Stanford MEDICINE | Neurology & Neurological Sciences

Updates in Therapeutics for Parkinson's Disease

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Disclaimer

- I am not involved in any of the trials discussed today and I do not endorse any of them
- The goal of this talk is to educate you on the major trials going on in Parkinson's Disease today
  - I have focused on trials that you are likely to hear about in the news

Types of treatments

Disease Modifying Therapies

- **Slow** or **halt** the progression of neuron dysfunction / neuron death (i.e. therapies that prevent further neurons from being impacted by the disease)

Symptomatic Therapies

- **Improve** / **restore function** for the patient (i.e. therapies that improve motor function, cognitive function, etc)

Disease Modifying Approaches

Hundreds of approaches at some stage in development

Approaches in Phase 3:	
	GLP-1R agonists
	Ambroxol
	Buntanetap
	LRRK2 Inhibition

Targeting α-synuclein

Hypothesis:

- Various triggers cause the α-synuclein protein to misfold
- This misfolded protein propagates throughout the brain causing neuron dysfunction and neuron death resulting in PD

Goal:

- Stop α-synuclein misfolding and propagation

Strategies:

- Passively provide antibodies against α-synuclein
- Have the body generates its own antibodies to α-synuclein (i.e. an α-synuclein vaccine)
- Have a small molecule interfere with α-synuclein
- Create a protein that breaks misfolded α-synuclein

Targeting α-synuclein

Mixed results so far (mostly negative, but some signs of small benefit in post-hoc analysis)

Concern: Once a patient is showing signs of PD lots of neuronal injury has already occurred and many biological pathways throughout the brain are behaving abnormally. Misfolded α-synuclein may have *triggered* the cascade, but the cascade is already in motion and removing misfolded α-synuclein at this stage may not stop it

This appears to be the case in Alzheimer's disease and β-Amyloid

Studies will need to be done in *prodromal* patients (patients who are likely to develop PD but do not meet the diagnosis yet)

Targeting α-synuclein – What's next

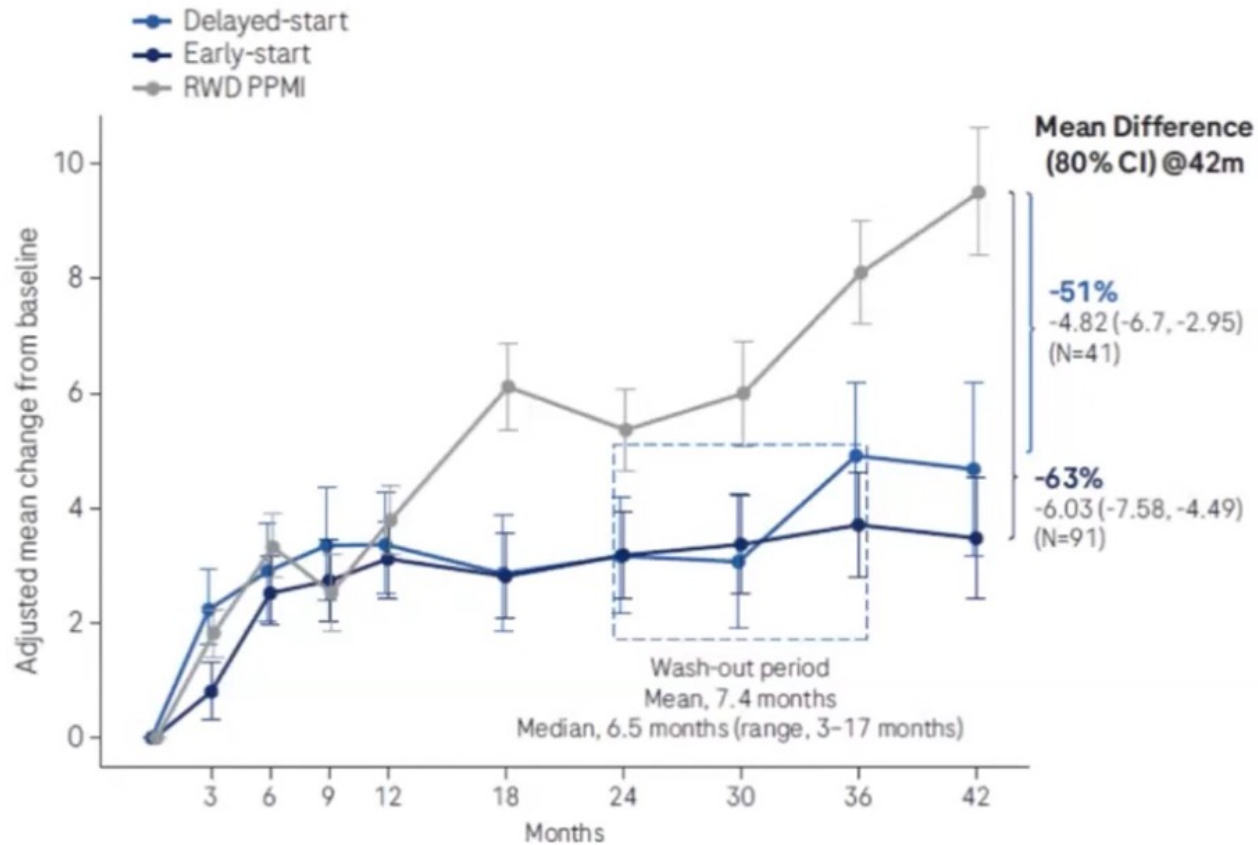
Prasinezumab updates:

- Phase 2 PASADENA trial in early Parkinson's disease (could not be on dopamine medications at start of trial) was overall negative (2022)
- However, possibly a positive signal on the digital/wearable markers
- Additionally, on analysis of open label extension data there may be a positive signal when comparing the data to a 'real world group'
- A Phase 2 PADOVA trial in early Parkinson's disease (but you *could* be on dopamine medications at the start of the trial) has been completed and we are awaiting results

Many other Phase I trials in this category recently completed, underway, or to be initiated soon

Possible interpretations

- Unblinded phase (open label) opens up for placebo effects and investigator bias
- The upcoming datapoint (48 mo) will provide us with more insight
- It has not escaped our notice that the limited worsening in prasinezumab-treated participants suggests a possible slowing of disease progression due to the therapy
- These results are exploratory and need to be confirmed in a randomized controlled trial
- PADOVA trial (n=586; single dose prasinezumab vs placebo, 1:1; Primary endpoint: time to reach 5 pt deterioration in MDS-UPDRS III; >76 wks) reads out *around* Q1 2025



GLP-1R Agonists

Isolated from Gila Monster venom in 1992 by Dr. John Eng

Commonly used drug class for **diabetes** (and recently, obesity)

- Stimulates the pancreas to release more insulin

Parkinson's animal models showed disease benefit

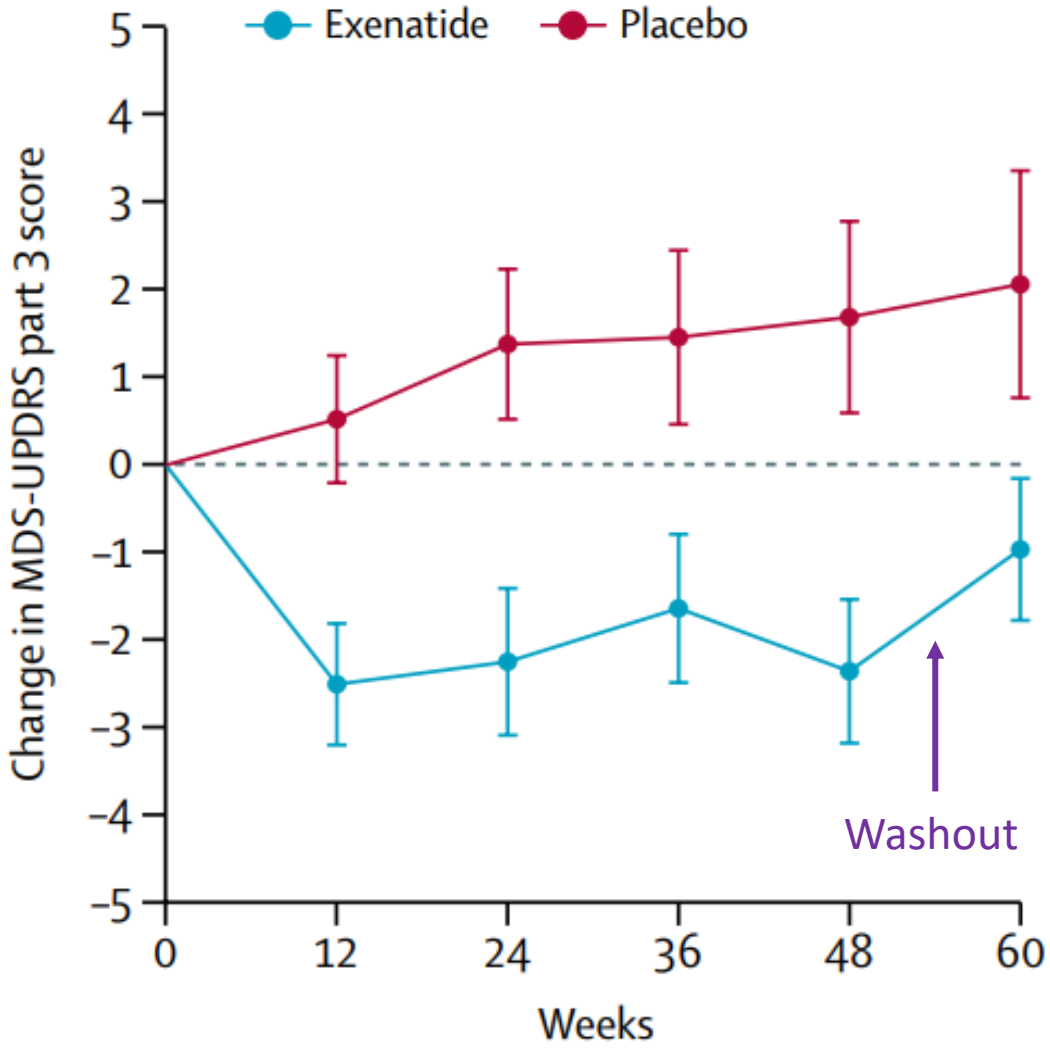
GLP-1R Agonist (Exenatide) Phase 2 Trial

Published in 2017

32 PD patients received Exenatide, 30 PD patients received placebo

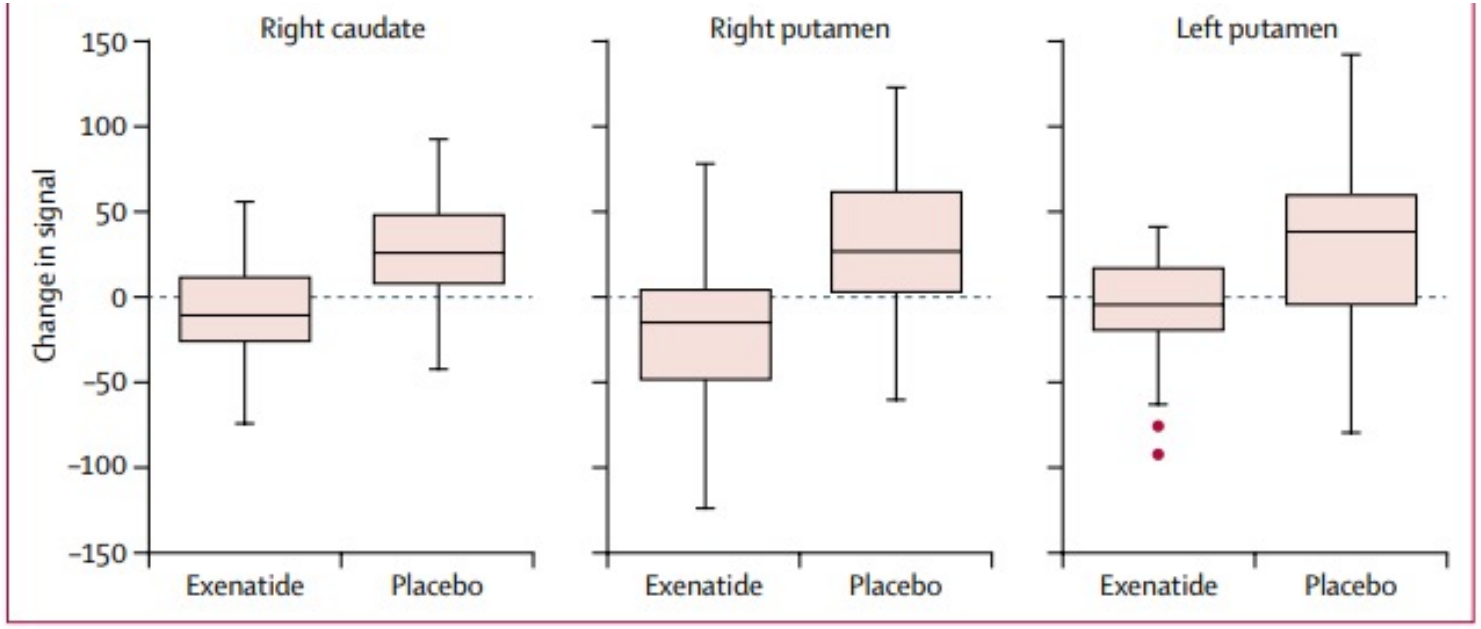
- 48 weeks on medication, 12-week washout period

