

# Emerging Therapies in Parkinson Disease



Kelly Mills, MD, MHS  
Johns Hopkins Parkinson's Disease and Movement Disorders Center

# Disclosures / Funding

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  - Research support from Abbott
  - Research support from Global Kinetics Corporation (GKC)
  - This presentation is not to be used for reprint without permission.
- Funding
  - National Institutes of Health / NINDS
  - Parkinson Foundation

# Overview

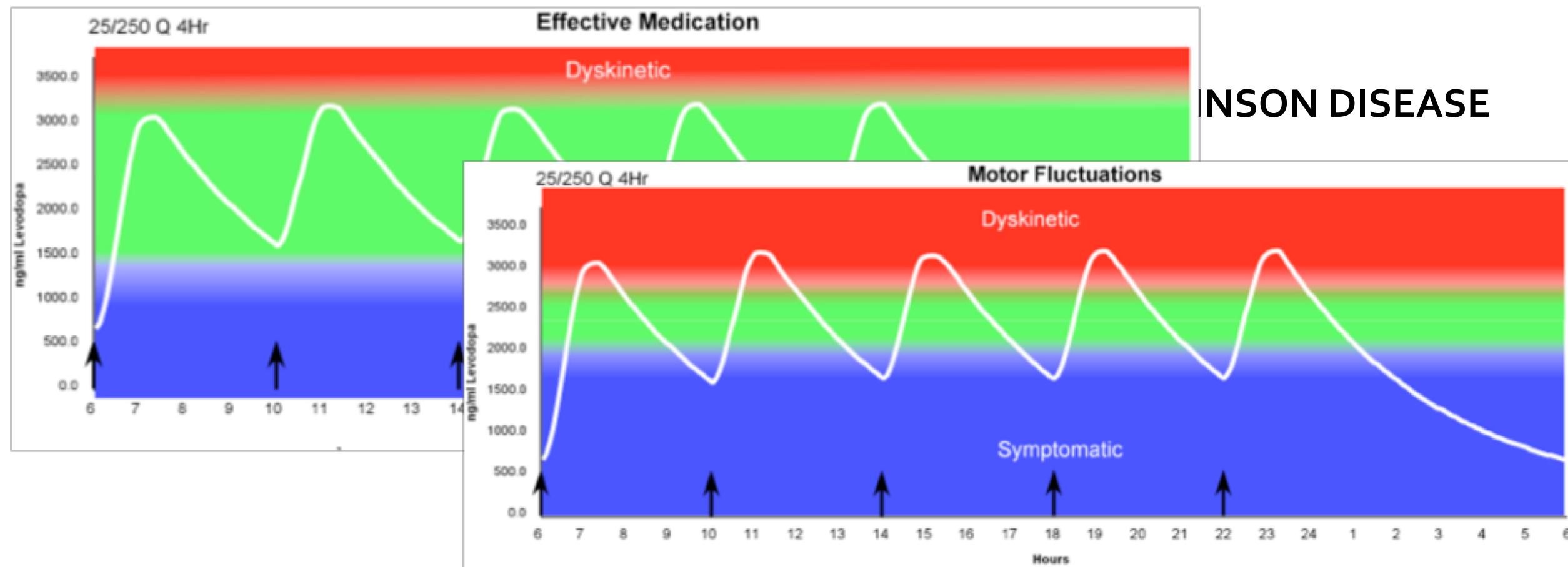
- New therapies for symptom management
- Future therapies for symptom management
- Future therapies to slow disease progression
- Recent breakthroughs that may lead to therapies

# Overview

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- Future therapies for symptom management
- Future therapies to slow disease progression
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# Symptom Management

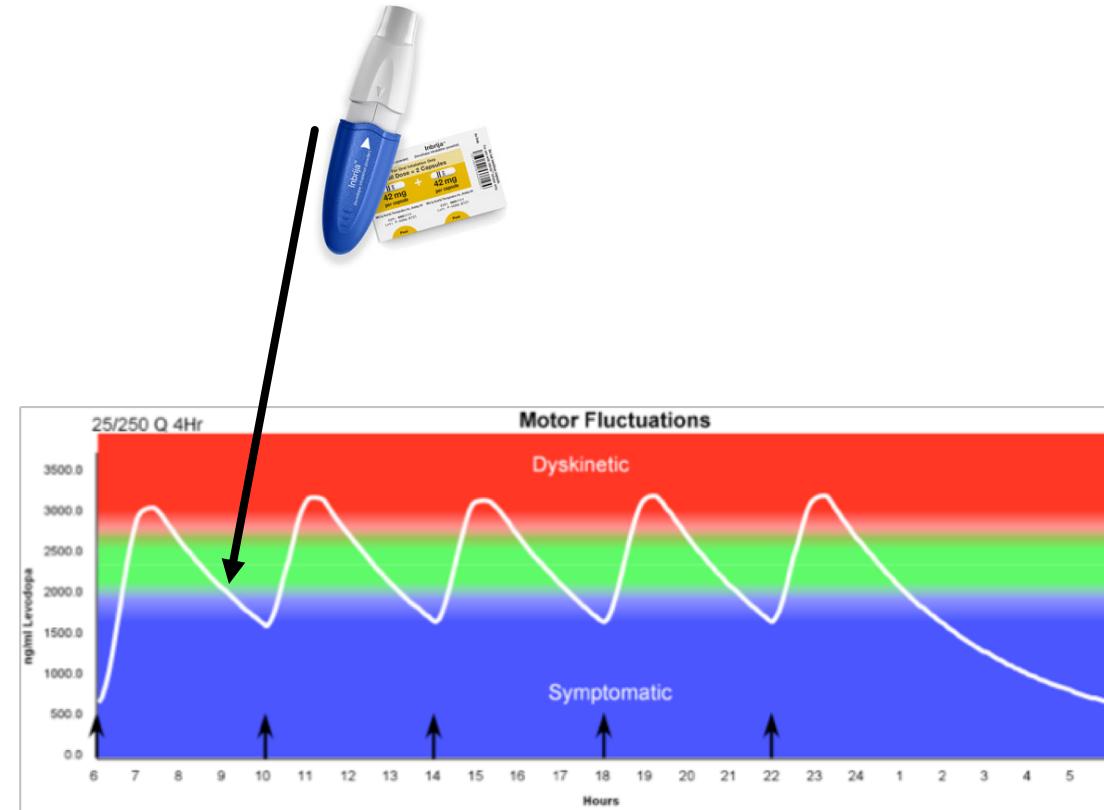
## EARLY PARKINSON DISEASE



# Inbrija (levodopa inhalation powder)

## ■ SPAN-PD –

- Methods
  - Patients taking carbidopa/levodopa up to 4+ times per day
  - Randomized to **placebo** vs. **50 mg inhaled levodopa used up to 3 times per day**
- Results
  - 4 weeks: placebo improved 3 points on rating scale, inhaled levodopa improved 10 points on rating scale
  - Improvement as early as 10 minutes, highest improvement 30 minutes
  - ~1 hour more “on” time per day

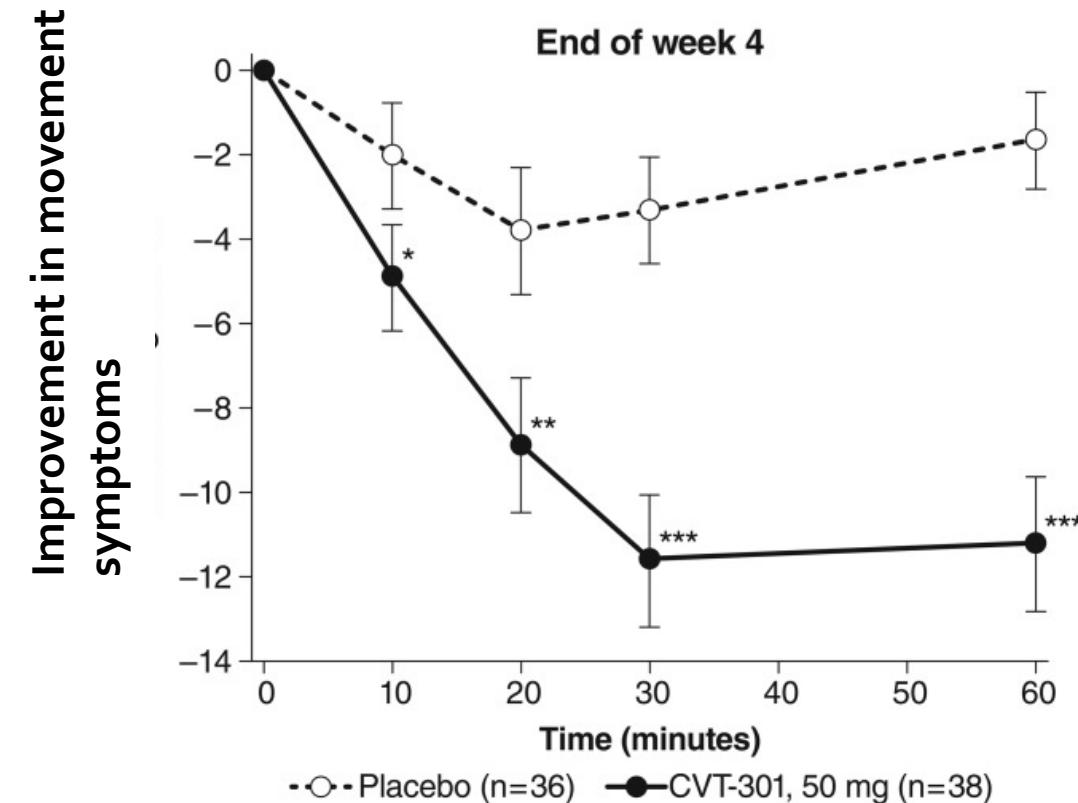
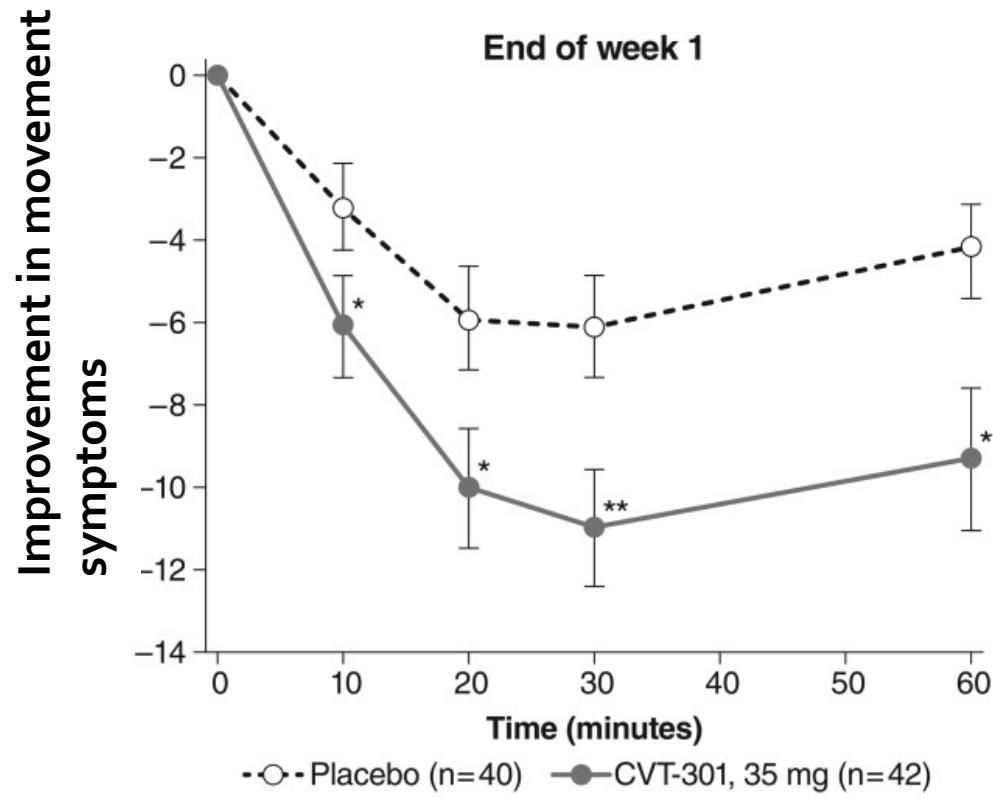


