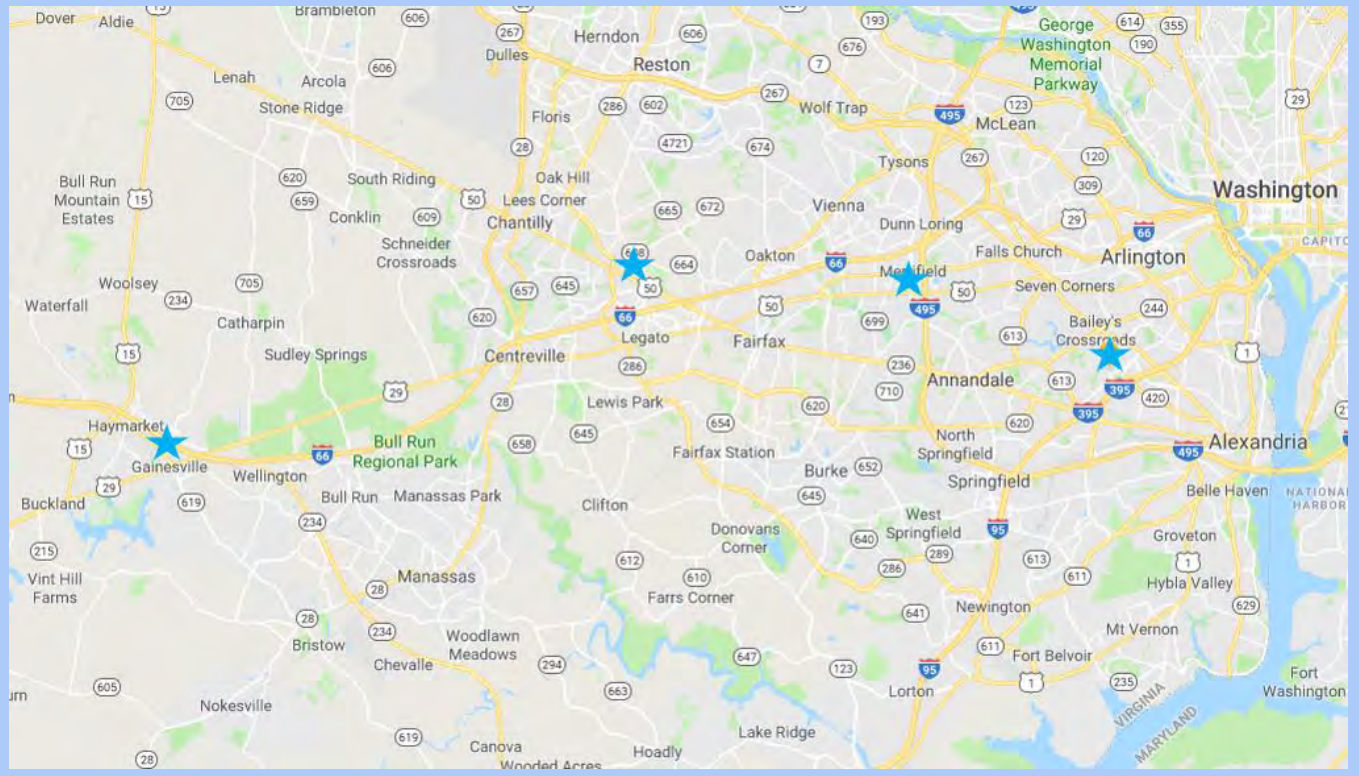
INOVA MOVEMENT DISORDERS CENTER

1500 N. Beauregard Street
Suite 300
Alexandria, VA 22311

8505 Arlington Boulevard
Suite 450
Fairfax, VA 22031

3580 Joseph Siewick Dr.
Suite 206
Fairfax, VA 22033

7051 Heathcote Village Way
Suite 230
Gainesville, VA 20155



703-845-1500

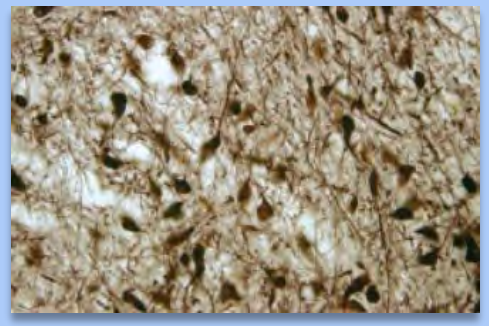
www.inova.org/move

INOVA®
Movement Disorders Center

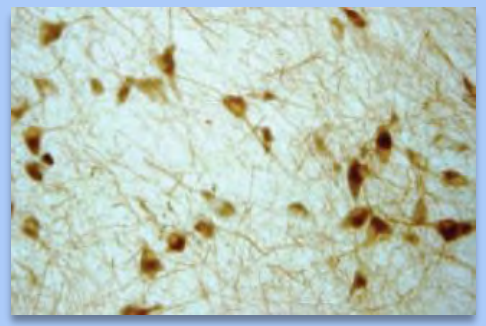
WHAT IS PARKINSON'S?

WHAT CAUSE PARKINSON'S DISEASE?

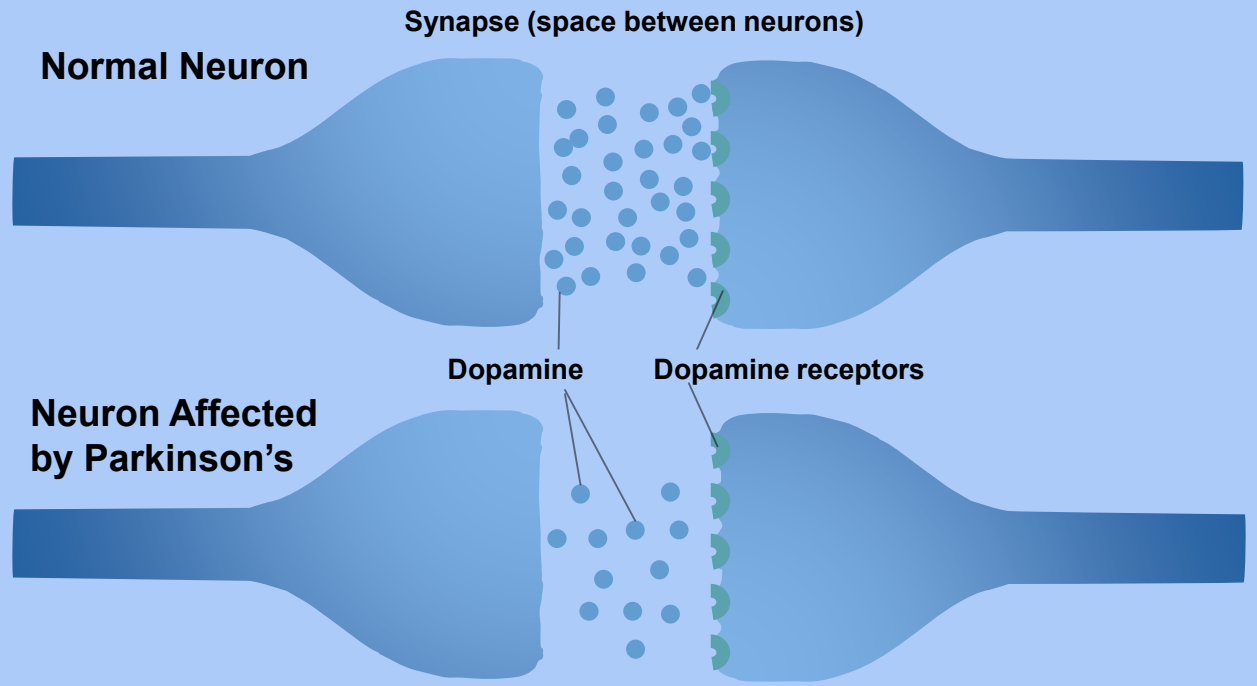
PARKINSON'S DISEASE IS CAUSED BY A DECREASE IN DOPAMINE PRODUCTION IN THE BRAIN



Healthy Brain Cells (Neurons)



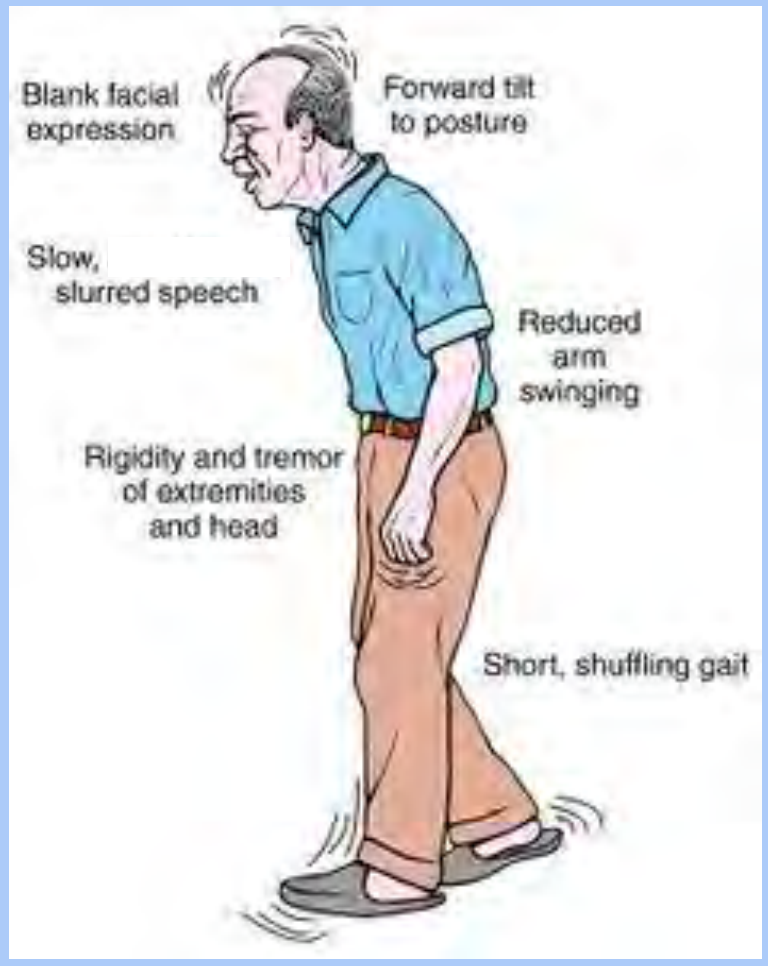
Brain Cells with Parkinson's Disease



WHAT HAPPENS IF YOU HAVE REDUCED DOPAMINE?

- Motor and Non-motor Symptoms
  - Systems which function inappropriately due to reduction in Dopamine or one of its byproducts

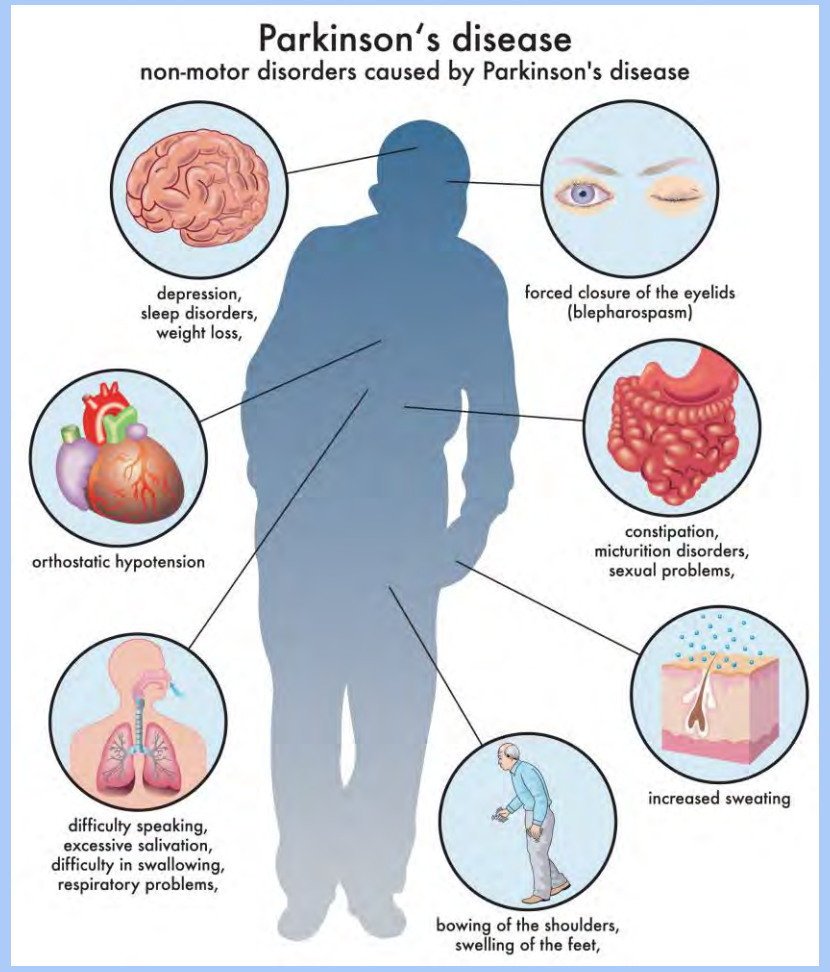
- **Motor Symptoms**
  - Resting tremor
  - Tremor with position
  - Bradykinesia (slowness)
  - Rigidity (stiffness)
  - Slow walking, shuffle, reduced arm swing
  - Balance issues
  - Reduced facial expression (flat affect)
  - Speech changes (hypophonia)