Mild adverse effects, not worse than placebo



GLP-1R Agonist (Exenatide) Phase 2 Trial

Reduced rate of decline in DaT Scan



3 other Phase 2 GLP-1R Agonist Trials now complete

Liraglutide (+/-)

37 patients received Liraglutide, 18 received placebo for 52 weeks

Non-motor symptoms, activities of daily living and quality of life appeared to significantly improve in the group on liraglutide treatment.

However, there was no clear difference in motor symptoms between those on liraglutide and those on the placebo

It was noted that there appeared to be a strong placebo effect in this study.

NLY-101 (Pegylated Exenatide) (-)

85 patients received 2.5mg NLY-101 daily, 85 received 5mg NLY-101 daily, 85 received placebo for 36 weeks

No difference between either medication group and placebo in both non-motor and motor symptoms

Post-hoc analysis suggests maybe there was a small motor benefit in younger patients

Lixisenatide (+)

78 patients Lixisenatide, 78 patients received placebo for 12 months. Then there was 2 month washout period.

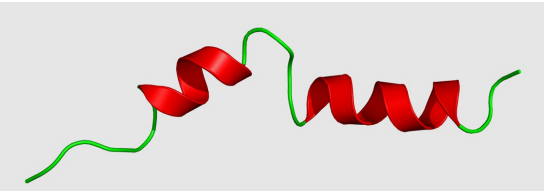
At 12 months, patients on placebo had slight worsening of motor symptoms while patients taking Lixisenatide remained stable (no worsening)

Washout period was not properly analyzed in my opinion

No differences in non-motor symptoms

Nausea (46%) and vomiting (13%) was unfortunately a common side effect

GLP-1R Agonists – What's Next



- **2019 to 2024: Exenatide Phase III (UK)**
  - 200 patients, each patient followed over 24 months

Ambroxol

Glucocerebrosidase is a protein that helps brain cells clean up ‘waste’ they no longer need

Mutations in Glucocerebrosidase are associated with an increased risk in Parkinson’s disease

Ambroxol appears to increase Glucocerebrosidase activity in brain cells, allowing cells to clean up ‘waste’ better which may protect the brain cells

It was tested in a Phase 2a trial in 17 PD patients in 2020

- It was safe and they showed it was able to get into the brain and act on Glucocerebrosidase their target

Ambroxol is used in cough syrup in some countries as it helps break up phlegm.

It is NOT approved in the United States.

In PD trials, a very high dose of Ambroxol was used. Please do not take Ambroxol on your own.