LeWitt et al. 2016. Mov Dis. 31(9):1356

# Inbrija (levodopa inhalation powder)



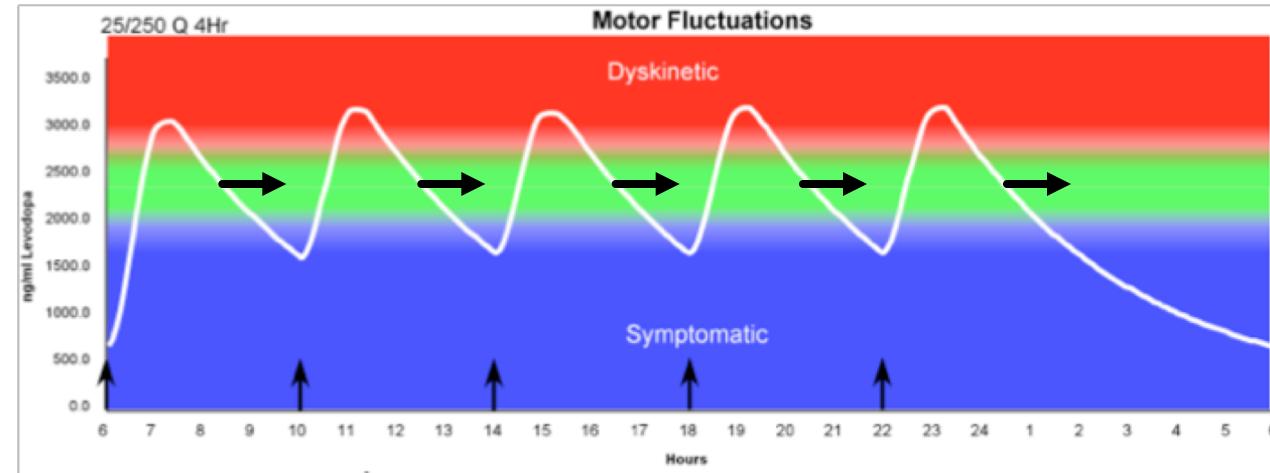
SPAN-PD –



# Xadago (Safinamide)

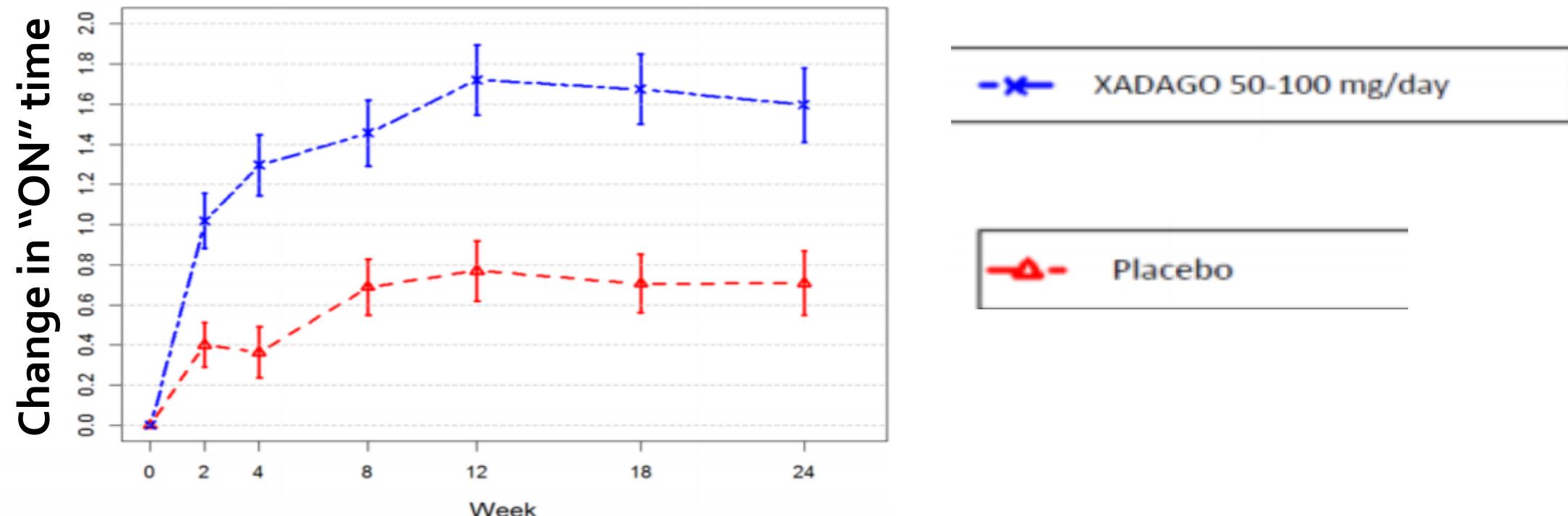
## ■ FDA:

- “a monoamine oxidase type B (MAO-B) inhibitor indicated as ***adjunctive treatment*** to levodopa/carbidopa in patients with Parkinson’s disease (PD) experiencing ‘off’ episodes”
- “XADAGO has not been shown to be effective as monotherapy for the treatment of PD”



# Xadago (Safinamide) 100 mg

- ~30 minute increase in “ON” time without troublesome dyskinesia
- ~35 minute decrease in “OFF” time
- ~3 point increase in UPDRS Part III scale



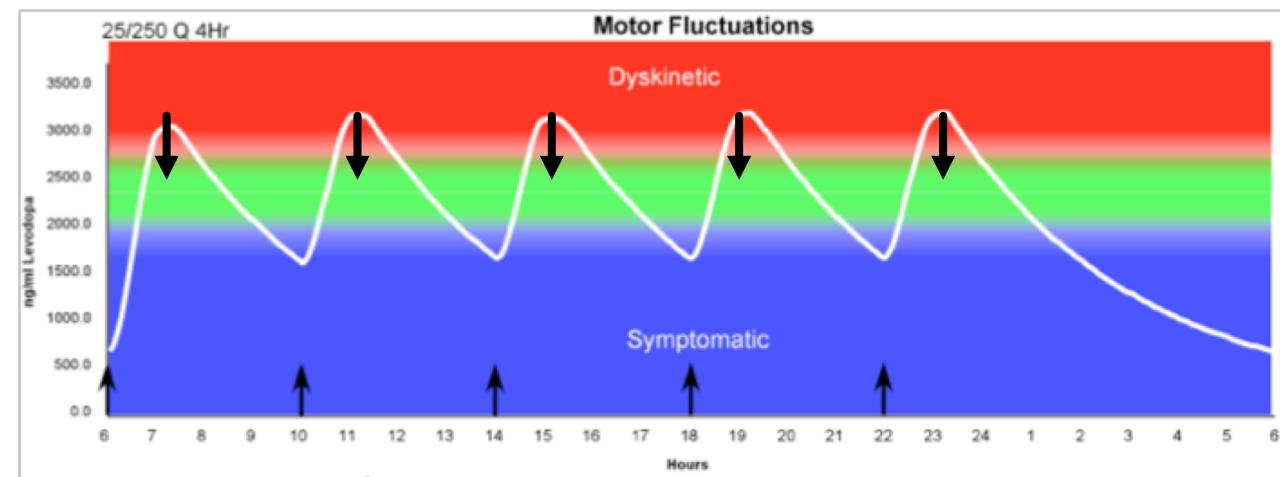
# Xadago (Safinamide)

- No decrease in dyskinesia

Adverse Reaction	XADAGO 50 mg/day (N = 223)	XADAGO 100 mg/day (N = 498)	Placebo (N = 497)
Dyskinesia	21	17	9
Fall	4	6	4
Nausea	3	6	4
Insomnia	1	4	2
Orthostatic hypotension	2	2	1
Anxiety	2	2	1
Cough	2	2	1
Dyspepsia	0	2	1

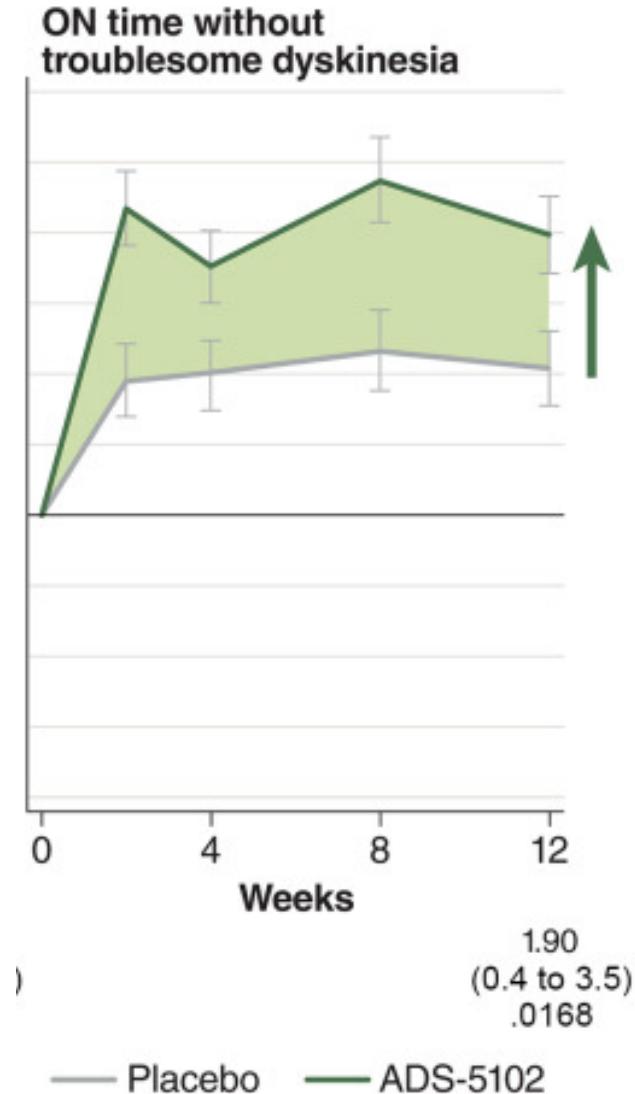
# Gocovri (amantadine extended release)

- FDA: "indicated for the treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications"



# Gocovri (amantadine extended release)

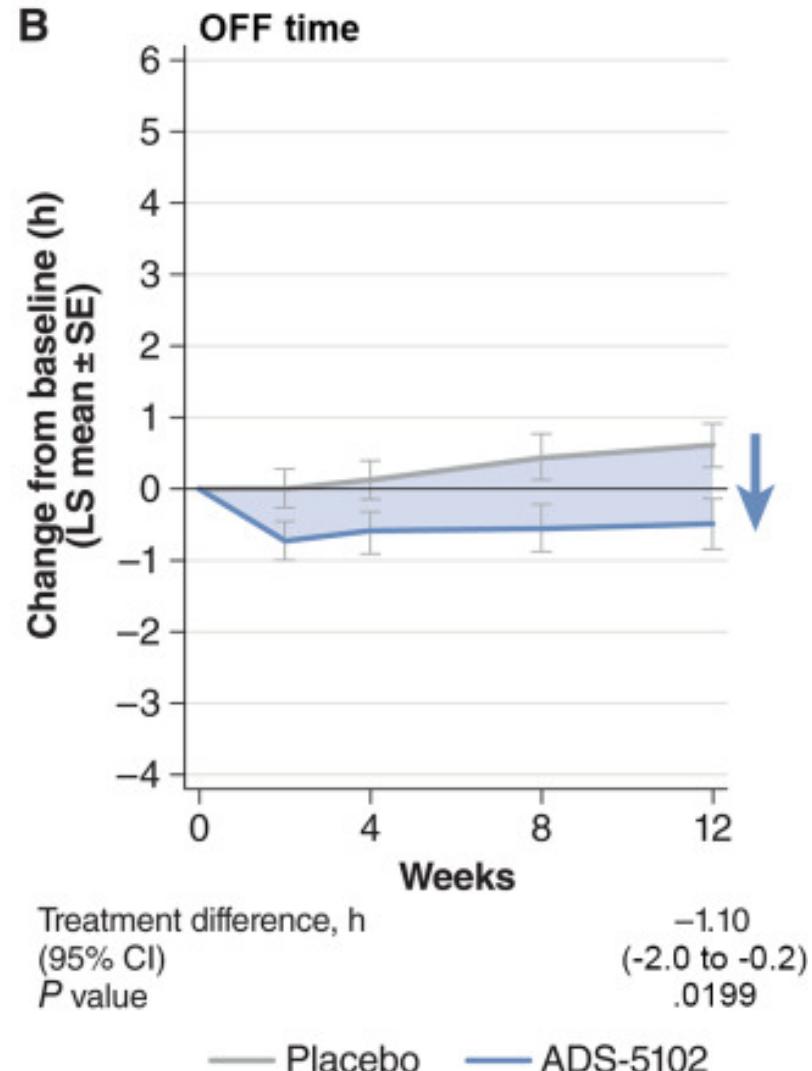
- ~2 hours increase in “ON” time without troublesome dyskinesia