NON-MOTOR SYMPTOMS

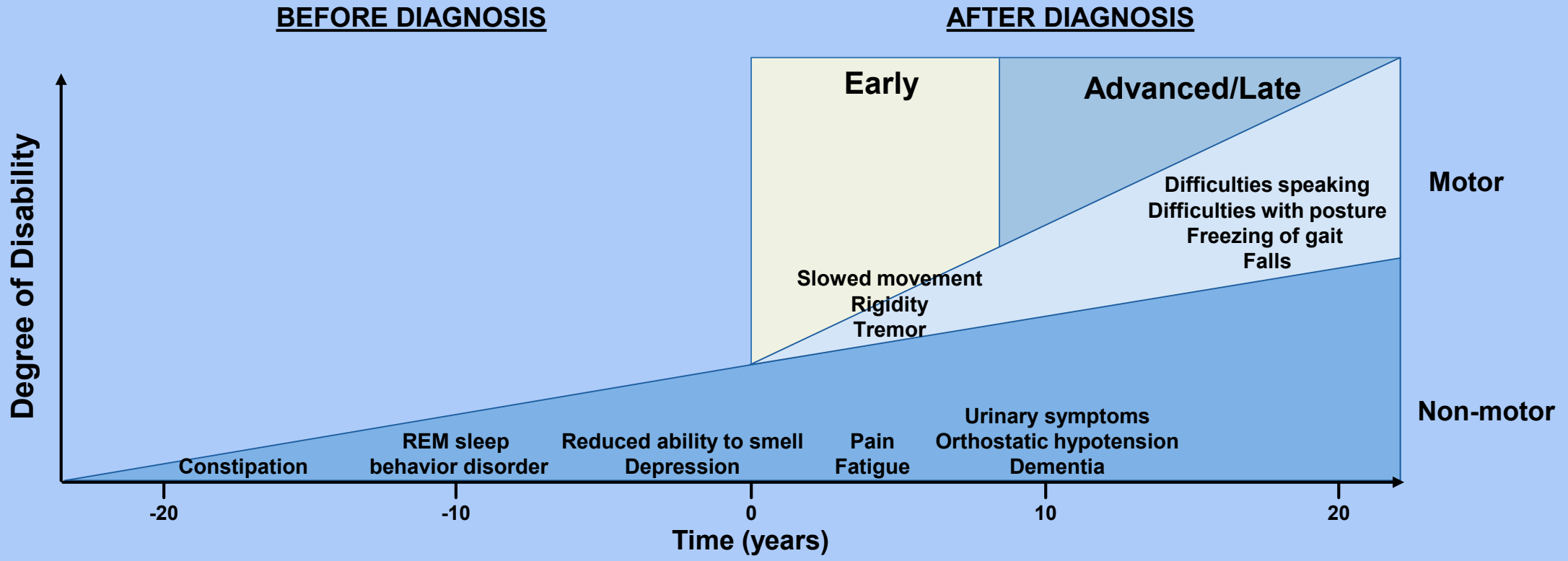
****Can present years before diagnosis****

- Loss of sense of smell
- Constipation
- Talking in sleep or acting out dreams
- Anxiety/Depression
- Bladder issues
- Excessive saliva/drooling
- Vision changes
- Problems sweating
- Lightheadedness/Dizziness on standing
- Fatigue
- Skin problems
- Cognitive changes



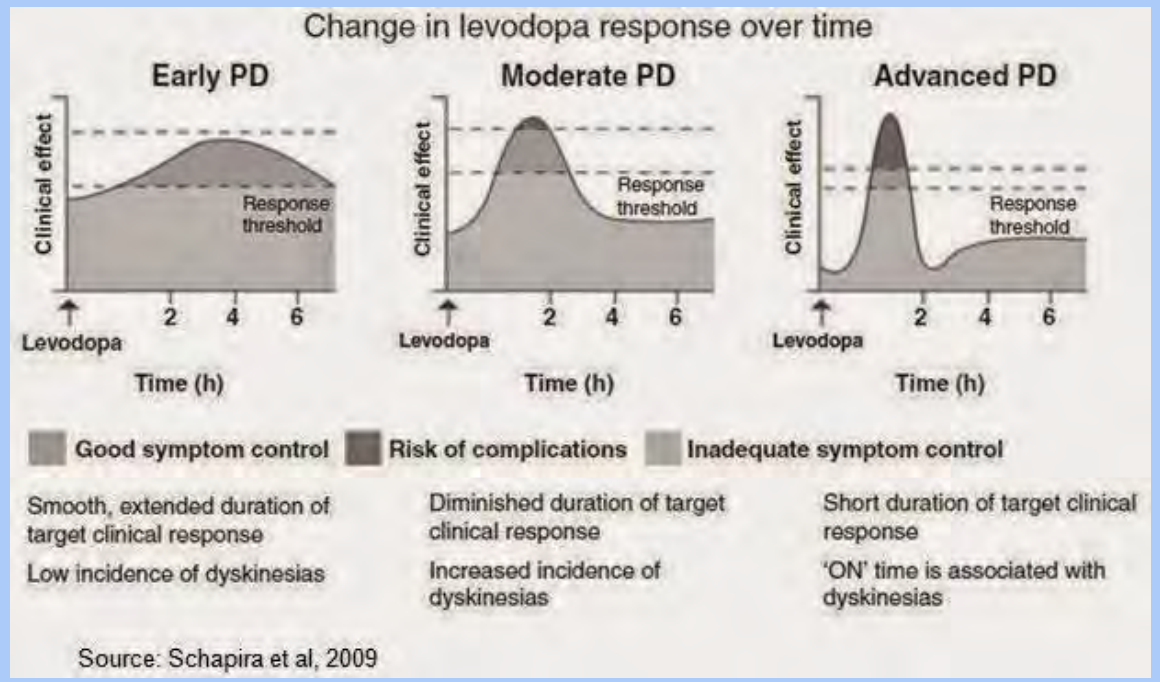
PARKINSON'S CHANGES OVER TIME

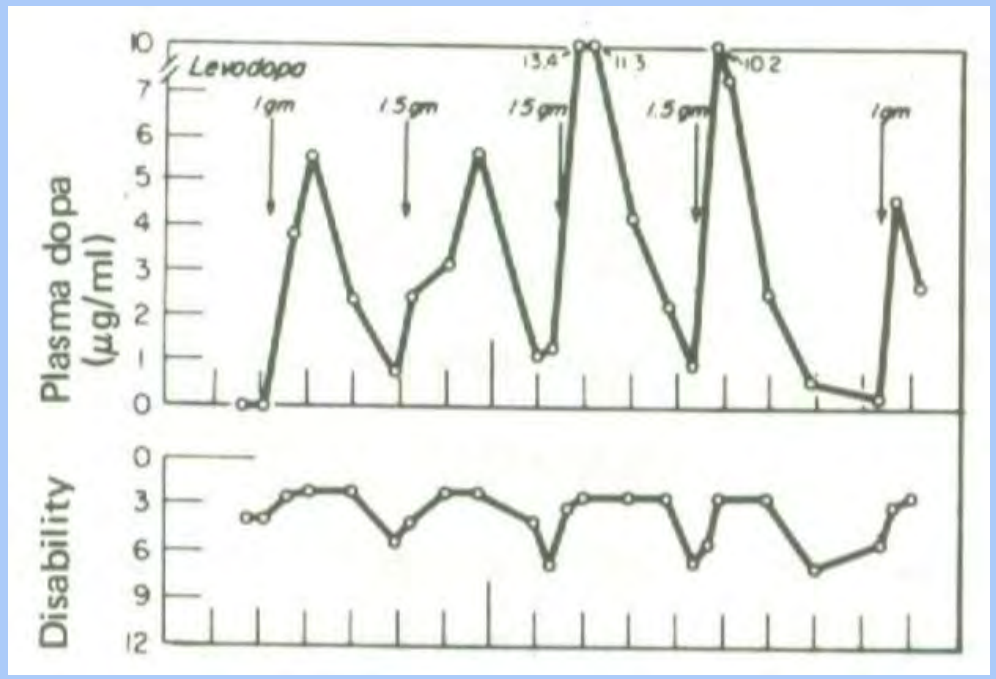
THE SYMPTOMS OF PARKINSON'S DISEASE VARY FROM PERSON TO PERSON, BUT MAY INCLUDE BOTH MOTOR AND NON-MOTOR SYMPTOMS



WHY DOES PD CHANGE OVER TIME?

Current debate - the disease itself AND medications used?





WHY DOES PD CHANGE OVER TIME?

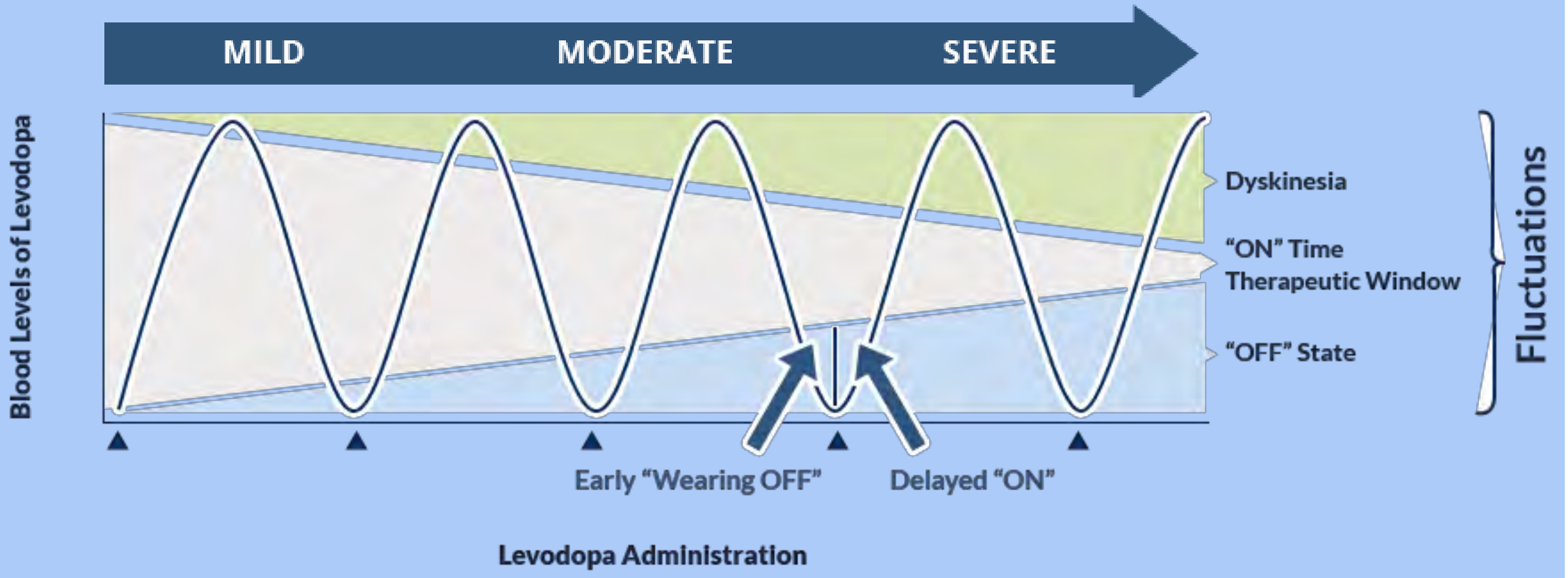
Classic carbidopa/levodopa

- 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)
- STRIDE-PD trial showed 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