Ambroxol – What's Next

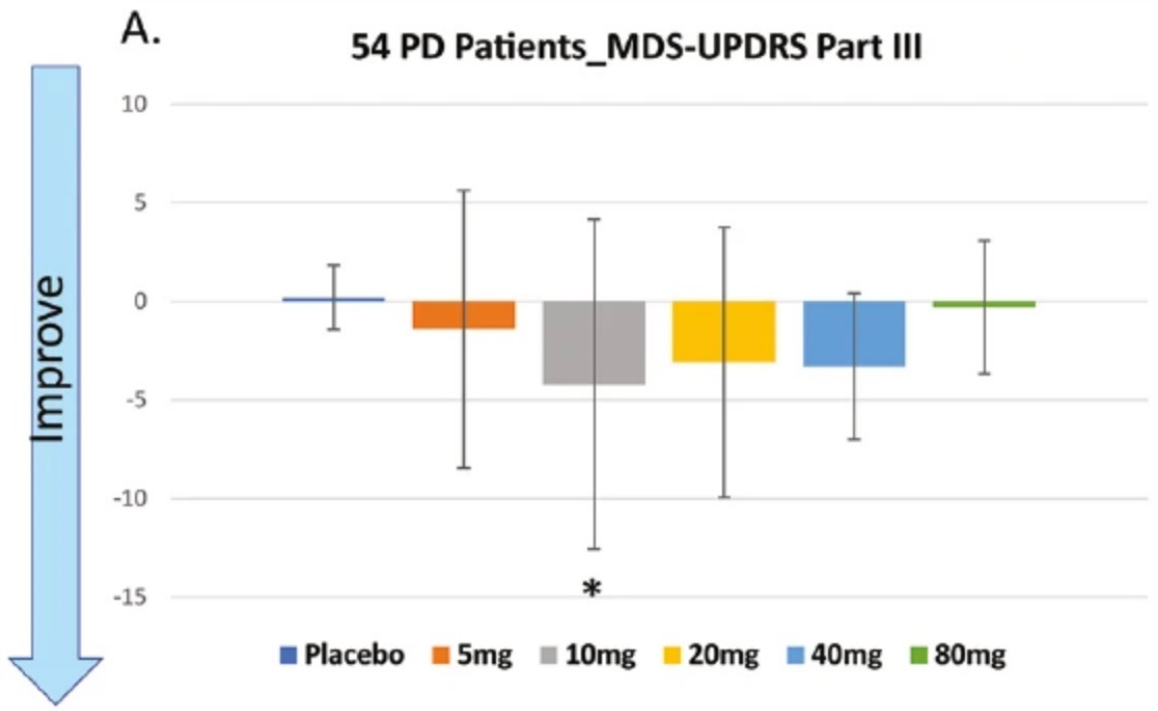
- A Phase 3 study is said to begin soon (initiation has been delayed)
- 330 patients total
  - Some patients will take Ambroxol and some will take placebo, for 2 years
  - Their quality of life and movement ability will be compared at the 2-year mark