Oertel et al. 2017. Mov Dis. 32(12):1701

# Gocovri (amantadine extended release)

- ~1 hour decrease in “OFF” time per day

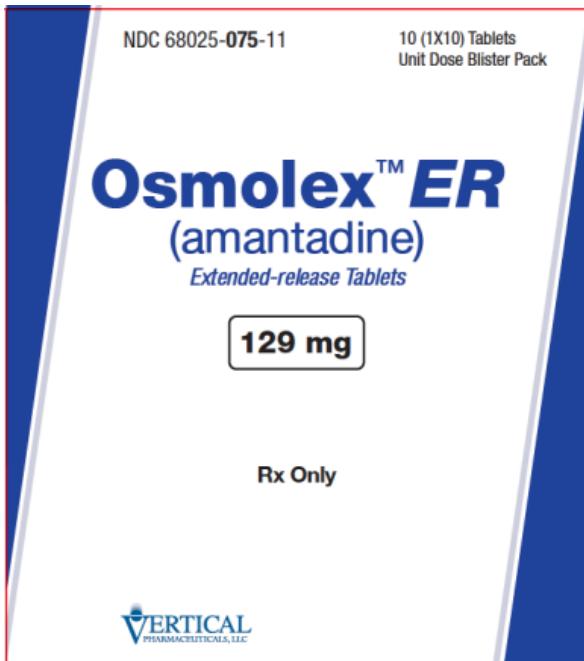


# Gocovri (amantadine extended release)

- 19% stopped Gocovri
- 8% stopped placebo
- Possible side effects
  - Dry mouth
  - Nausea
  - Decreased appetite
  - Insomnia
  - Orthostatic hypotension
  - Constipation
  - Falls
  - Visual hallucinations

# Osmolex ER (amantadine extended release)

- FDA: “for treatment of Parkinson’s disease...”



- No new clinical trials
- No Efficacy data yet
- Compared bioavailability to amantadine IR
- No long-term safety data yet

# Overview

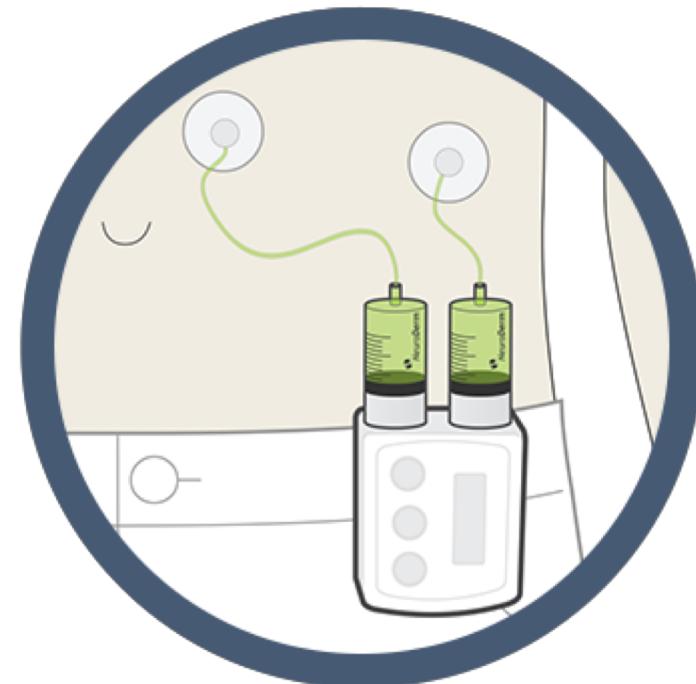
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# Future Therapies for Symptom Management

- Pharmacologic therapies
- Advances in DBS / brain lesioning

# Continuous levodopa

- NeuroDerm NDo612H
  - Carbidopa/levodopa in solution
  - Continuous subcutaneous infusion
- Ongoing Phase II clinical trial



# Sublingual apomorphine (APL-130277)

- Maker reports “positive” phase III clinical trial – unpublished
- FDA rejects approval – requests additional information

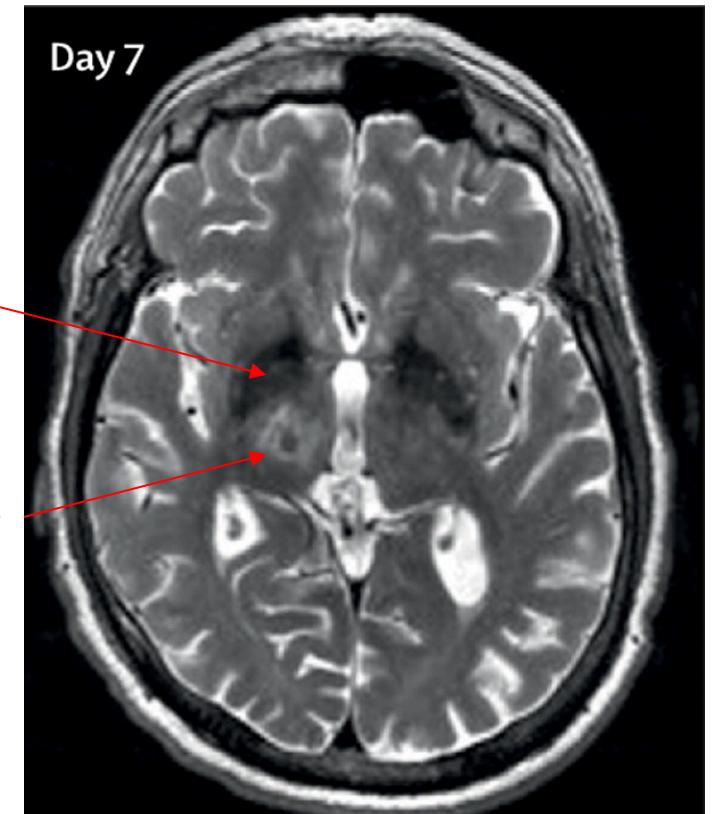
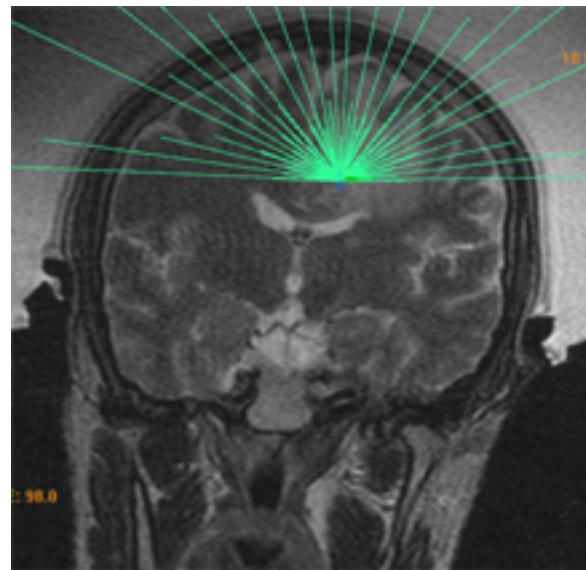


# Future Therapies for Symptom Management

- Pharmacologic therapies
- Advances in DBS / surgical lesioning

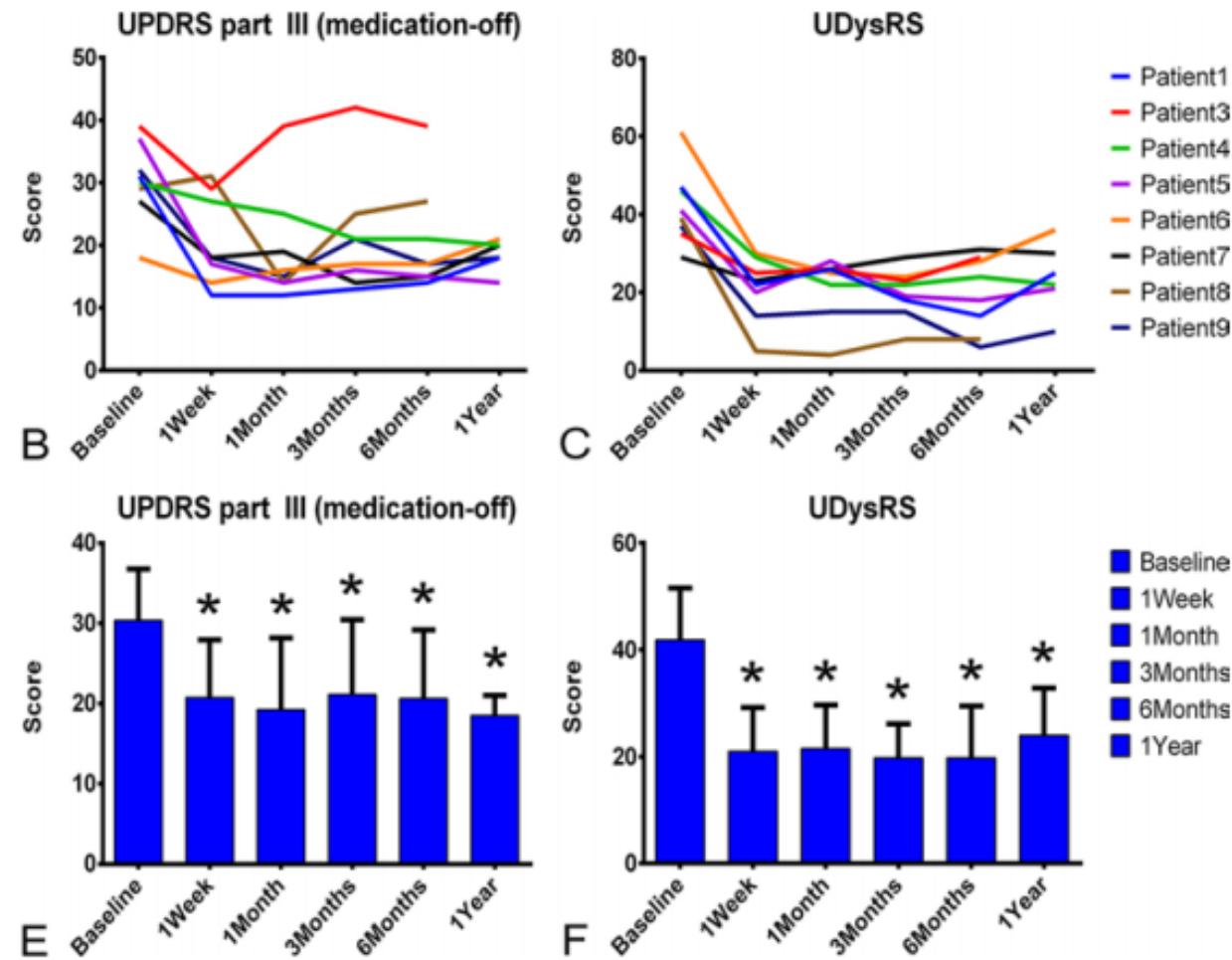
# MRI-guided Focused Ultrasound

- FDA-approved for essential tremor
- NOT approved for PD
  - Pallidotomy -> all PD symptoms
  - Thalamotomy -> mainly tremor