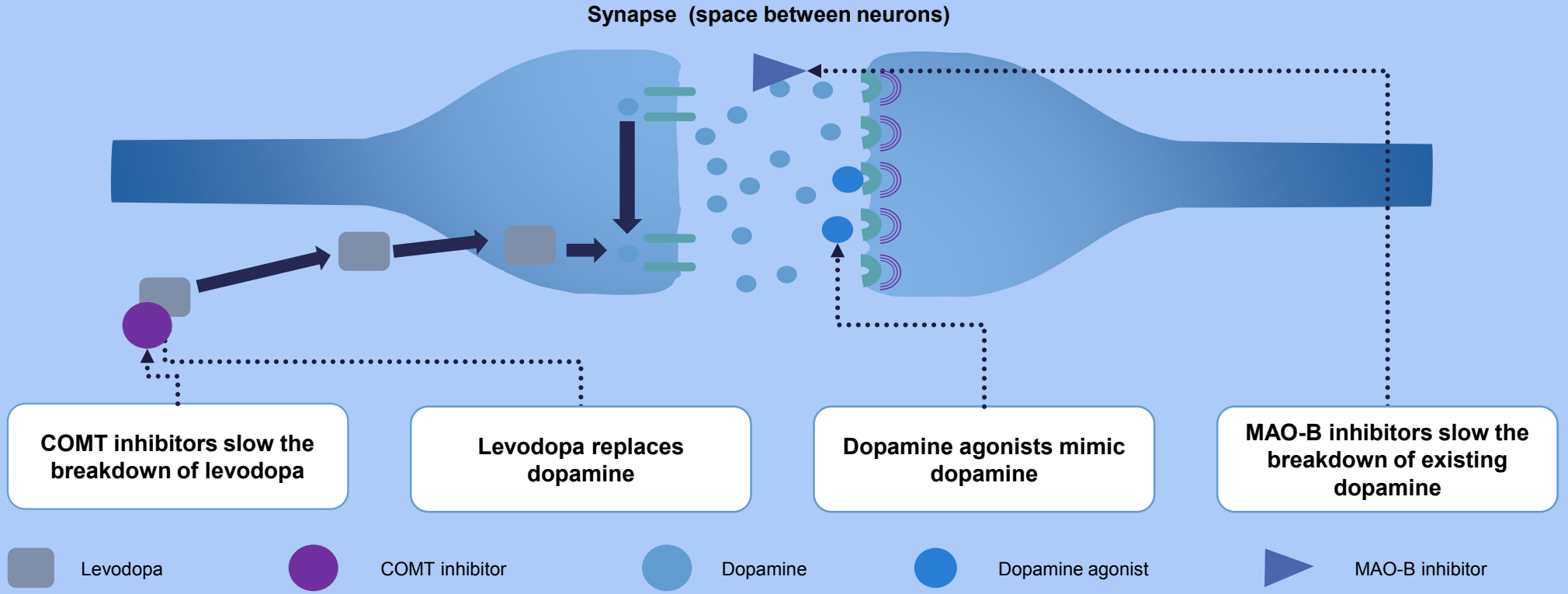


APPROACH TO THERAPY

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 ▪ Evergreen

MEDICATION CATEGORIES FOR PD

PARKINSON'S DISEASE MEDICINES WORK TO INCREASE DOPAMINE OR ACT LIKE DOPAMINE IN THE BRAIN



COMT = catechol-*O*-methyltransferase.
MAO-B = monoamine oxidase-B.
Kalia LV et al. *Lancet.* 2015;386:896–912

EXPANDED TOOLBOX UP UNTIL 8 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

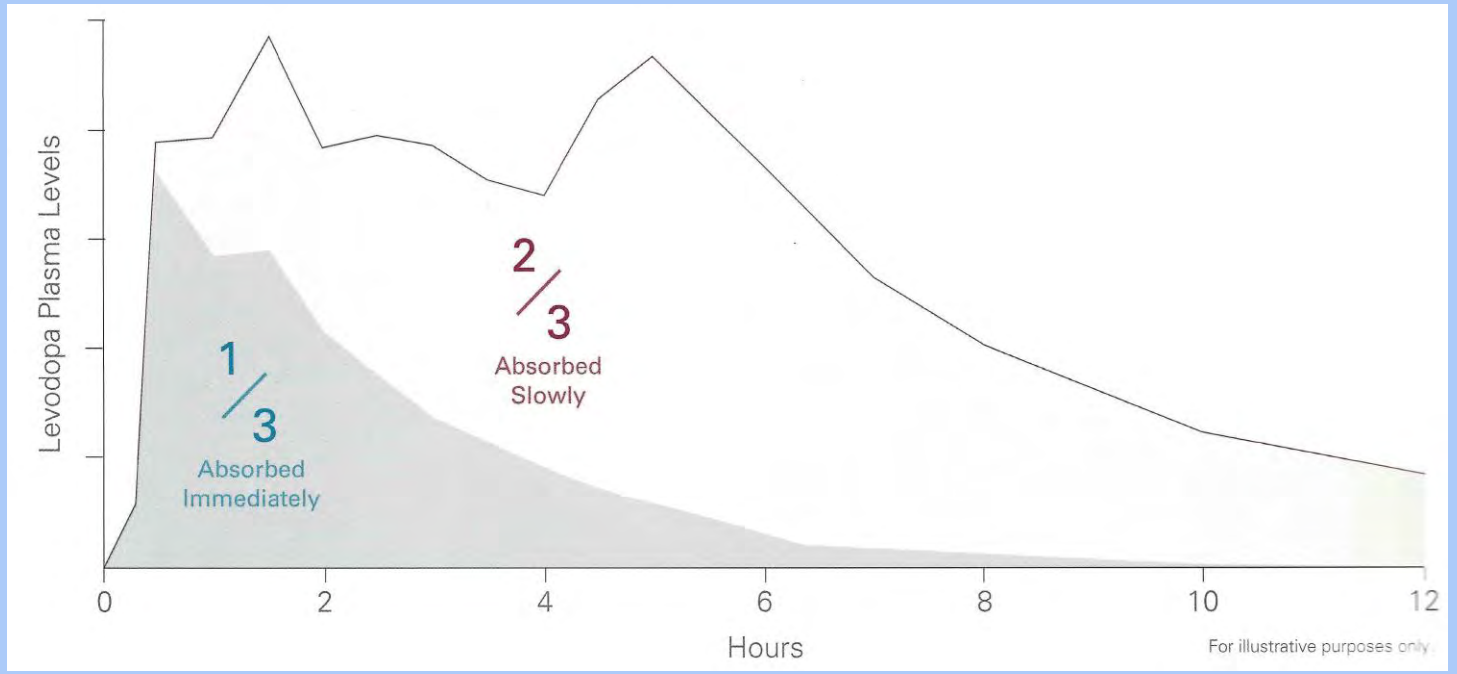
Stalevo® (levodopa, carbidopa and entacapone) tablets

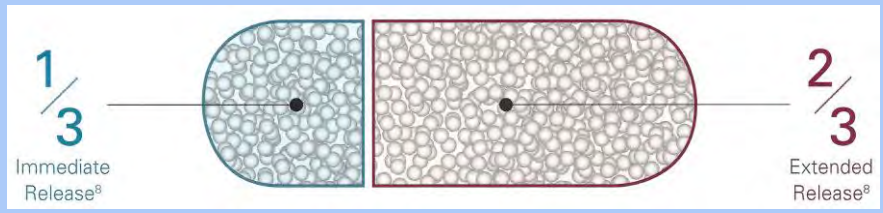
COMTan® (entacapone) tablets

NEW LEVODOPA 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.

NEW MAO-B INHIBITOR, AUGMENTING THE SYSTEM

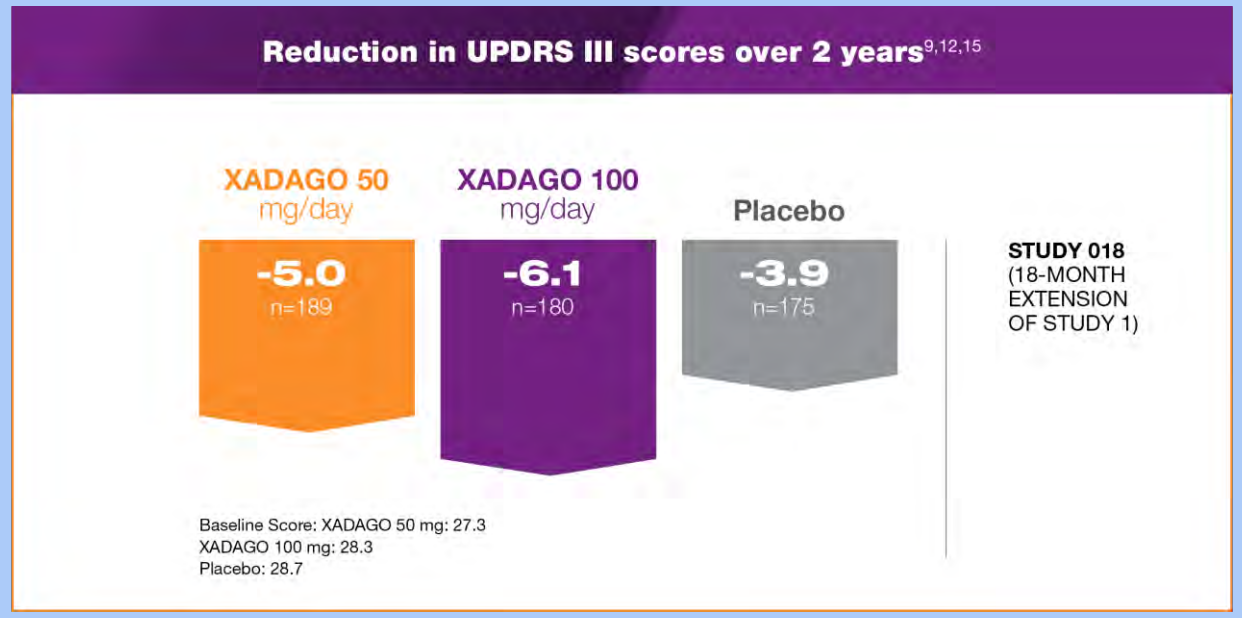
Safinamide (Xadago)

XADAGO®
(safinamide) tablets

- Reversibly inhibits the MAO-B enzyme
- Boosts natural dopamine and potentiates artificial dopamine

- 1x daily

- Similarity to rasagiline (Azilect) which is now generic but still expensive to some

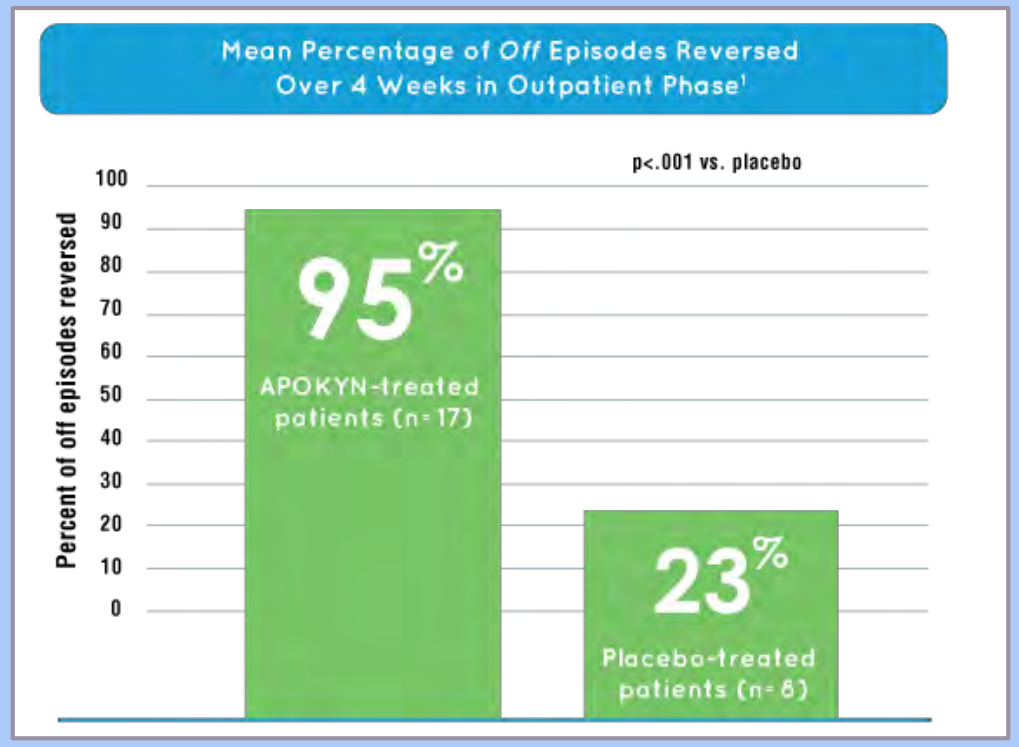


RESCUE OPTION #1 - APOKYN

Apokyn (apomorphine injection)

- Rapid onset Dopamine Agonist via injection
- For different types of OFF episodes:
  - Rapid off, wearing off
  - Dose failure / unexpected off
  - Delayed on
  - First AM symptoms or exercise intolerance
- Achieve ON within 10-20 minutes

APOKYN® apomorphine hydrochloride injection Be on. Live life.