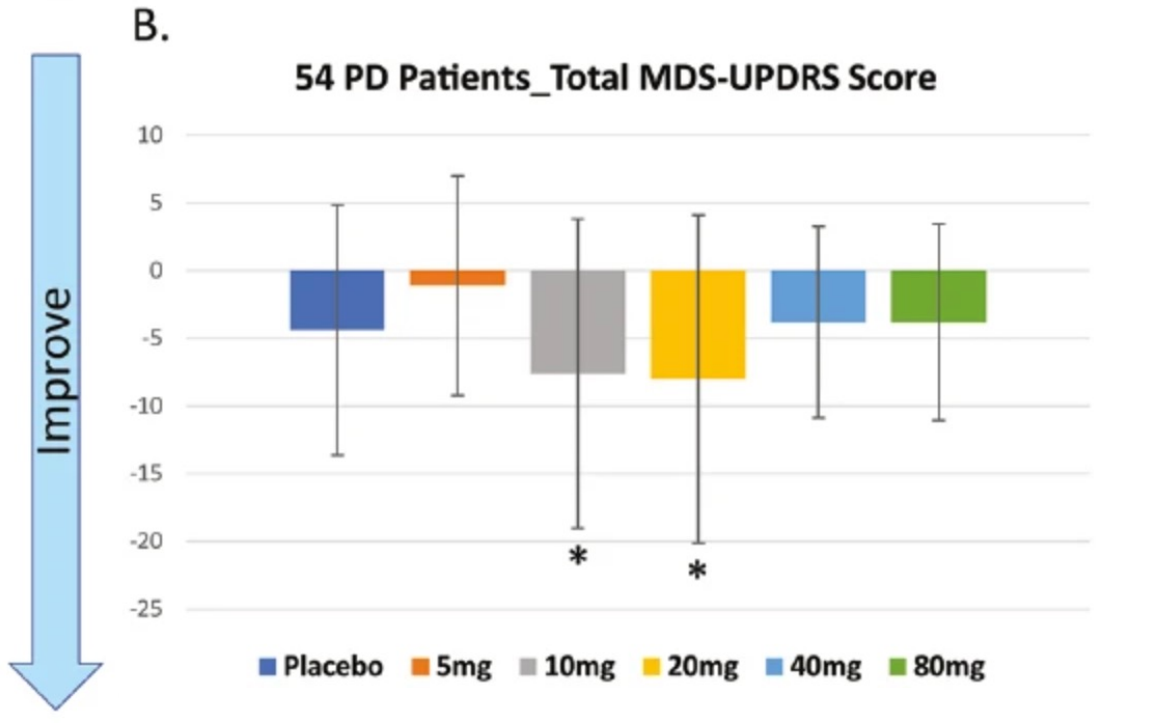
Buntanetap

Buntanetap may reduce brain cell production of α-synuclein

- α-synuclein is a protein that builds up in the brain of patients with Parkinson's disease
- Clumps of misfolded α-synuclein are thought to be toxic to brain cells

A Phase 2 trial published in 2022 found Buntanetap to be safe in PD patients and possibly effective in improving quality of life and motor symptoms at the 25-day mark





Buntanetap – What's Next

- A Phase 3 study has been completed. Results were supposed to be reported in January 2024, but they stated that this has been "postponed to ensure accuracy and reliability of data through diligent cleaning efforts"

- Patients were on Buntanetap 10mg, Buntanetap 20mg, or Placebo for 6 months then evaluated on their quality of life and movement ability

LRRK2 Inhibitors

Hypothesis:

- Certain mutations in the gene LRRK2 contribute to the development of PD
- The enzyme encoded by the mutated gene is hyperactive
- This LRRK2 enzyme hyperactivity leads to PD (exactly how is unclear)

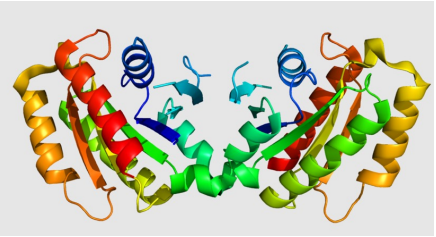
Goal:

- Design a way to slow down the LRRK2 enzyme

Strategies:

- Small molecules
  - BIIB122 by Denali shown to be safe in Phase 1 studies
- Genetic modifications

LRRK2 Inhibitors – What's Next



- Biogen/Denali have started:
  - Phase 2 trial in all PD patients
    - Results expected in 2025

There was also Phase 3 trial in patients with LRRK2 mutations but this has been terminated

List of LRRK2 inhibitors in development

Drug	Company	Properties	Status
BIIB122 (DNL151)	Biogen/Denali	Small-molecule kinase inhibitor	Phase III and II
BIIB094 (ION859)	Biogen/Ionis	Antisense oligonucleotide	Phase I
S221237	Servier/Oncodesign	Small-molecule kinase inhibitor	Phase I to start
NEU-723	Neuron23	Small-molecule kinase inhibitor	Phase I to start
PFE-360	Cerevel/Pfizer	Small-molecule kinase inhibitor	Preclinical
ESB5070	Escape Bio	G2019S-selective small-molecule kinase inhibitor	Preclinical
Undisclosed	Merck & Co.	Small-molecule kinase inhibitor	Undisclosed

UCSF LRRK2 Inhibitor Trial - Recruiting

[UCSF Parkinson's Disease Trial → BIIB122 Tablets and if it Can Slow the Worsening of Early-Stage Parkinson's Disease in Participants Between the Ages of 30 and 80]

☑ YOU CAN JOIN IF...