# MRgFUS Pallidotomy in PD

- Open label study 10 patients
- 32% improvement motor symptom
- 52.7% improvement dyskinesia



Current trial at University of Maryland  
NCT03319485

# MRgFUS Thalamotomy

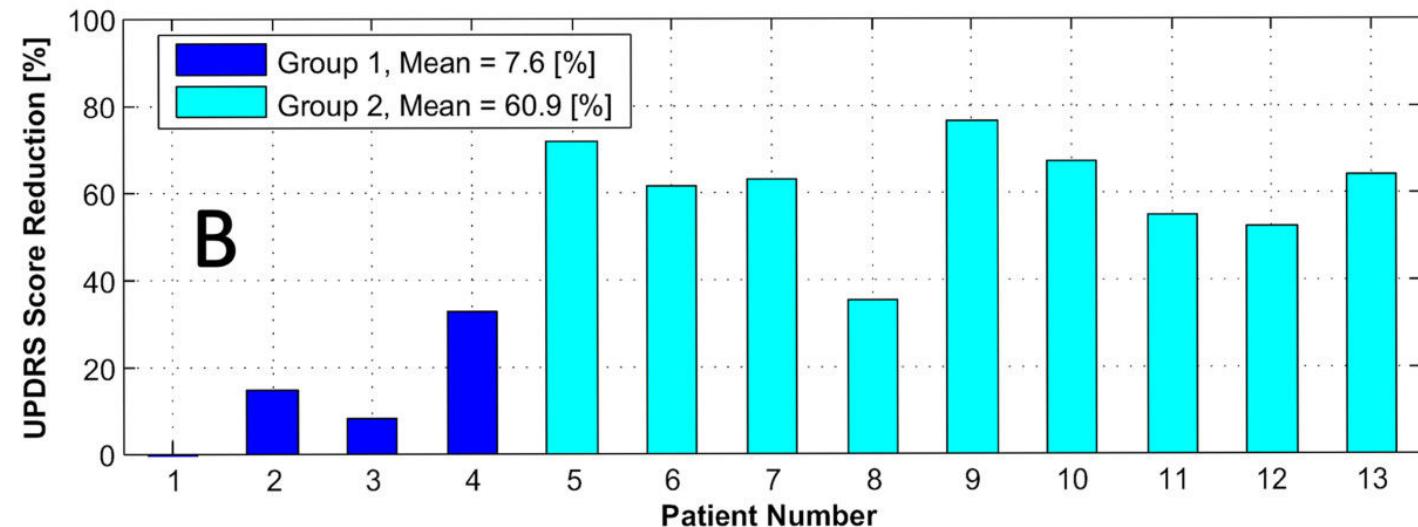
- 7 patients: moderate-severe PD tremor
- Tremor “abolished immediately”
- UPDRS reduced 50% 1 week later
- But...
  - Milder tremor reemerged in 3 of 7 patients
  - Detailed follow-up only given for 1 week
  - Short term side effects: headache (3), dizziness (2), vertigo (4)
  - Lasting side effects: reduced taste (1), unsteady feeling (1), gait imbalance (1)



Schlesinger et al. Park Dis. Pub Online 2015

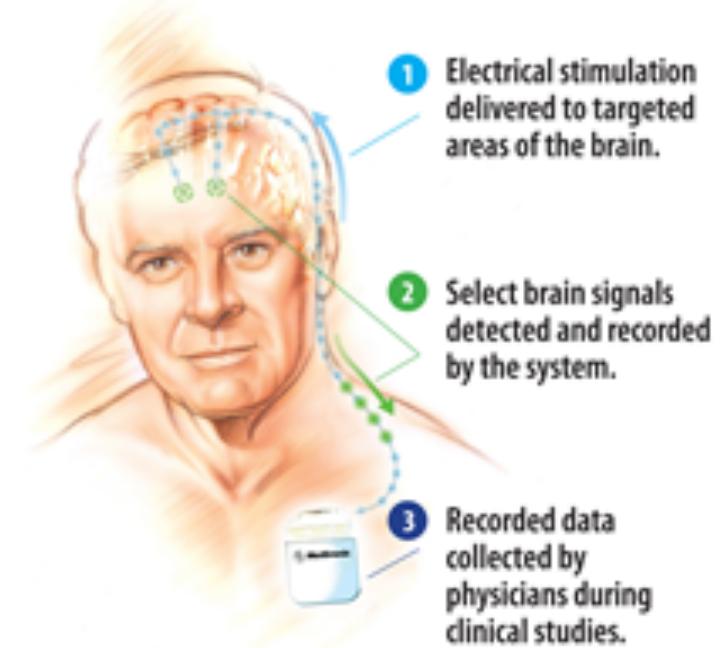
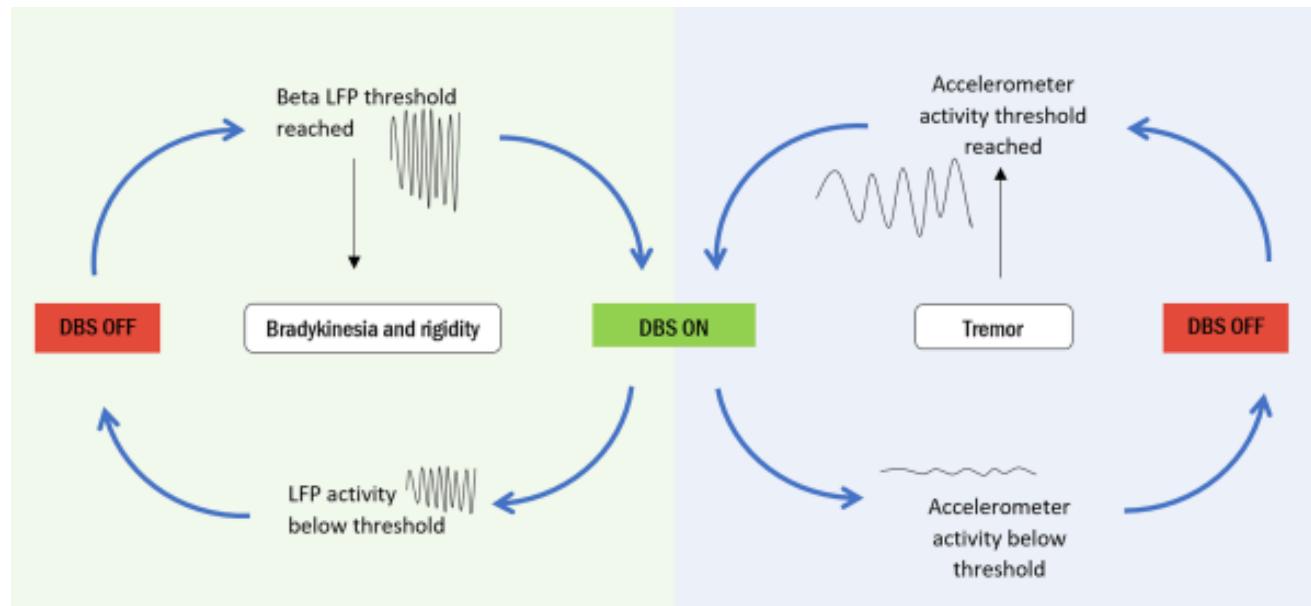
# MRgFUS Thalamotomy:

- 8 patients mostly tremor dominant
- Target: pallidothalamic tract
- UPDRS reduced 60.9% at 3 months
- No side effects



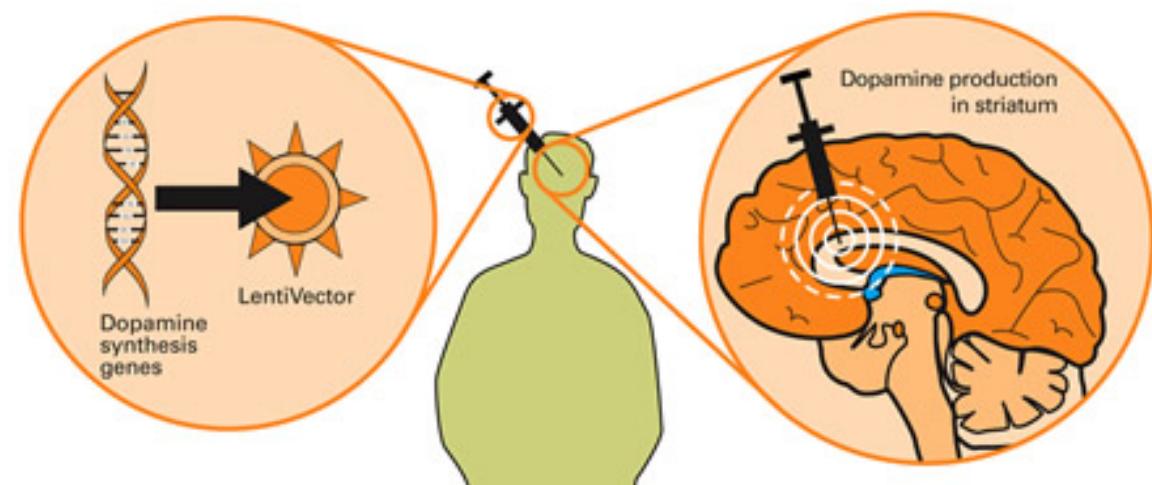
# Closed-Loop Deep Brain Stimulation

Stimulation adapts to symptoms (tremor) or brain signals



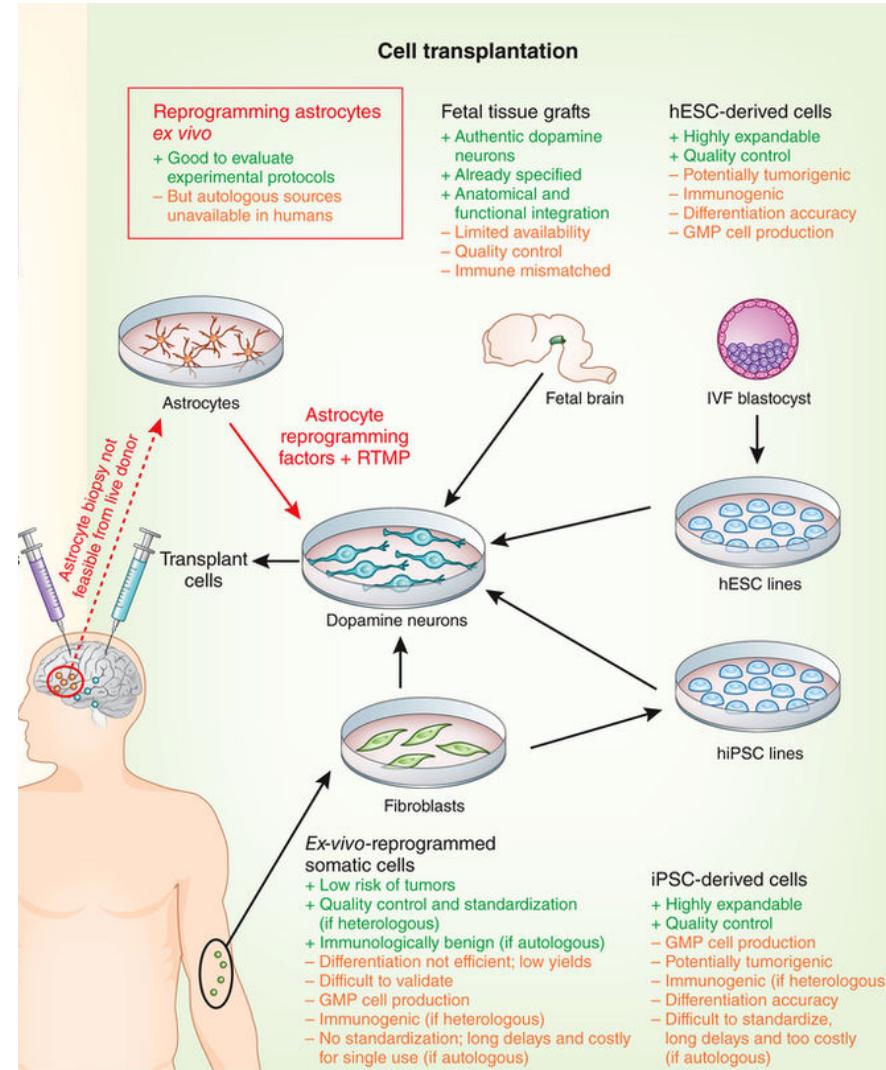
# Gene Therapy

- Increasing dopamine production where it's needed
  - AADC → phase I promising (Voyager Therapeutics)
    - Phase II starting now
  - AADC/TH/GCH (Oxford biomedica) → Phase 1/2 trial with moderate improvement (Palfi et al. Lancet. 2014 383:1138)
  - Glutamic acid decarboxylase