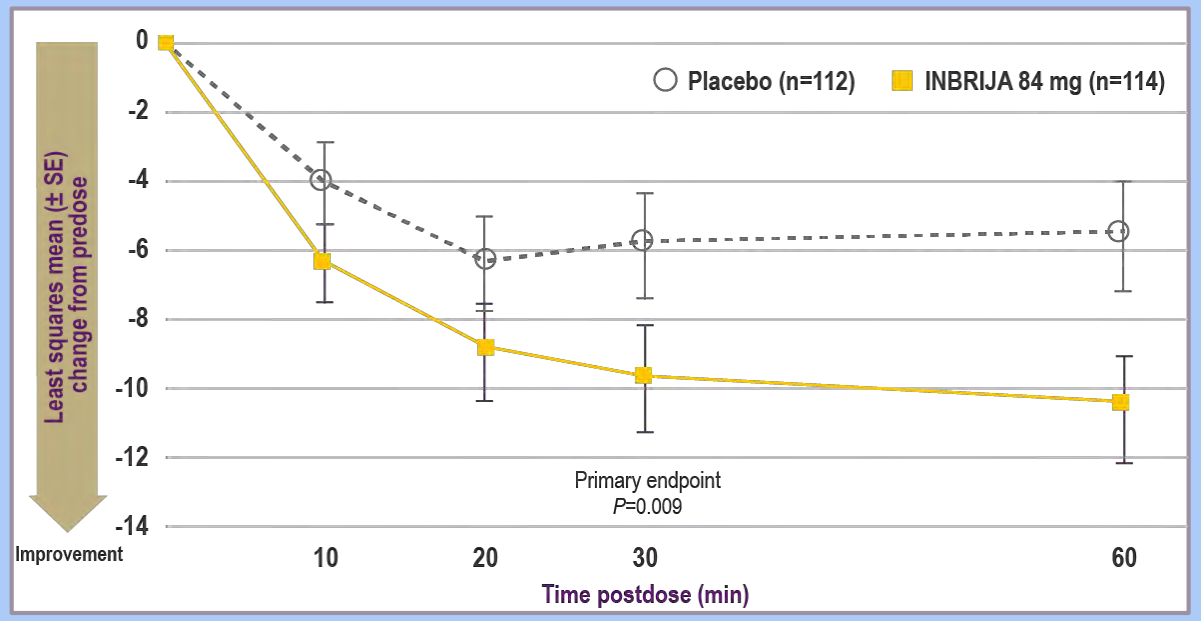
RESCUE OPTION #2 - INBRIJA

Inbrija (levodopa inhalation powder)

- Rapid onset levodopa through inhailer
- For different types of OFF episodes:
  - Rapid off, wearing off
  - Dose failure / unexpected off
  - Delayed on
  - First AM symptoms or exercise intolerance
- Achieve ON within 10 minutes, can take up to 5x daily

Inbrija™
(levodopa inhalation powder)
42 mg capsules

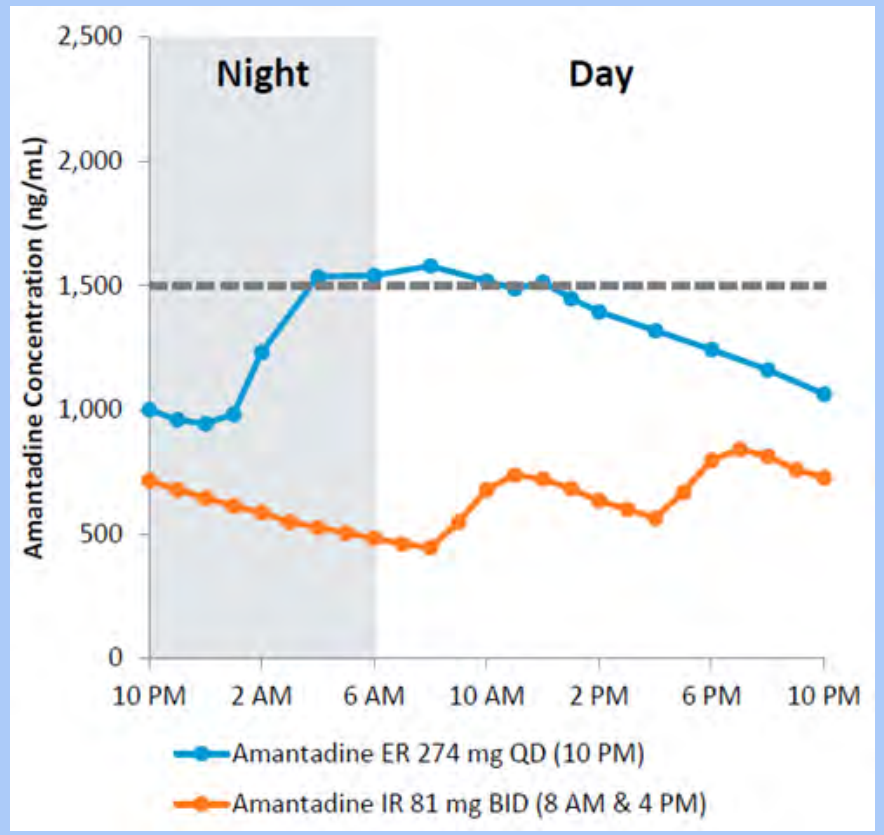
UPDRS Part III Score Change From 0-60 Minutes Postdose at Week 12



LONGER-ACTING AMANTADINE

Amantadine ER (Gocovri)

- 1x daily amantadine
- First “FDA approved” therapy for dyskinesia
  - Classic amantadine is ‘off label’
- Used to reduce dyskinesia (37% reduction)
- Reduced OFF time by 45%
- Available in 2 doses



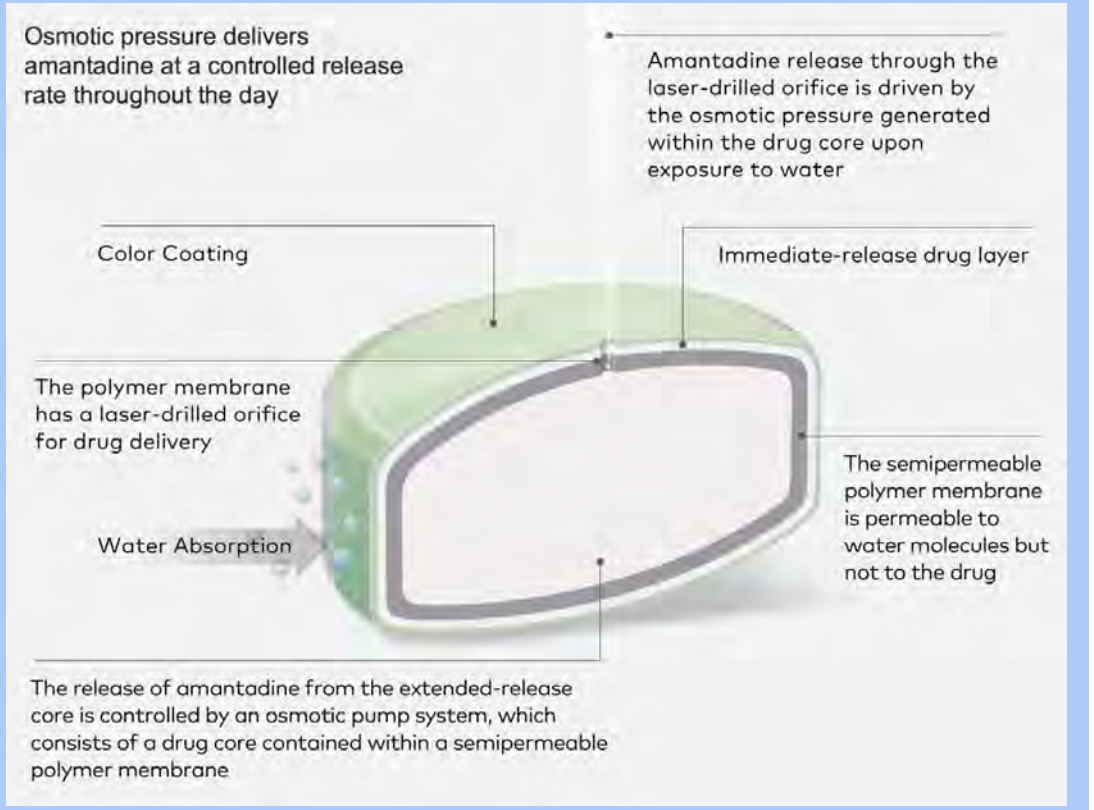
GOCOVRI™
(amantadine) extended release capsules
68.5 mg | 137 mg

LONGER-ACTING AMANTADINE

Osmolex ER (Amantadine)

- 1x daily amantadine
- Another 1x daily option, more for classic amantadine use without ‘off time’ reduction
- Cost

Osmolex ER™
(amantadine)
Extended-release Tablets



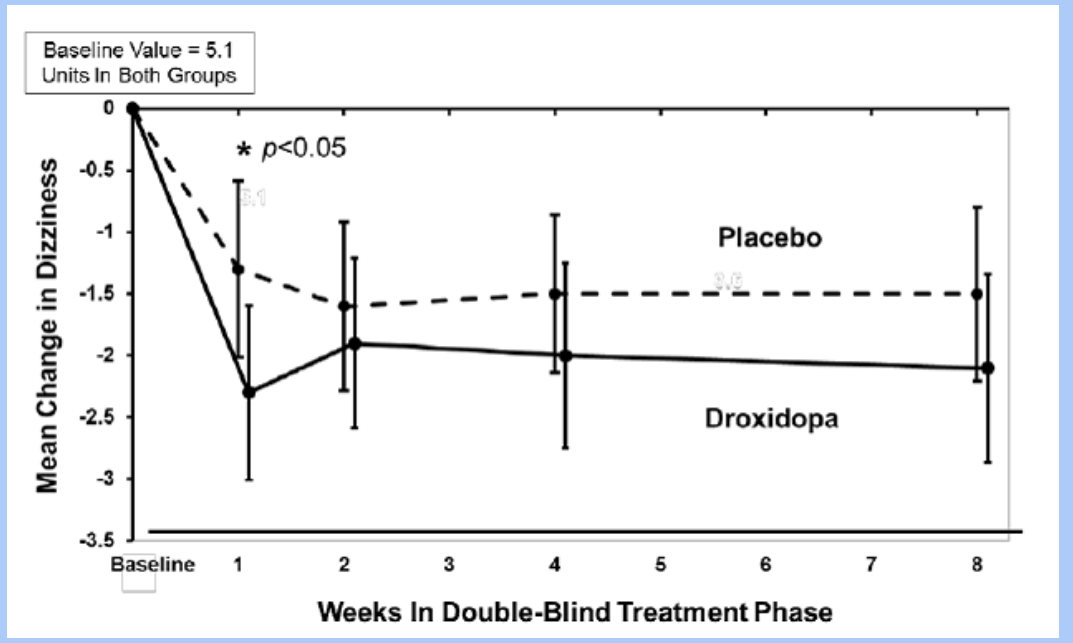
ORTHOSTATIC HYPOTENSION

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



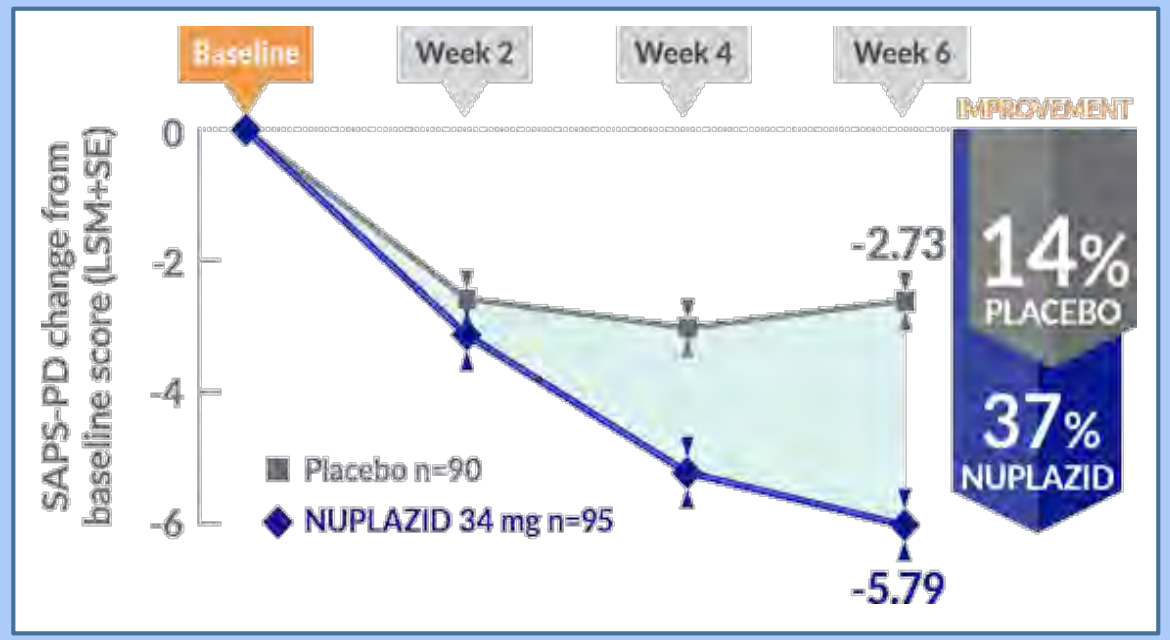
Kaufmann et al. Droxidopa for neurogenic orthostatic hypotension: a randomized, placebo-controlled, phase 3 trial. Neurology. 2014 Jul 22;83(4):328-35.