# “Stem Cell” Therapy

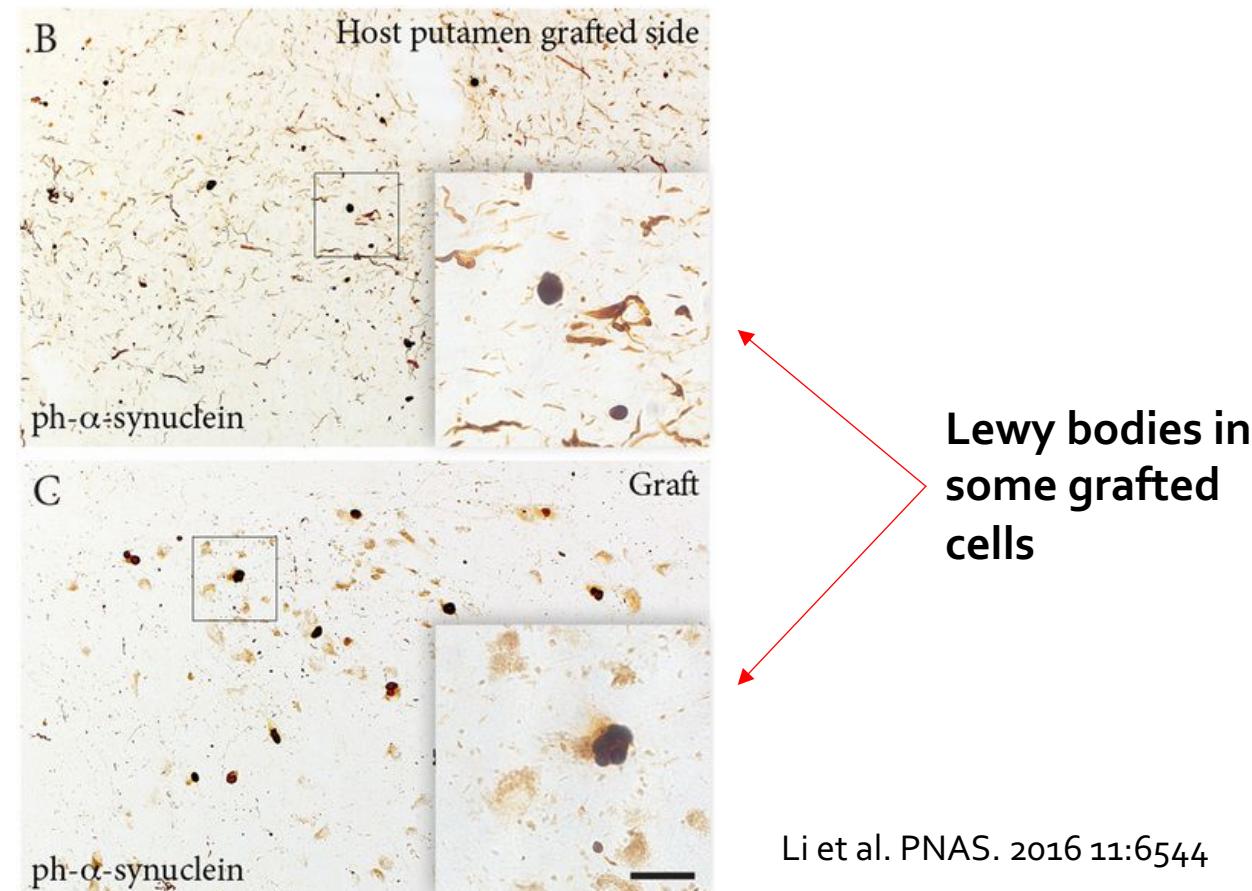
- Fetal ventral mesencephalon cells
- Embryonic stem cells
- Induced pluripotent stem cells
- Induced neurons



# “Stem Cell” Therapy

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Why only symptomatic and not a “cure”?



# “Stem Cell” Therapy

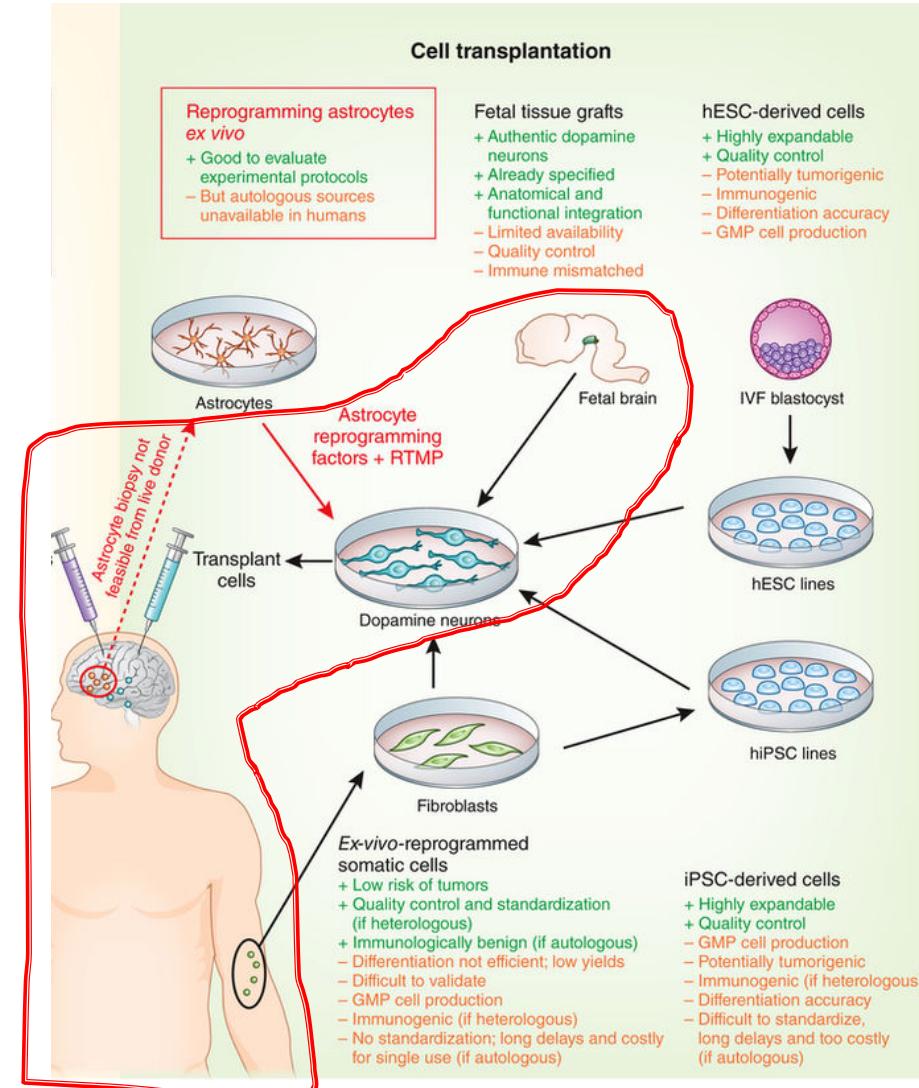
- Fetal ventral mesencephalon cells
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- Induced pluripotent stem cells
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From another person and requires immunosuppression

From you but has your same Parkinson disease risk genes

# “Stem Cell” Therapy

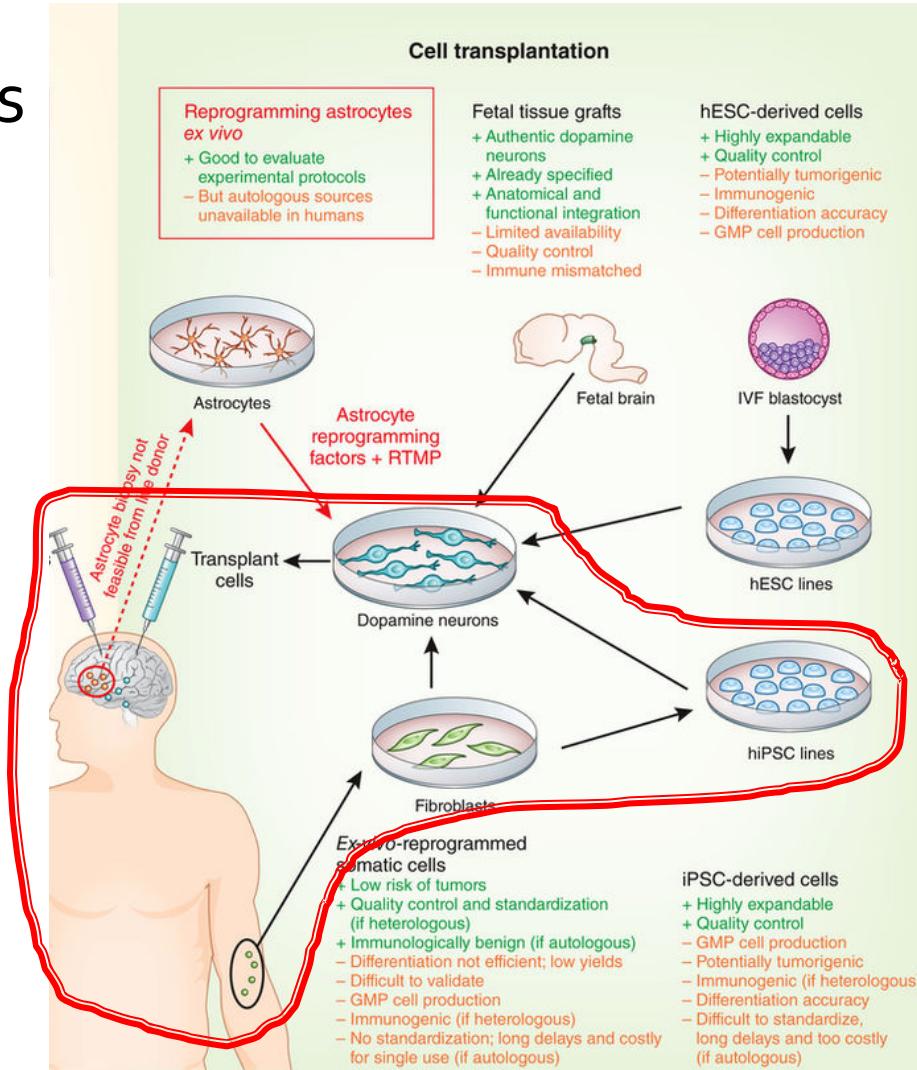
- Fetal ventral mesencephalon cells
  - 2 randomized trials -> no benefit  
(Freed et al. NEJM 2001; Olanow et al. Ann Neurol 2003)
  - New trial (TRANSNEURO)  
publication expected 2020
    - Cambridge, UK: NCT01898390