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

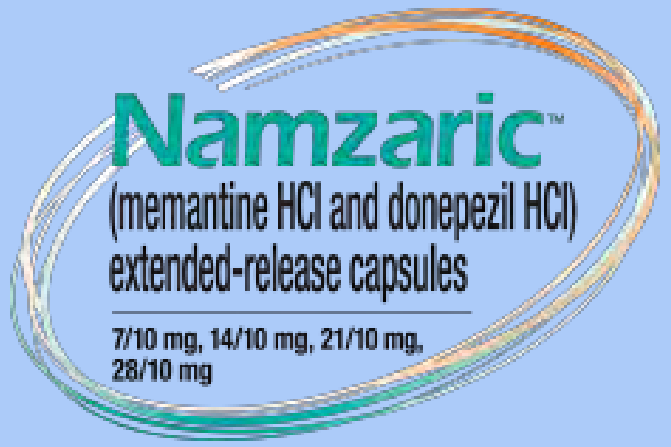


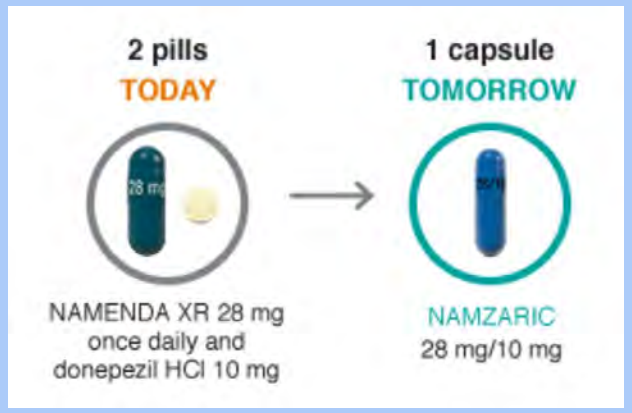
Hacksell, Uli et al. “On the Discovery and Development of Pimavanserin: A Novel Drug Candidate for Parkinson’s Psychosis.” *Neurochemical Research*39.10 (2014): 2008–2017. *PMC*. Web. 4 June 2015.

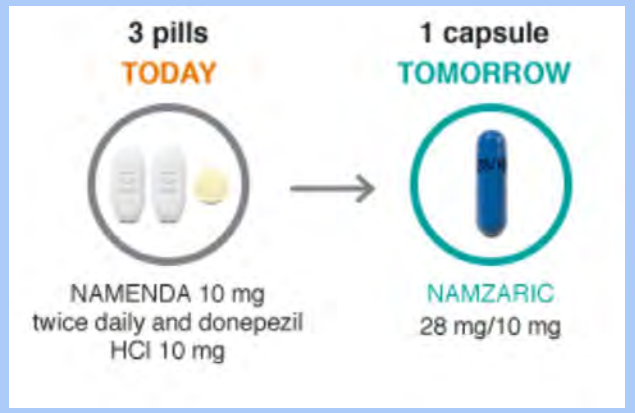
COMBINATION MEDICATION

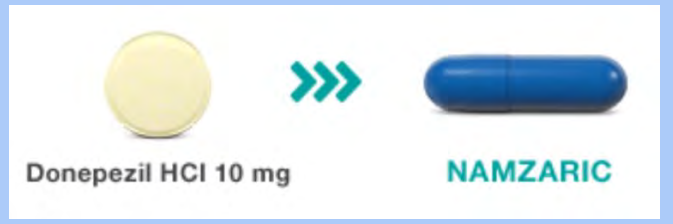
Namzaric™ (Donepezil + Memantine)

- Once a day combination of the two agents
- Moderate disease to severe.
- Can be opened and sprinkled to administer.







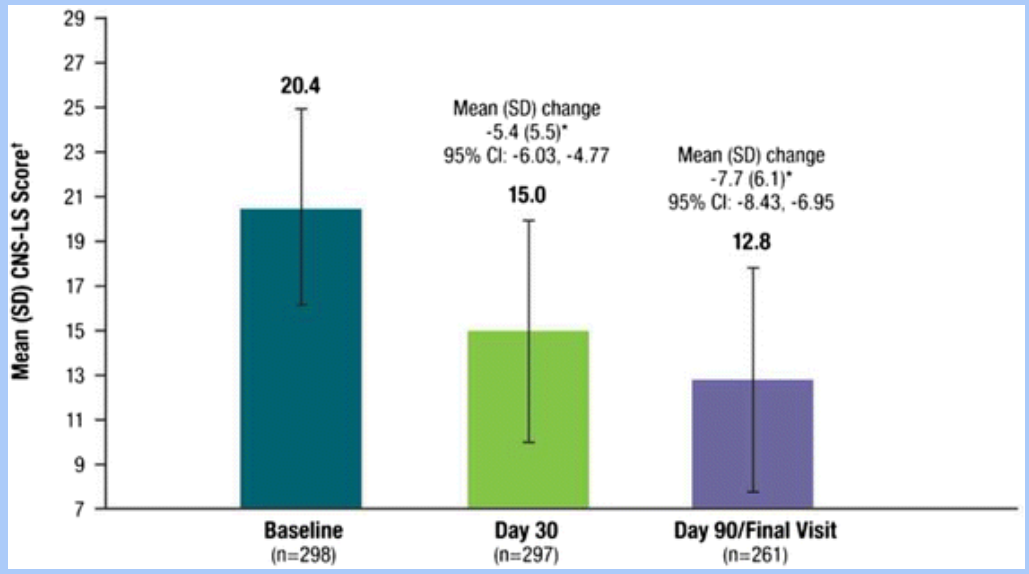


PSEUDOBULBAR AFFECT

Nuedexta

- "Uncontrollable episodes of crying and/or laughing, or other emotional displays."
- Disconnect between emotion and display, or inappropriate display
- PRISM study – 26%, though up to 40% in PD
- CNS-LS Screening reflects symptoms
- **Reduction in episodes at 90 days was 72.3%.**

NUEDEXTA®
(dextromethorphan HBr and quinidine sulfate) capsules 20 mg / 10 mg



PHYSICAL/OCCUPATIONAL/SPEECH THERAPY

LSVT BIG® and LSVT LOUD®

But also non-LSVT Therapy aimed at balance/gait and strengthening

TECHNOLOGY

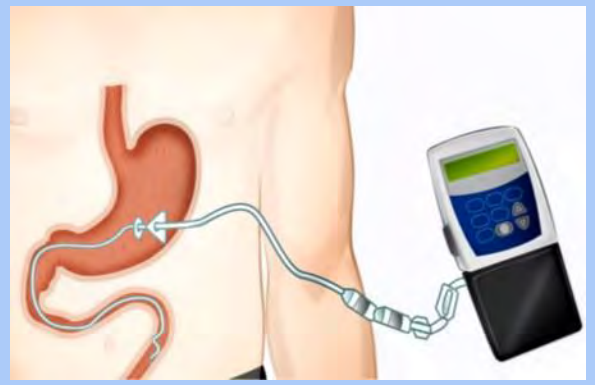
- DUOPA Intestinal Gel
- Focused Ultrasound
- Deep Brain Stimulation

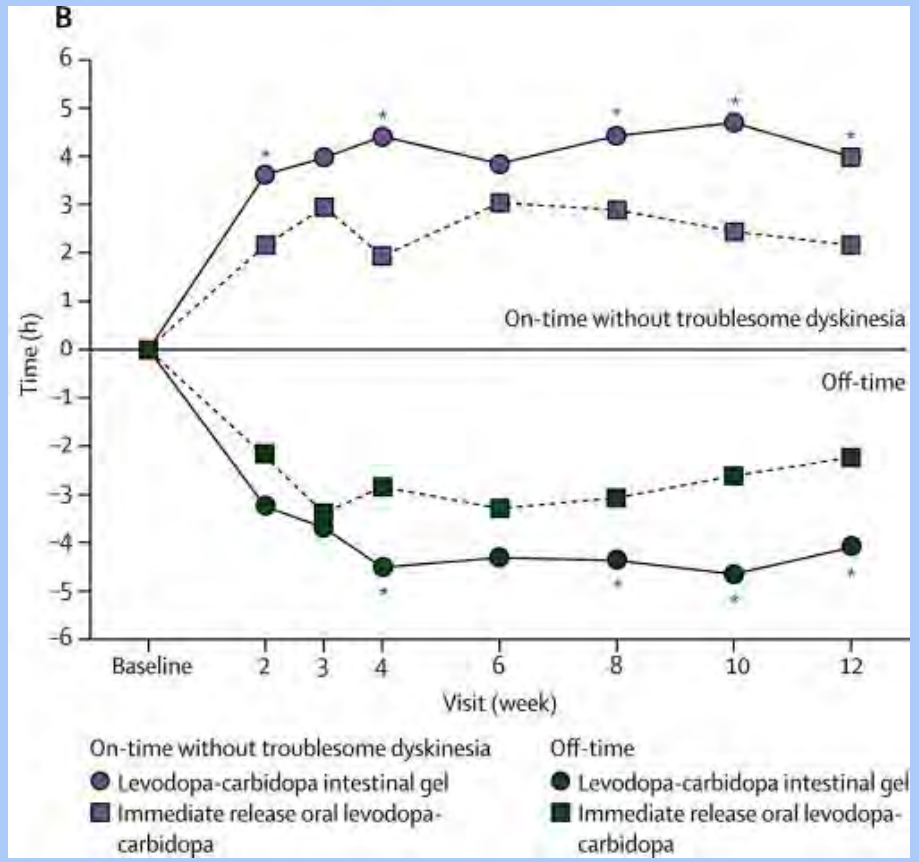
CONSTANT DELIVERY OF LEVODOPA

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]

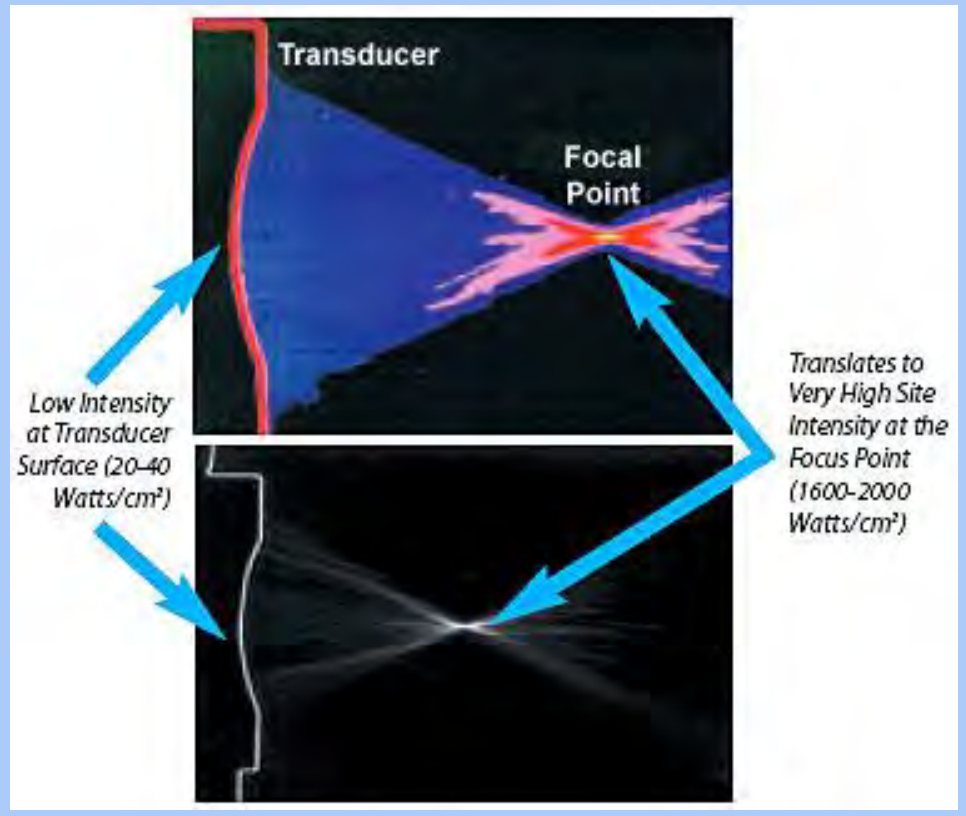
Duopa
carbidopa/levodopa
enteral suspension
4.63 mg/20 mg per mL