# “Stem Cell” Therapy

## ■ Induced pluripotent stem cells

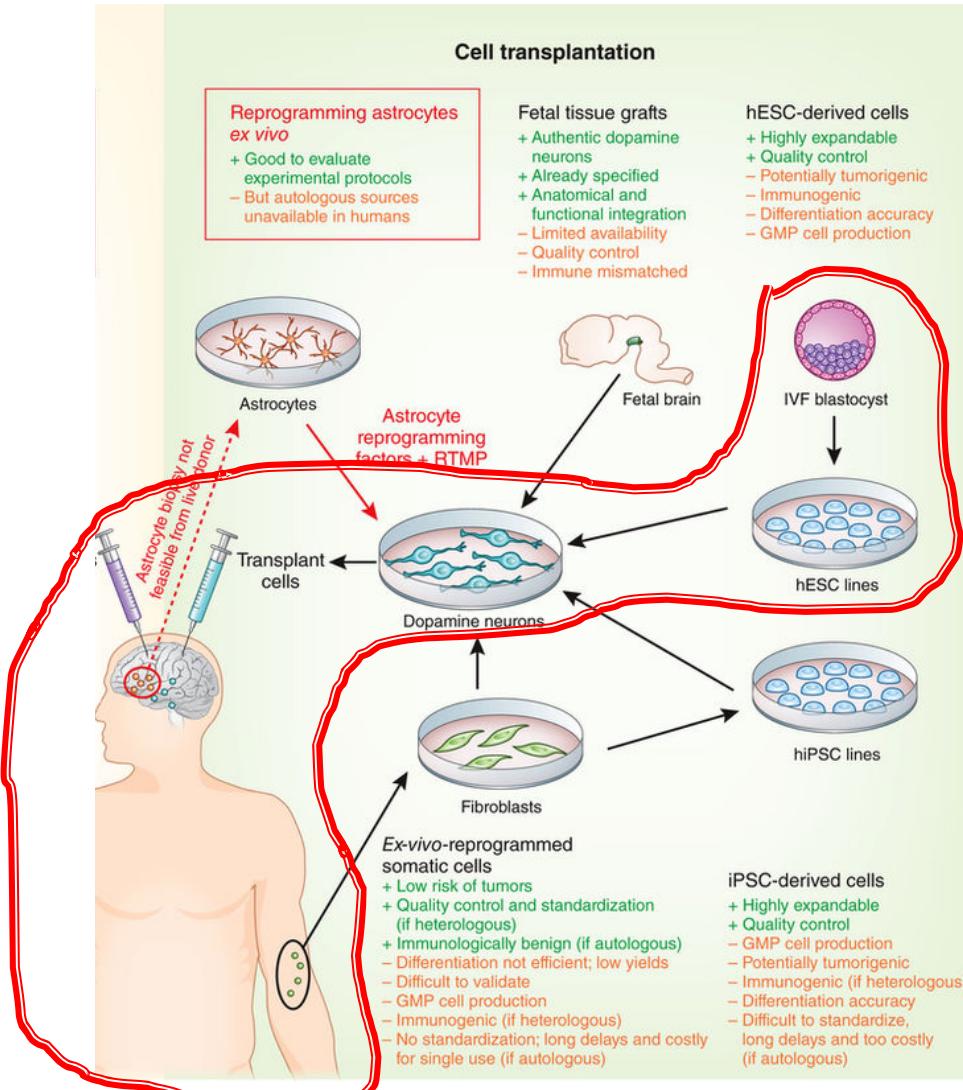
- New trial
  - Jun Takahashi MD, PhD
  - Kyoto University, Japan



# “Stem Cell” Therapy

## ■ Embryonic stem cells

- New trial (Phase I/II)
  - Wang Liu & Hao Jie
  - Zhengzhou University, China



# Overview

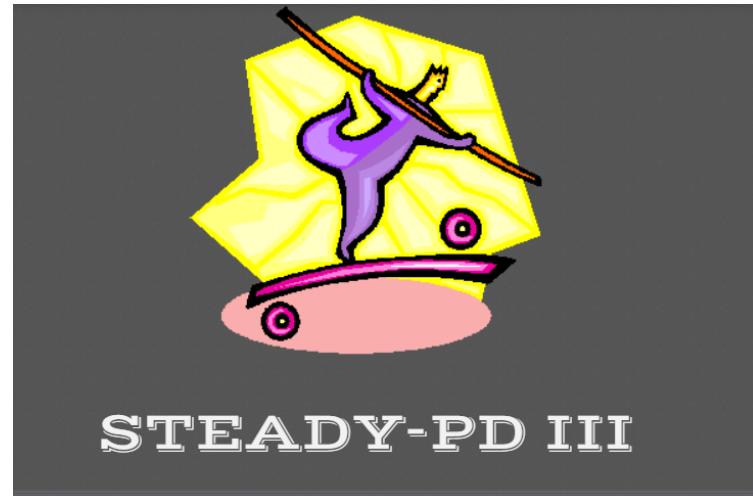
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# Parkinson neuroprotection: Current Trials

- Isradipine (STEADY-PD III) – finished, results in April
- Elevating Urate (SURE-PD III) – stopped early, futile
- Nilotinib – Phase II trials enrolling
- Anti-  $\alpha$ -synuclein therapies – Phase I-II trials
- GLP1-antagonists – Phase II complete (exenatide), Phase I (NYLo1)
- Gene therapy - GDNF

# Parkinson's “neuroprotection”: STEADY-PD III

- Background
  - It was found that people taking a certain type of blood pressure medication (Dihydropyridine calcium channel blockers) had a low incidence of developing Parkinson's disease
  - This medication slowed progression of Parkinson's brain pathology in animals with experimental Parkinson's disease
- Goal of Study: does taking **isradipine** slow or prevent progression of Parkinson's disease
- Study now ended
- Results public April 2019



# Parkinson's "neuroprotection": Nilotinib

Cancer Drug That May Help Alzheimer's Headed to Parkinson's Test

March 15, 2017 · 12:29 PM ET  
Heard on All Things Considered

JON HAMILTON

STUDY: CANCER DRUG RESTORES BRAIN DOPAMINE, REDUCES TOXIC PROTEINS IN PARKINSON, DEMENTIA  
Cancer Drug That May Help Alzheimer's Headed to Parkinson's Test  
Dopamine -  
Parkinson's Symp.  
Early Study in Patients

JULY 18, 2016



BY MAGDALENA KEGEL

IN NEWS.

# Parkinson's “neuroprotection”: Nilotinib

## ■ In the lab

- c-Abl protein acts to promote neurodegeneration in mouse model  
(Ko et al. PNAS 2010 107:16691)
- c-Abl protein inhibitor, nilotinib (cancer therapy), protects dopamine-producing neurons in animal model (Karuppagounder et al. Sci Rep. 2014 4:4874), (Imam et al. PLoS One. 2013 8:e65129)

## ■ In Humans

- Nilotinib slowed progression in 12 persons with Parkinson disease or dementia with Lewy bodies (Pagan et al. J Park Dis. 2016 6:503)
  - Motor symptoms improved 3.6 points after 6 months on 300 mg nilotinib



# Parkinson's “neuroprotection”: Nilotinib

- Current studies:
- PD Nilotinib: Single-center phase II
  - Estimated completion date: 5/2020
  - <https://clinicaltrials.gov/show/NCT02954978>
- NILO-PD: Multi-center phase II
  - Cohort 1: 5 years or more (enrollment closed)
  - Cohort 2: Under 3 years (enrolling in future)
  - Estimated completion date: 10/2020
  - <https://clinicaltrials.gov/ct2/show/NCT03205488>
  - [www.michaeljfox.org](http://www.michaeljfox.org)

*ClinicalTrials.gov*

# Parkinson's “neuroprotection”: Exenatide

Lizard venom offers hope for  
Parkinson's disease patients

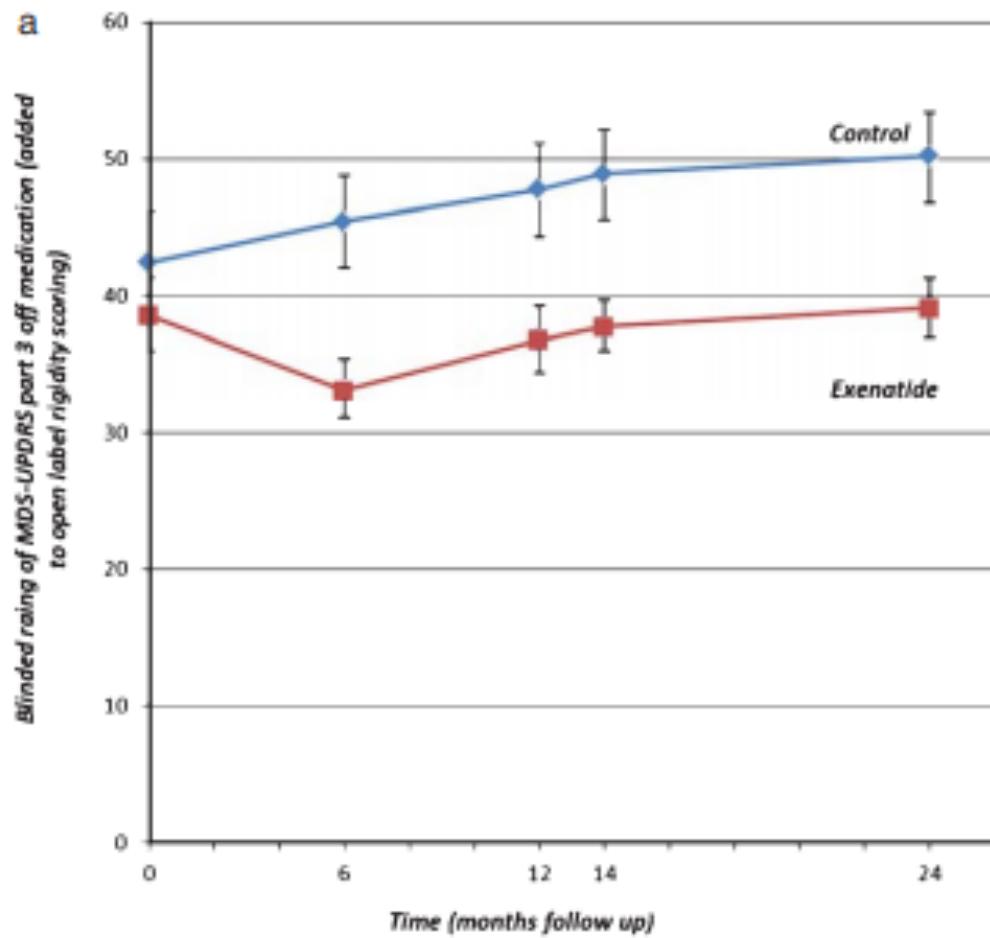
26 August 2010



Diabetes drug (Exenatide) found in lizard venom

# Parkinson's “neuroprotection”: Exenatide

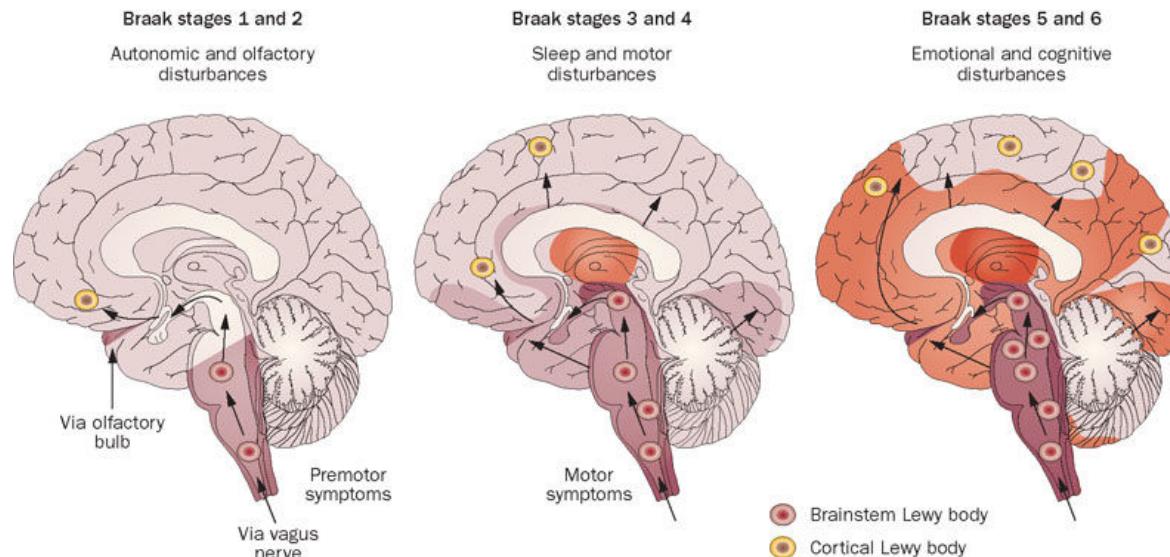
- Currently used for diabetes
- Slowed PD disease progression in phase II study (Athauda et al. Lancet. 2017 390:1664)
  - Increased dyskinesia -> levodopa reduced
  - Weight loss
- Other GLP-1 agonists being tested
  - NLYo1