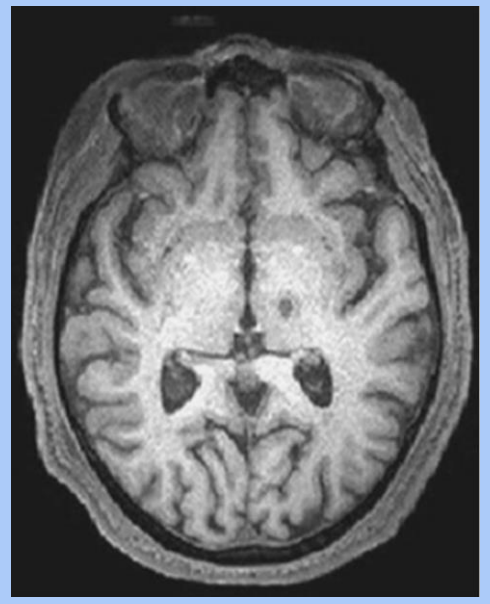


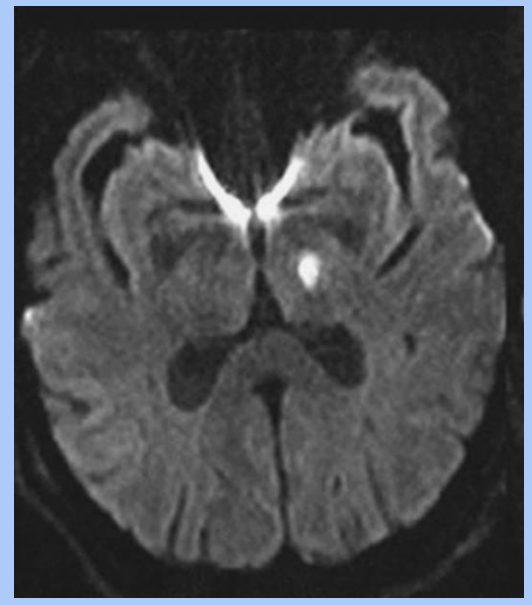
Olanow et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. Lancet Neurol. 2014 Feb;13(2):141-9.
http://www.parkinson-italia.it/

FOCUSED ULTRASOUND (FUS)



- 1,000 ultrasound beams
- Non-invasive
- Creates focal lesion at target
- Approved unilateral ET, unilateral PD tremor

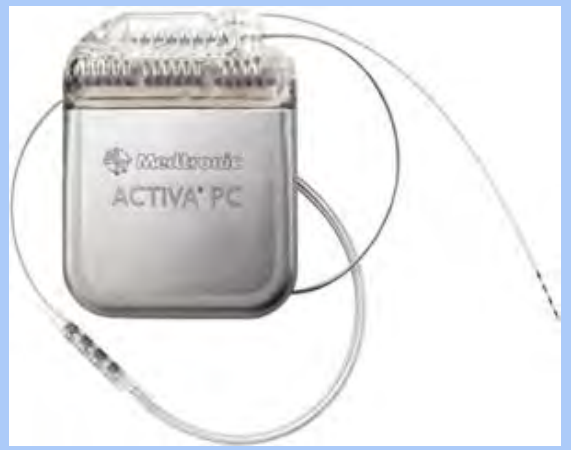




DEEP BRAIN STIMULATION (DBS)

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

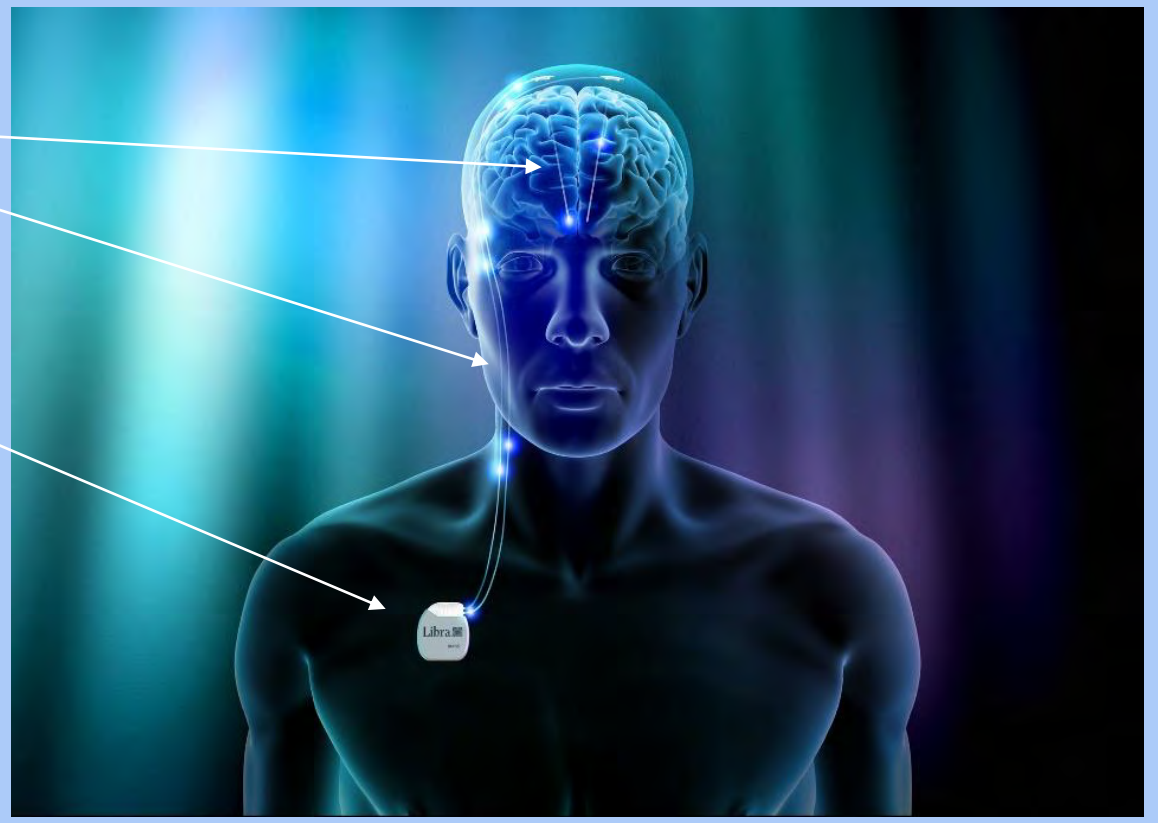
- Surgically implanted device to deliver a controlled stimulation of electricity to a specific region of the brain.
- Implanted in 2 step procedure, then programmed as outpatient.
- Unlike previous surgeries for PD (pallidotomy or thalamotomy), DBS does not damage healthy brain tissue by destroying nerve 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

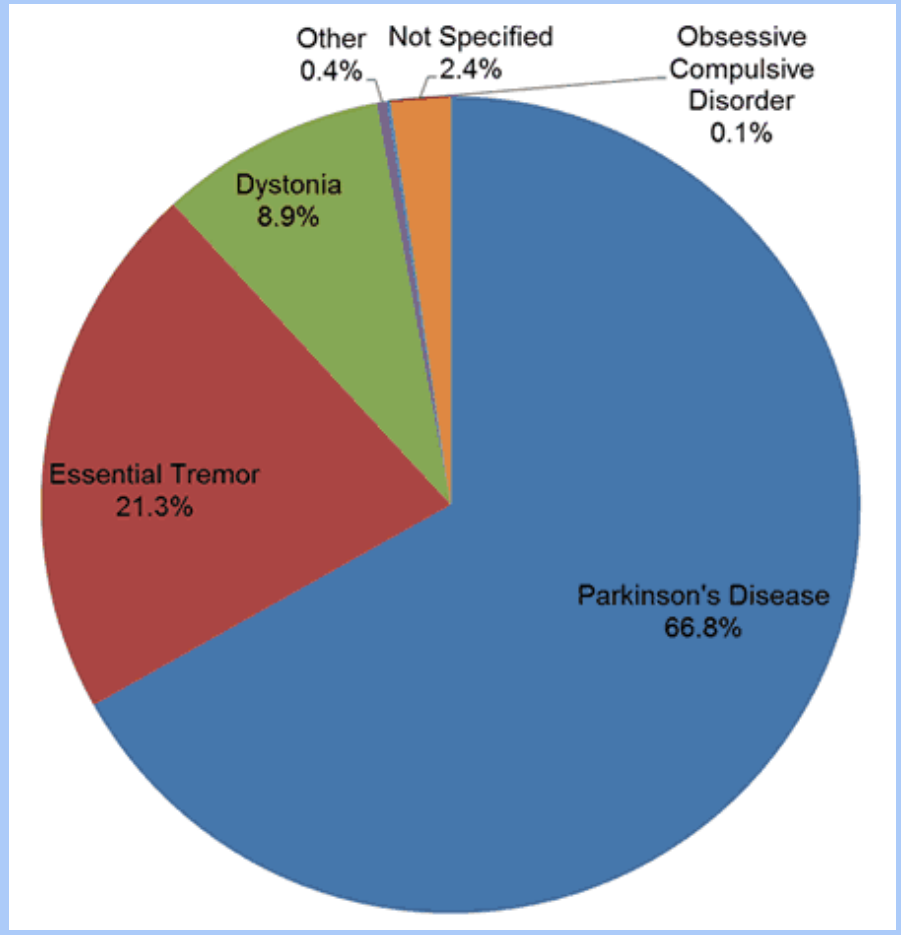


DBS INDICATIONS

- 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.



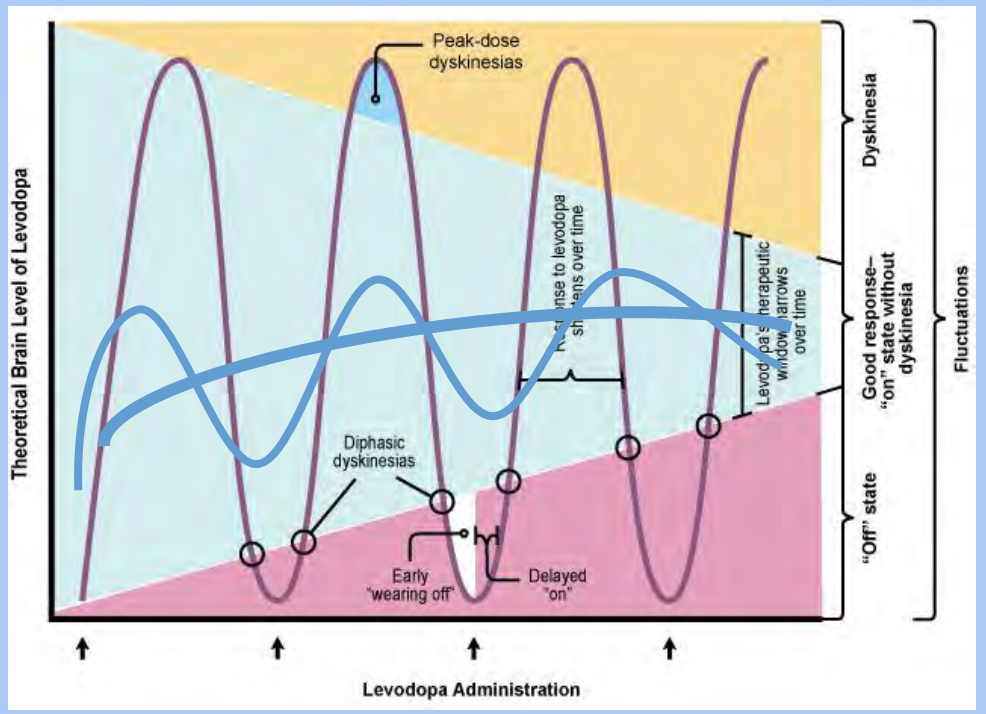
Iplantable Systems Performance Registry (ISPR) for deep brain stimulation systems. July 2009 -July 31, 2013.

BENEFIT FOR OUR PATIENTS

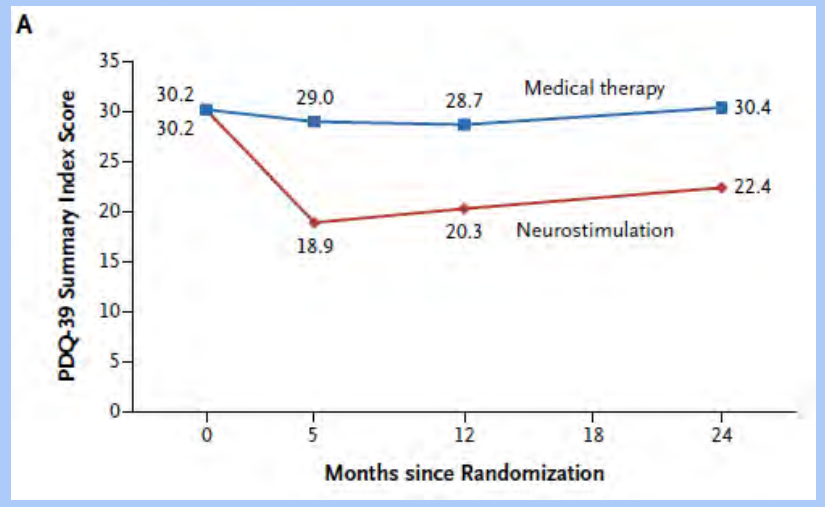
Parkinson's Disease:

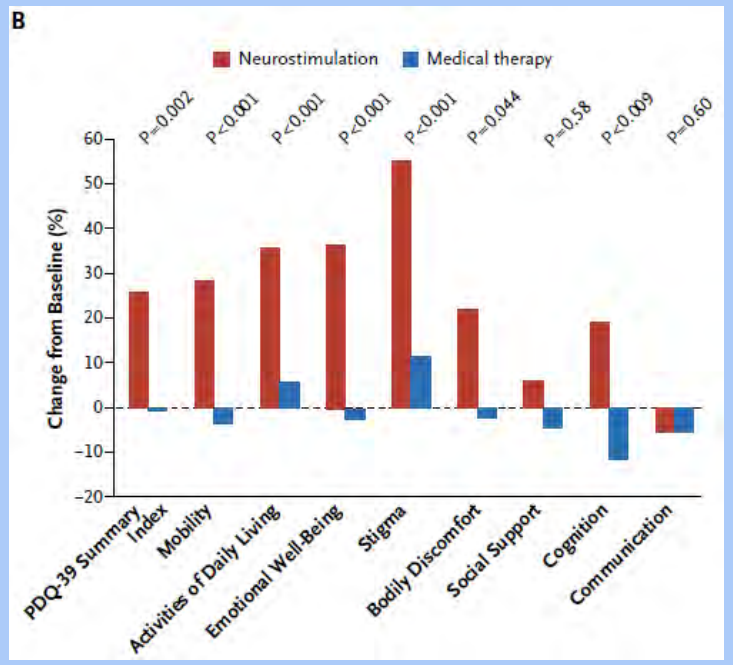
- **80-90%** of patients note improvement
- **60%** reduction in medications
- **60%** reduction in dyskinesias
- **80%** improvement in "off" periods
- **10%** improvement in "on" periods
- 4.6 hours MORE on time without dyskinesia

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



EARLY-STIM STUDY






The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

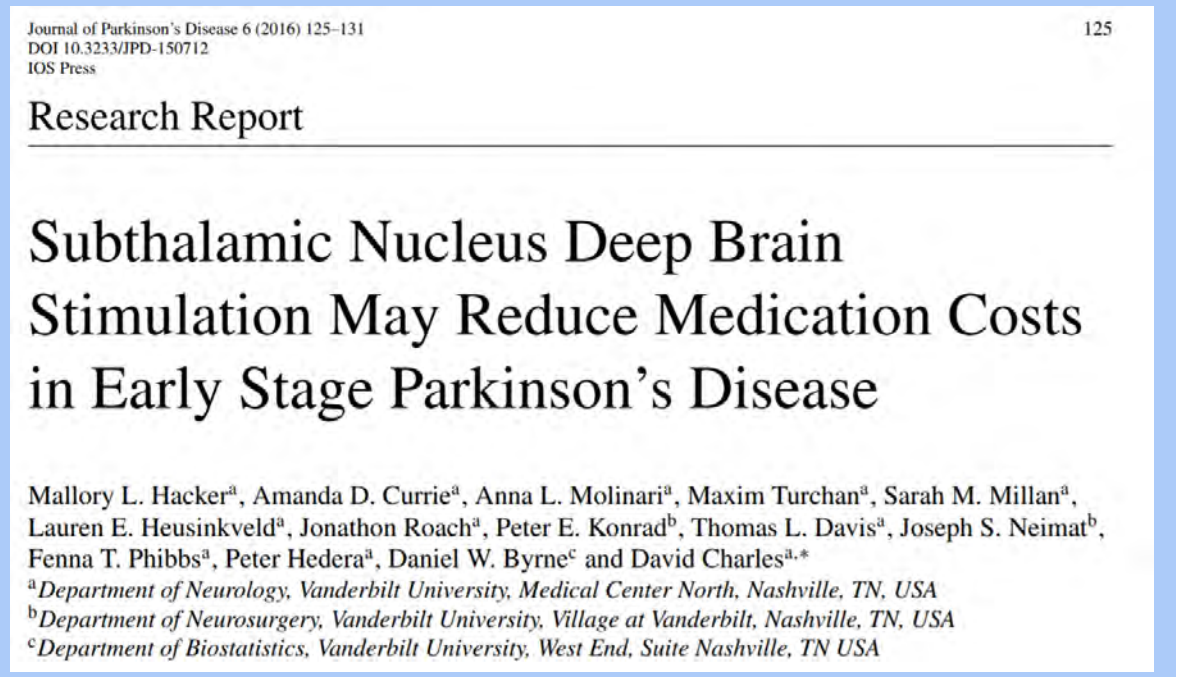
Neurostimulation for Parkinson's Disease with Early Motor Complications

W.M.M. Schuepbach, J. Rau, K. Knudsen, J. Volkmann, P. Krack, L. Timmermann, T.D. Hälbig, H. Hesekamp, S.M. Navarro, N. Meier, D. Falk, M. Mehdorn, S. Paschen, M. Maarouf, M.T. Barbe, G.R. Fink, A. Kupsch, D. Gruber, G.-H. Schneider, E. Seigneuret, A. Kistner, P. Chaynes, F. Ory-Magne, C. Brefel Courbon, J. Vesper, A. Schnitzler, L. Wojtecki, J.-L. Houeto, B. Bataille, D. Maltête, P. Damier, S. Raoul, F. Sixel-Doering, D. Hellwig, A. Gharabaghi, R. Krüger, M.O. Pinsker, F. Amtage, J.-M. Régis, T. Witjas, S. Thobois, P. Mertens, M. Kloss, A. Hartmann, W.H. Oertel, B. Post, H. Speelman, Y. Agid, C. Schade-Brittinger, and G. Deuschl, for the EARLYSTIM Study Group*

- **Conclusions:** DBS was found to be superior to medical therapy in patients with PD and early motor complications

REDUCTION IN MEDICATION COST AND POLYPHARMACY

- Medication costs over 24 months
  - Increased **72%** in optimal drug therapy (ODT)
  - Decreased **16%** in DBS+ODT
    - $7,150 cost savings over study period
    - Projected to 10 years – $64,590 savings
- Polypharmacy at 24 months
  - DBS+ ODT subjects were **80%** less likely to require polypharmacy compared to ODT subjects



Journal of Parkinson's Disease 6 (2016) 125–131
DOI 10.3233/JPD-150712
IOS Press

Research Report

Subthalamic Nucleus Deep Brain Stimulation May Reduce Medication Costs in Early Stage Parkinson's Disease

Mallory L. Hacker[a], Amanda D. Currie[a], Anna L. Molinari[a], Maxim Turchan[a], Sarah M. Millan[a], Lauren E. Heusinkveld[a], Jonathon Roach[a], Peter E. Konrad[b], Thomas L. Davis[a], Joseph S. Neimat[b], Fenna T. Phibbs[a], Peter Hedera[a], Daniel W. Byrne[c] and David Charles[a,*]
[a]*Department of Neurology, Vanderbilt University, Medical Center North, Nashville, TN, USA*
[b]*Department of Neurosurgery, Vanderbilt University, Village at Vanderbilt, Nashville, TN, USA*
[c]*Department of Biostatistics, Vanderbilt University, West End, Suite Nashville, TN USA*

REDUCTION IN MEDICATION COST AND POLYPHARMACY

- Same group, followed out to **5 years**

- Polypharmacy at 5 years
  - ODT increased from 43% to 93%
  - DBS+ODT from 36% to 43%

Subthalamic Nucleus Deep Brain Stimulation in Early Stage Parkinson's Disease Reduces the Risk of Polypharmacy: Five-Year Analysis

M. Hacker, M. Turchan, A. Currie, L. Heusinkveld, S. Millan, T. Davis, F. Phibbs, P. Hedera, P. Konrad, D. Charles (Nashville, TN, USA)

Meeting: 21st International Congress

Abstract Number: 1341

Conclusions: These results suggest that people with early stage PD treated with medications alone are 17 times more likely to require polypharmacy after five years compared to those treated with STN-DBS.

DBS, DISEASE MODIFYING THERAPY?

Effects of deep brain stimulation on rest tremor progression in early stage Parkinson disease

Mallory L. Hacker, Mahlon R. DeLong, Maxim Turchan, Lauren E. Heusinkveld, Jill L. Ostrem, Anna L. Molinari, Amanda D. Currie, Peter E. Konrad, Thomas L. Davis, Fenna T. Phibbs, Peter Hedera, Kevin R. Cannard, Lea T. Drye, Alice L. Sternberg, David M. Shade, James Tonascia, David Charles

- **Results** UPDRS-III "off" rest tremor score change from baseline to 24 months was worse in patients receiving ODT vs DBS + ODT ($p = 0.002$). Rest tremor slopes from baseline to 24 months favored DBS + ODT both "off" and "on" therapy ($p < 0.001$, $p = 0.003$, respectively). More ODT patients developed new rest tremor in previously unaffected limbs than those receiving DBS + ODT ($p = 0.001$).

- **Conclusions** These results suggest the possibility that DBS in early PD may slow rest tremor progression. Future investigation in a larger cohort is needed, and these findings will be tested in the Food and Drug Administration–approved, phase III, pivotal, multicenter clinical trial evaluating DBS in early PD.

- **Classification of evidence** This study provides Class II evidence that for patients with early PD, DBS may slow the progression of rest tremor.

Neurology®

BENEFIT FOR OUR PATIENTS

Essential Tremor:

- **80%** improvement in tremor.
- **70%** improvement in handwriting.
- **Significant** reduction in medications with possibility of stopping medication.

Pre DBS on high dose Primidone

Post DBS on no medication

- Reduction in medications leads to decrease in the following:
  - Cost
  - Side effects (cognitive change, fatigue, lethargy, etc.)

WHO IS A CANDIDATE

- A good candidate for DBS per our center:

1. Parkinson's Disease at least 4 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

AN EXPANDING FIELD

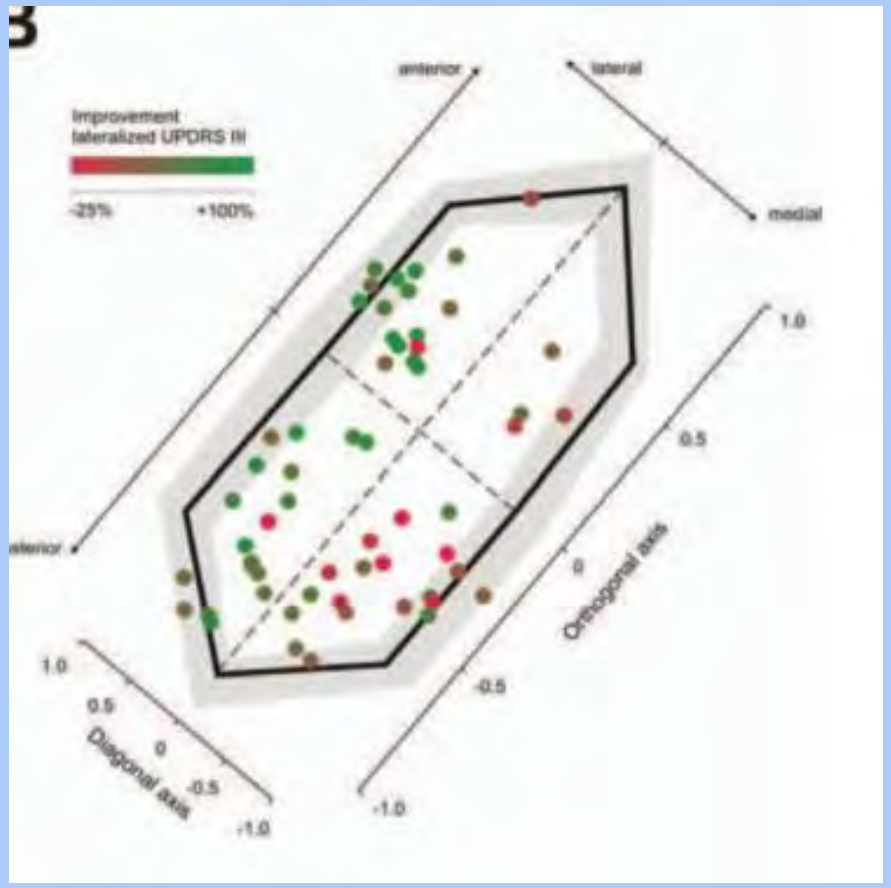
- Directional stimulation
- Improved technology
- Smaller technology, thinner
- Longer battery life