# Parkinson's “neuroprotection”: $\alpha$ -synuclein antibodies

## ■ Background

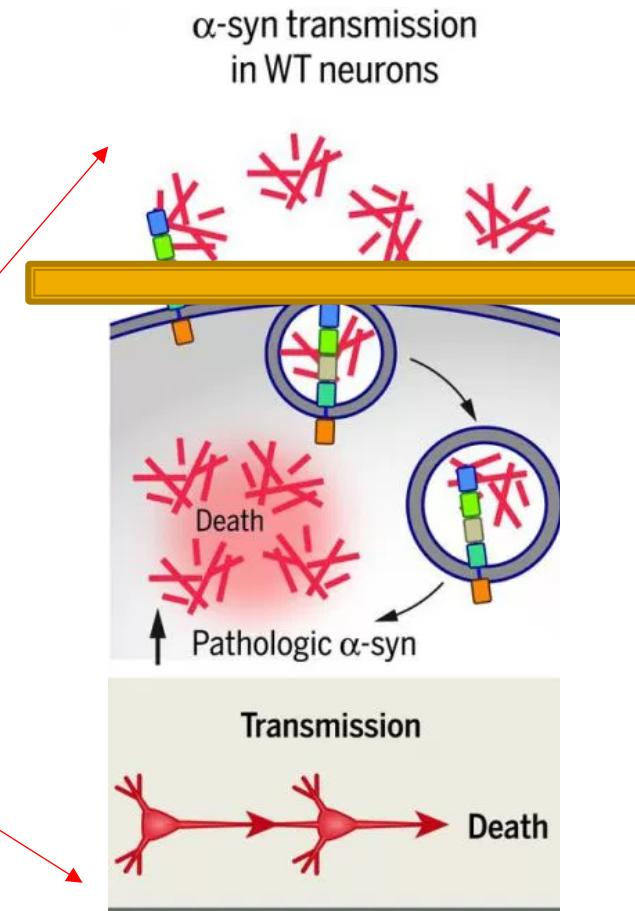
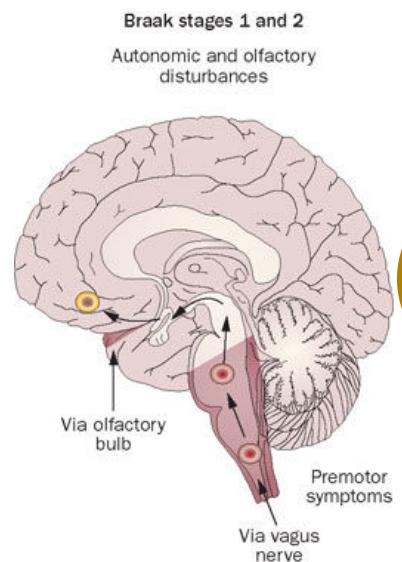
- $\alpha$ -synuclein misfolds and clumps then accumulates in brain cells
- Causes brain cells (neurons) to malfunction or die
- Protein spreads from one cell to another, affecting more of the brain with time



# Parkinson's "neuroprotection": $\alpha$ -synuclein antibodies

## Background

- $\alpha$ -synuclein spreads from cell-to-cell
- Stopping spread and clumping may slow or stop progression of PD



Mao et al. Science. 2016 353:1607

# Parkinson's “neuroprotection”: alpha-synuclein antibodies

## ■ Current anti- $\alpha$ -synuclein trials

- Prothena / Roche – **antibody** against  $\alpha$ -synuclein (PASADENA, phase II)
- Biogen – **antibody** against  $\alpha$  -synuclein (SPARK, phase II)
- AFFiRiS – **vaccinating** against  $\alpha$  -synuclein (Affitope PDo1, phase I)
- Bioartic / AbbVie- **antibody** against  $\alpha$  -synuclein (Phase I)
- Neuropore / UCB – compound **reducing clumping** of  $\alpha$ –synuclein (Phase I)
- Proclara – compound **reducing clumping** of  $\alpha$ –synuclein (Phase I)

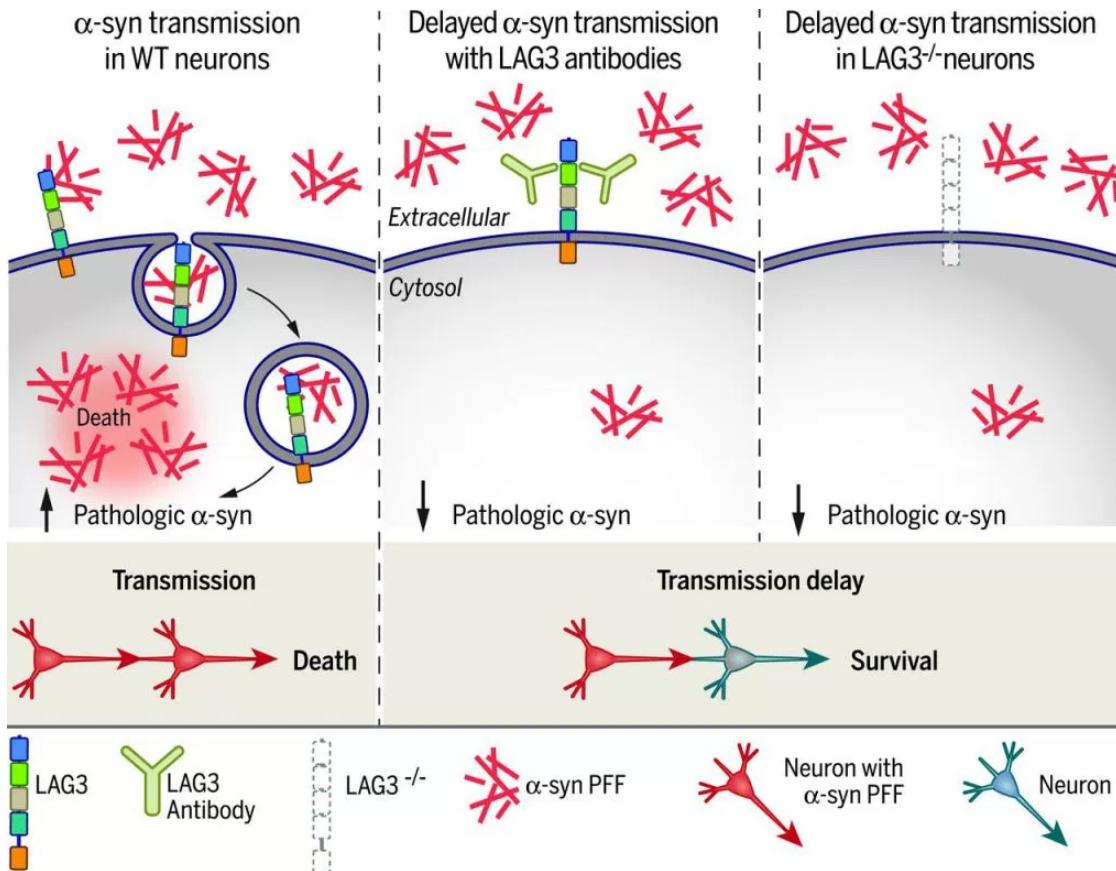


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# Stopping spread of $\alpha$ -synuclein