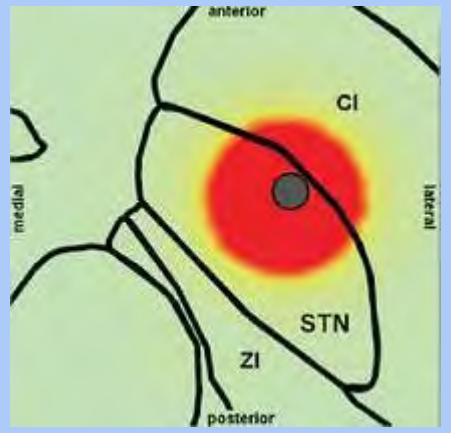
Medtronic

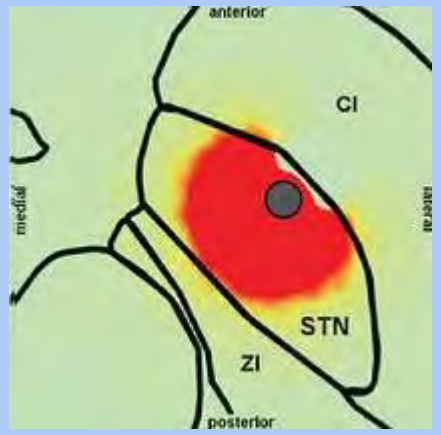
ST. JUDE MEDICAL

Boston Scientific

DIRECTIONALITY, THE PRESENT AND FUTURE OF STIM







DIRECTIONALITY, THE PRESENT AND FUTURE OF STIM

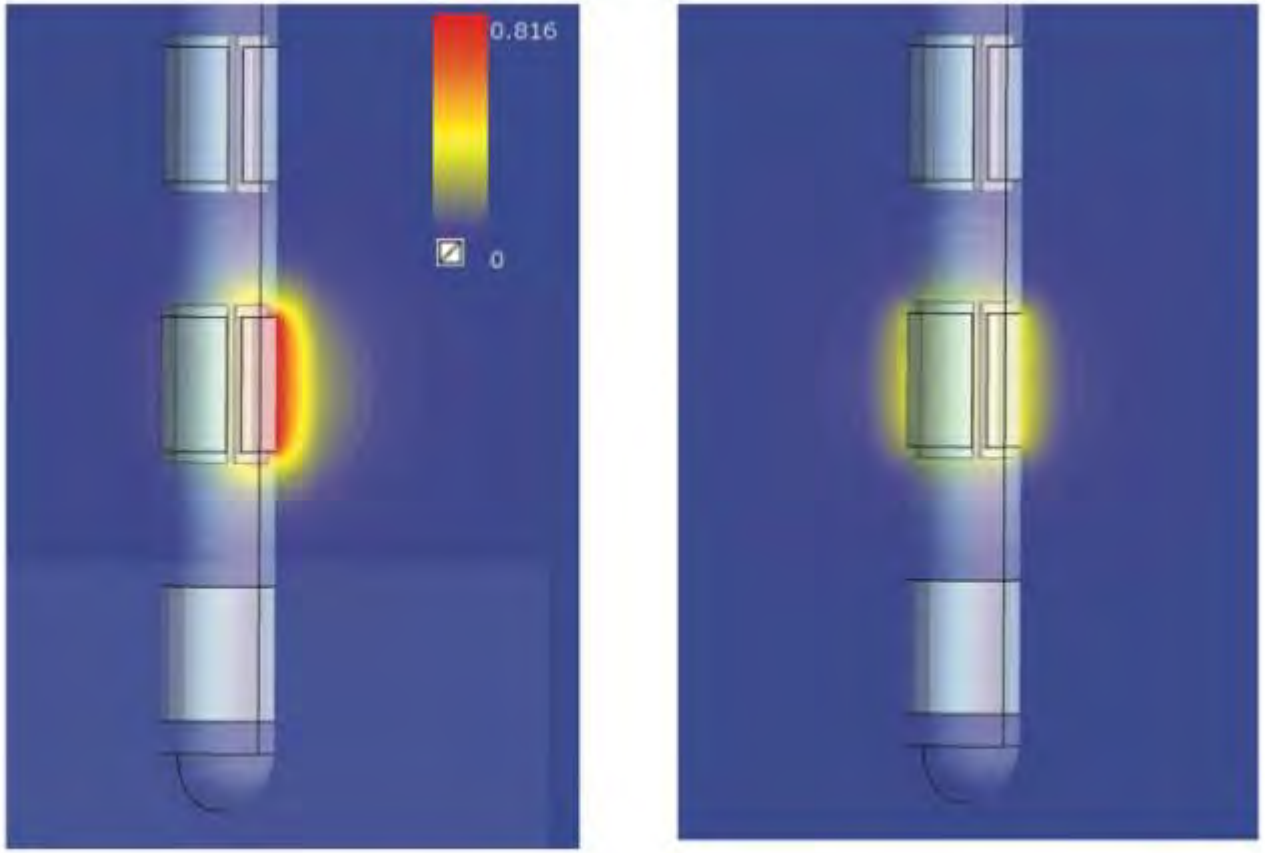
4 = Full-ring contact

3 = Contact with equally spaced segments

2 = Contact with equally spaced segments

1 = Full-ring contact

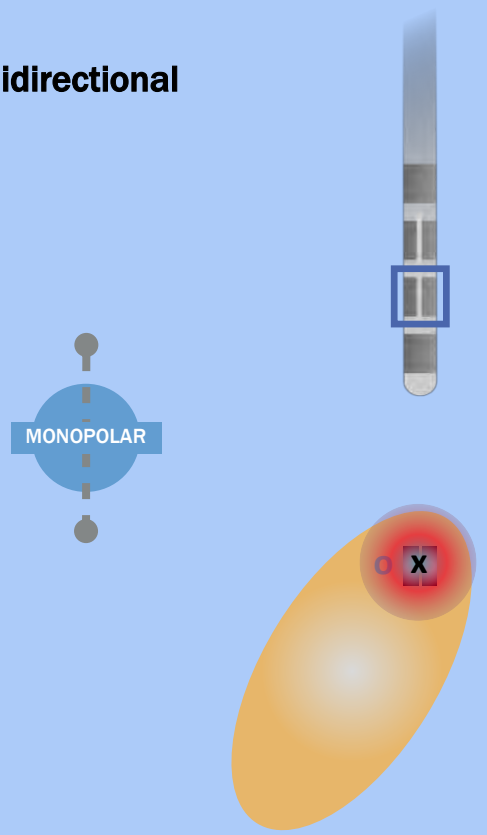
DIRECTIONALITY, THE PRESENT AND FUTURE OF STIM



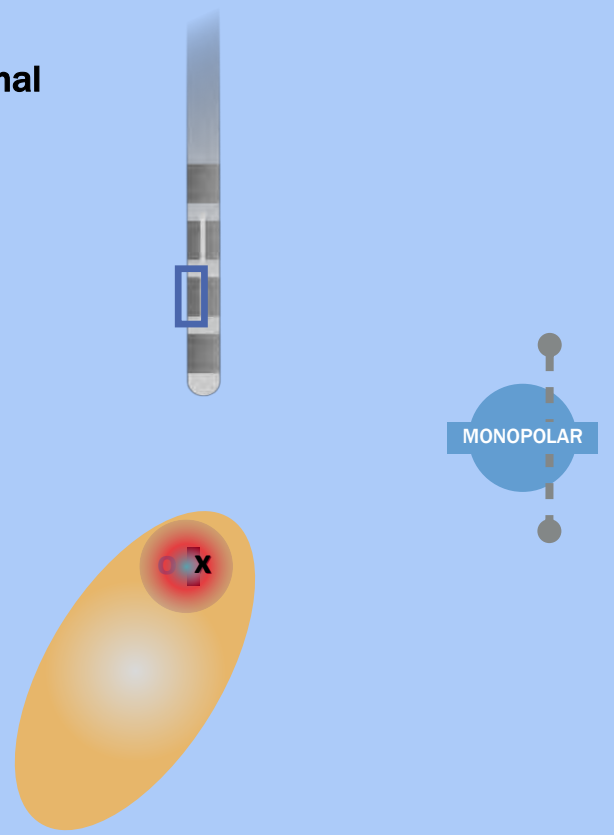
Reference: Poster: VTA Modelling studies- Cheeran, Venkatesan, Kent- WSSFN 2017

DIRECTIONALITY, THE PRESENT AND FUTURE OF STIM

Omnidirectional



Directional



COMPETITION ONLY BENEFITS THE PATIENT

3 years ago

Medtronic

NOW

Medtronic

ST. JUDE MEDICAL

Boston Scientific

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

TO THE FUTURE

- Longer-acting levodopa formulations (10 hours or greater)
- New inhibitors
- Inhaled, sublingual, pump-based formulations
- Improved technology
- Targeted protein therapy
- Cure

All of this equals

HOPE

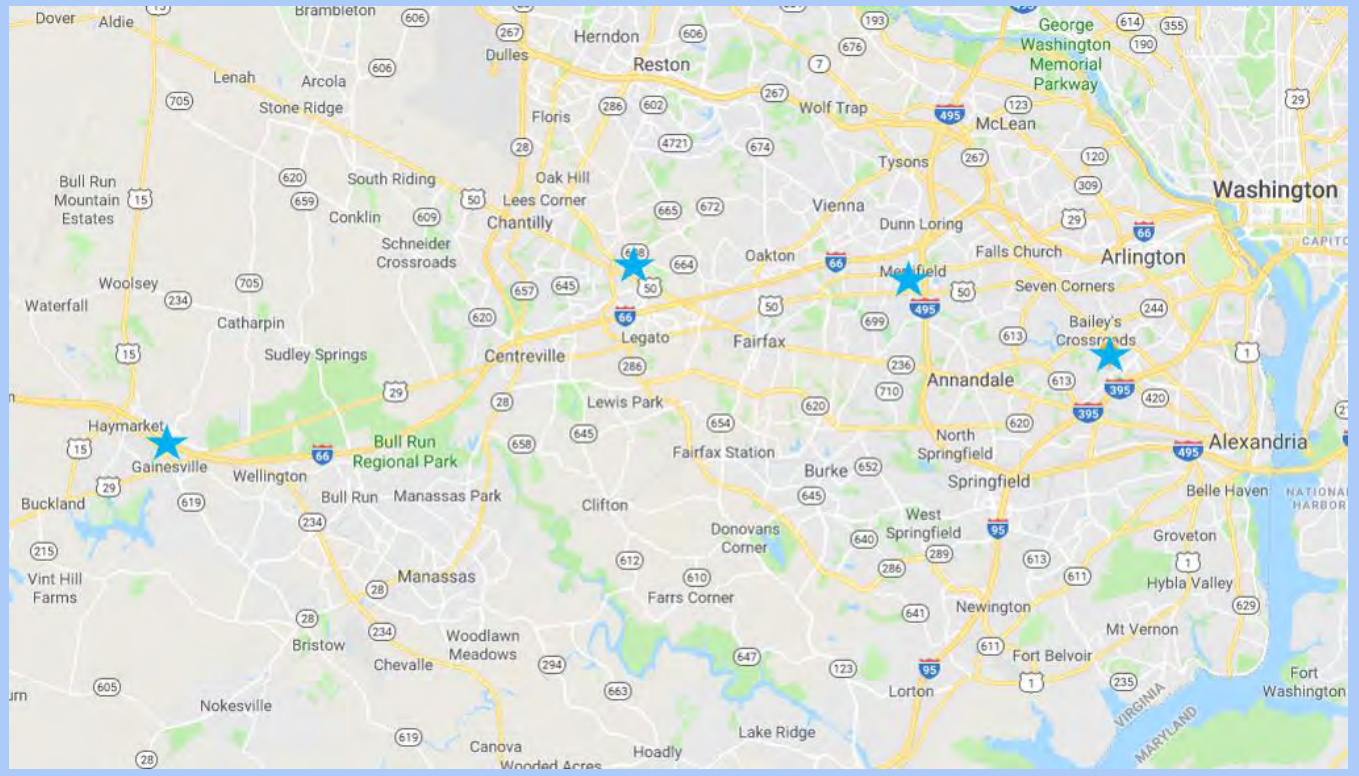
INOVA MOVEMENT DISORDERS CENTER

1500 N. Beauregard Street
Suite 300
Alexandria, VA 22311

8505 Arlington Boulevard
Suite 450
Fairfax, VA 22031

3580 Joseph Siewick Dr.
Suite 206
Fairfax, VA 22033

7051 Heathcote Village Way
Suite 230
Gainesville, VA 20155



703-845-1500

www.inova.org/move

INOVA®
Movement Disorders Center

THANK YOU – Q&A WITH OUR TEAM

703-845-1500

www.inova.org/move