- LAG3 identified as protein that allowed  $\alpha$ -synuclein entry into cells



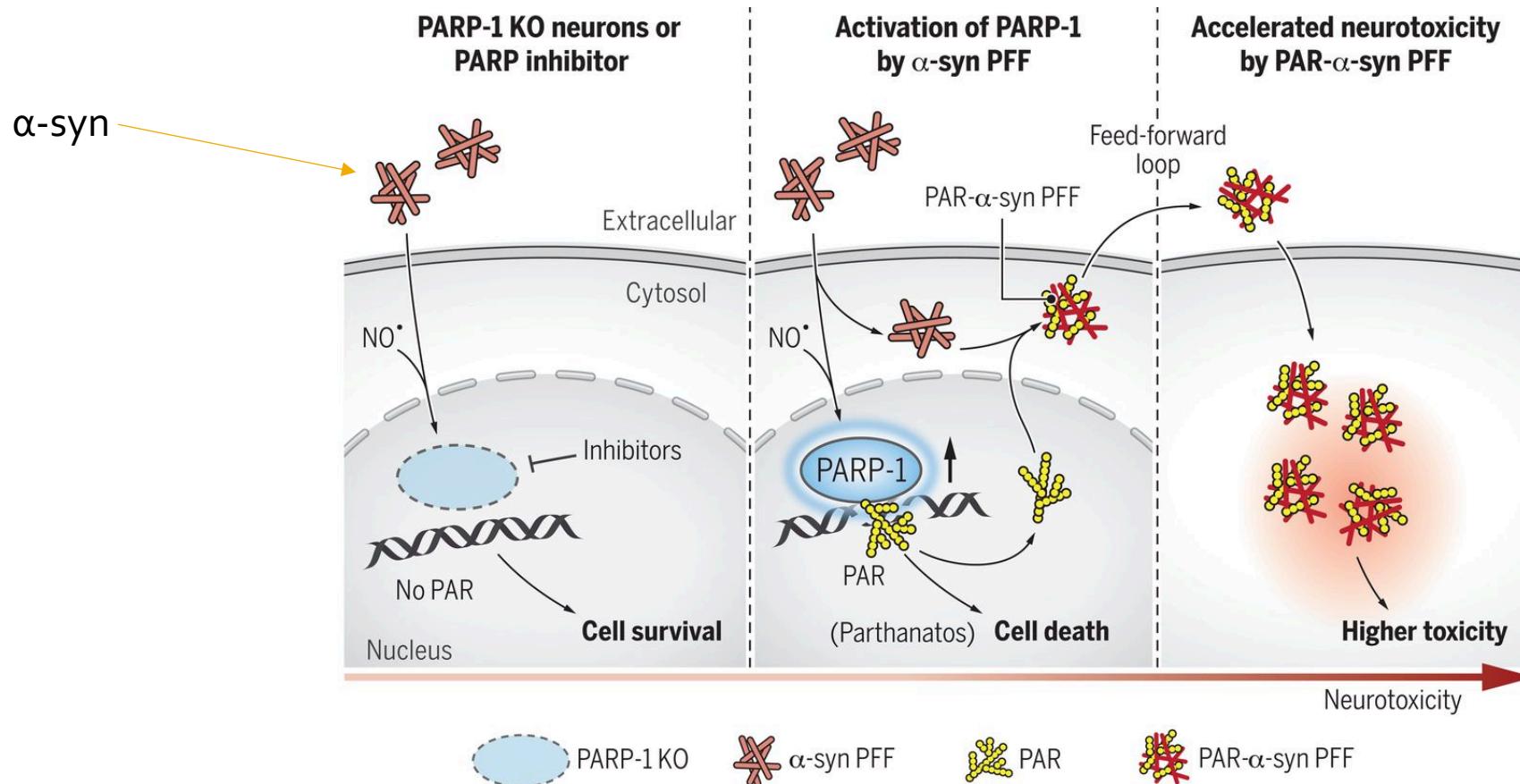
Lab of Drs. Ted and Valina Dawson

Mao et al. Science. 2016 353:1607

# How $\alpha$ -synuclein kills neurons

## ■ PARP-1 activated by $\alpha$ -synuclein

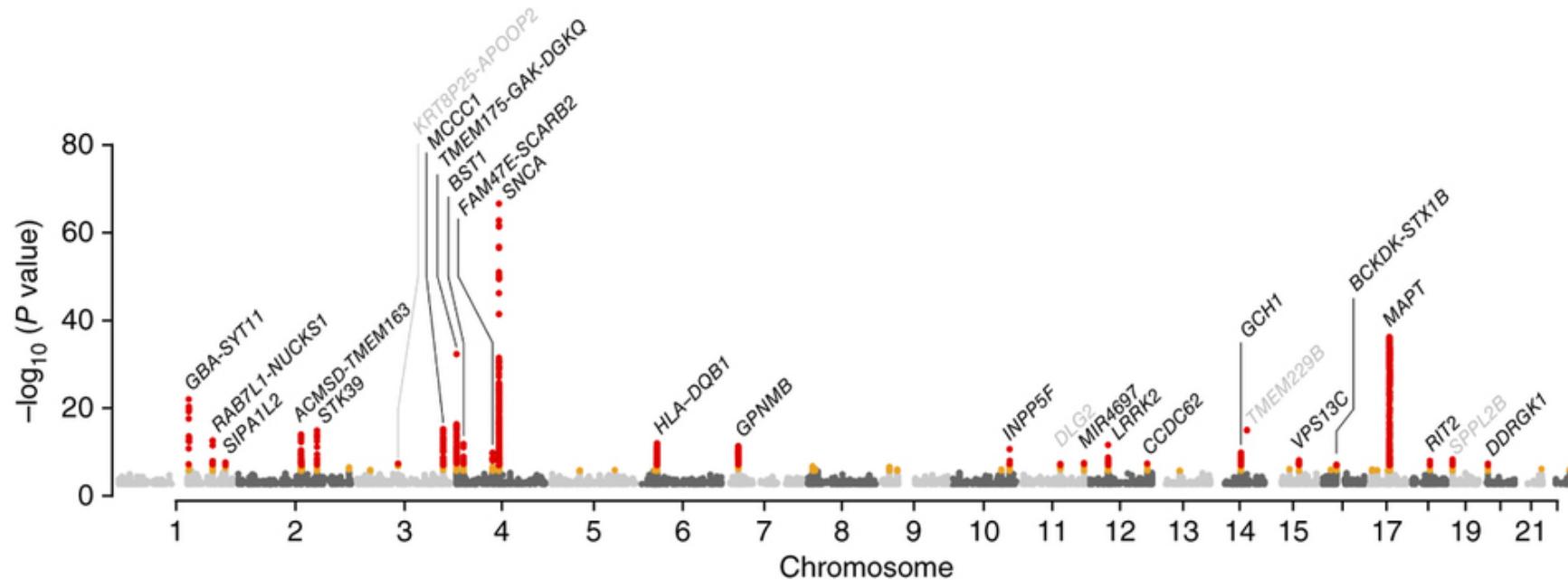
- Accelerates  $\alpha$ -synuclein clumping
- Makes more toxic form of  $\alpha$ -synuclein



# Approach to finding new treatments

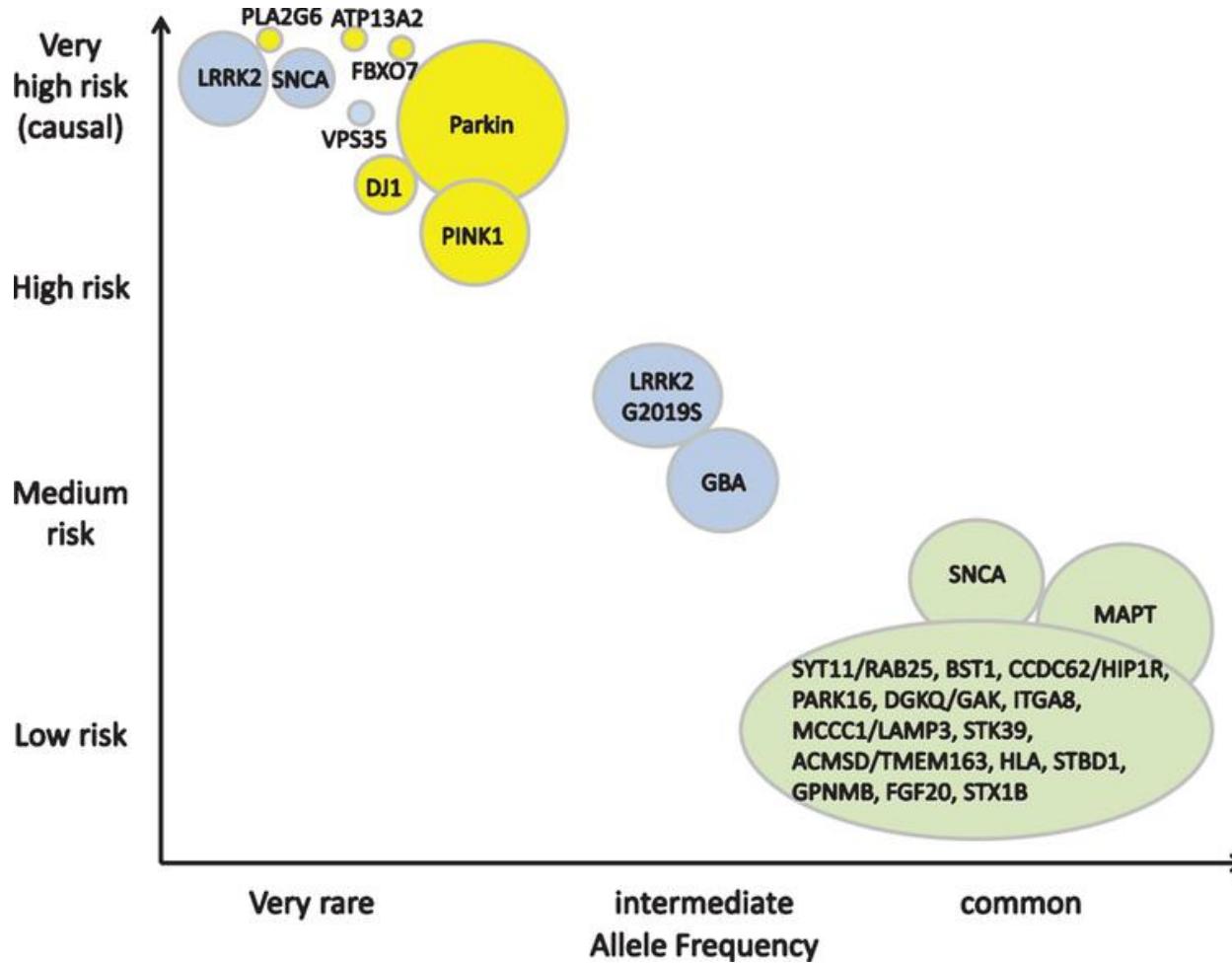
- Define genes involved
- Explore biology of why gene mutations causes cell death
- Develop drugs to correct these deficits

# Genetics of Parkinson's disease



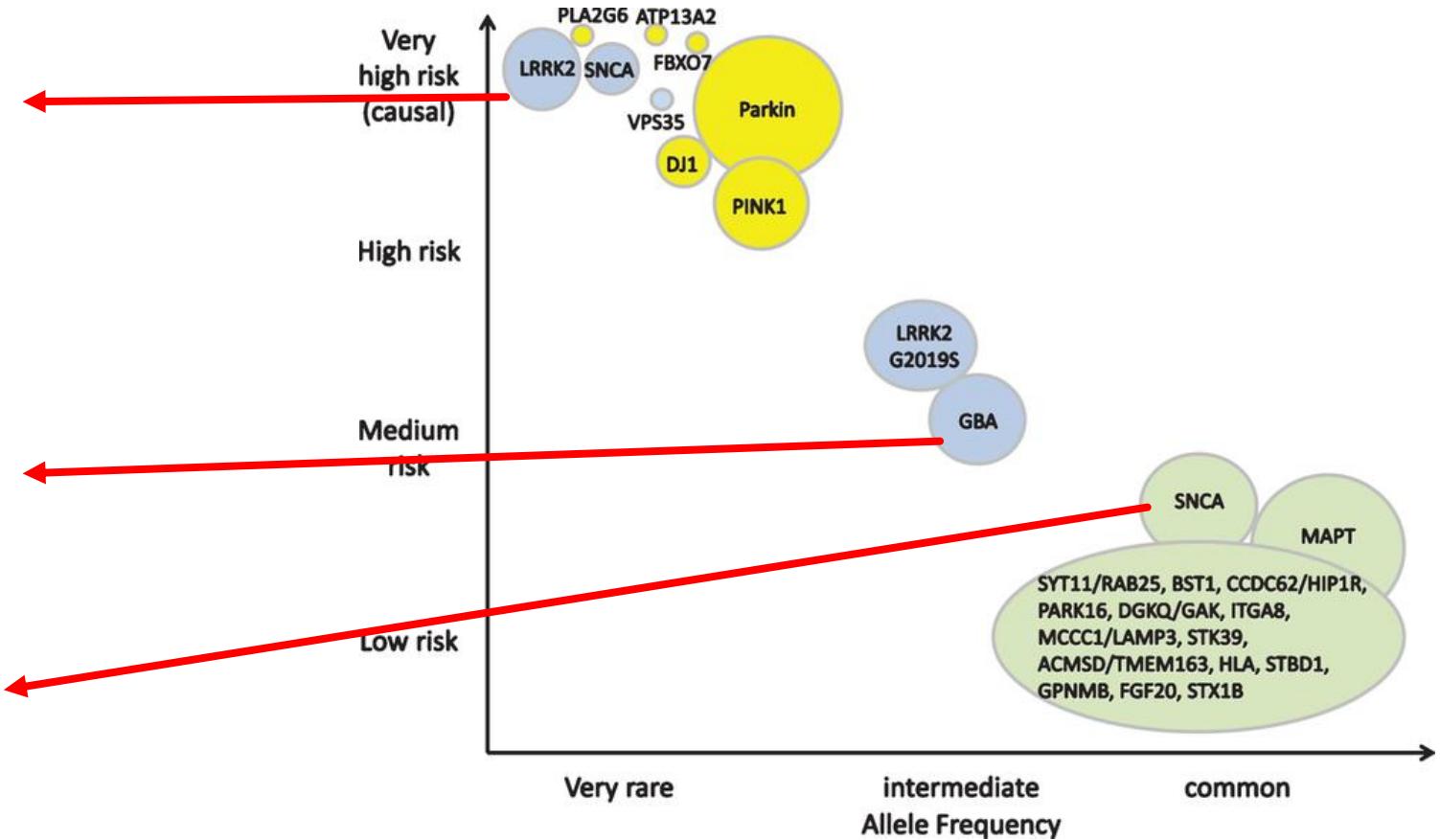
- Genomes of 13,700 PD patients and 95,282 controls compared
- 44 genes found to influence PD risk
- Risk is cumulative with the more genes you have

# Genetics of Parkinson's disease



# Treatments for specific genetic variants

- **LRRK2 inhibitors –**  
DNL201 (Phase I),  
DNL151 (Phase I)
- **GBA chaperone –**  
Ambroxol (AiM-PD)
- **$\alpha$ -synuclein therapies**



# Questions?

- Need advice?
- PFNCA ([parkinsonfoundation.org/](http://parkinsonfoundation.org/))
- National Parkinson Foundation ([NPF.org](http://NPF.org))
- Michael J. Fox Foundation ([MJFF.org](http://MJFF.org))
- Call **410-502-0133** ask for **Chelsea**
  - Advice on referrals
  - Direct you to a local support group
  - Other questions

# Thanks



The Johns Hopkins  
Parkinson's Disease  
and Movement  
Disorders Center  
Team!