Open to people ages 30-80

- Clinical diagnosis of PD meeting the Movement Disorder Society Clinical Diagnostic Criteria within 2 years of the Screening Visit, inclusive, and at least 30 years of age at the time of diagnosis
- Modified Hoehn and Yahr scale stages 1 to 2 (in OFF state), inclusive, at screening
- MDS-UPDRS Parts II and III (in OFF state) combined score less than or equal to (≤)40 at screening

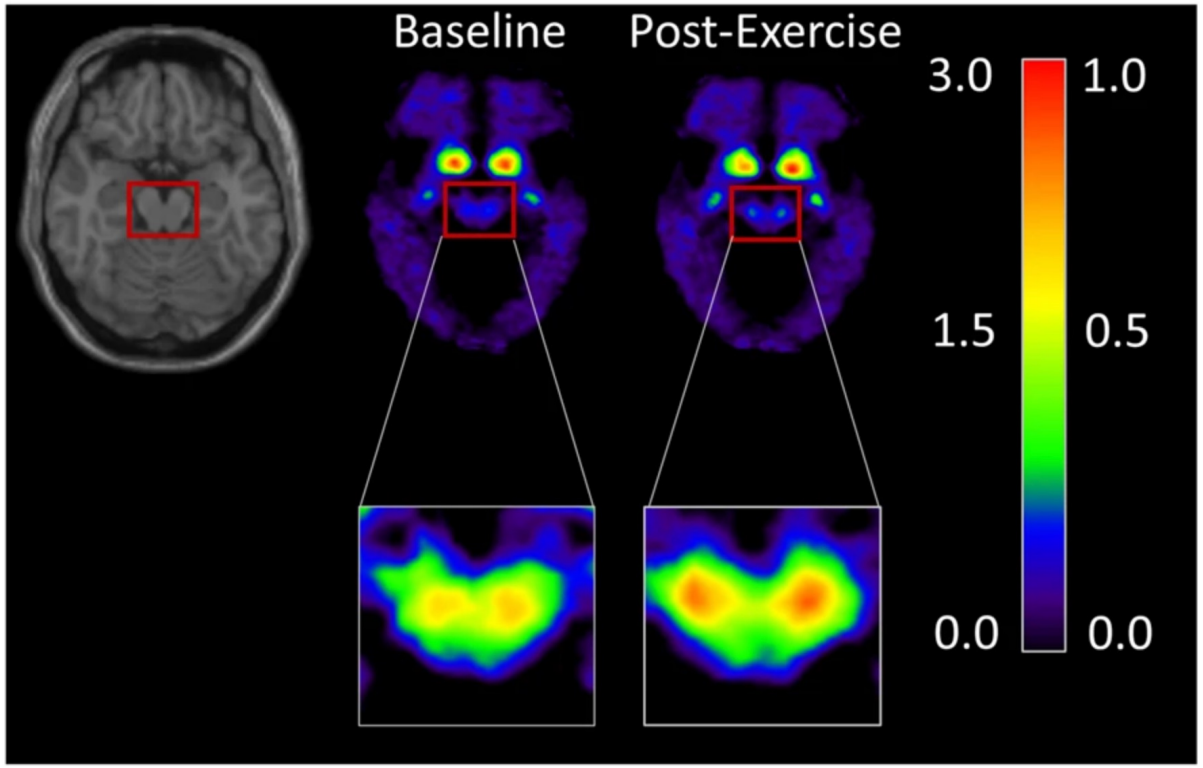
⊘ YOU CAN'T JOIN IF...

- Clinically significant neurological disorder other than PD, including but not limited to stroke, dementia, or seizure, within 5 years of screening visit, in the opinion of the Investigator
- Clinical evidence of atypical parkinsonism (e.g., multiple-system atrophy or progressive supranuclear palsy) or evidence of drug-induced parkinsonism.
- Montreal Cognitive Assessment (MoCA) score <24 at the screening visit.

New (small) trial supporting exercise for PD as a disease modifying therapy

10 patients had DaT Scans done before and after undergoing 6 months in the “Beat Parkinson’s Today” high-intensity interval training program, showing some improvement in the scan with exercise

[Beat Parkinson's with Beat PD - Visit Our Official Website (beatpdtoday.com)]



Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson's disease: a double-blind, randomised controlled trial

Nicolien M van der Kolk, Nienke M de Vries, Roy P C Kessels, Hilde Joosten, Aeilko H Zwinderman, Bart Post, Bastiaan R Bloem

	Baseline		6 months		Within-group change from baseline after 6 months		Between-group difference in change from baseline	
	Aerobic intervention group (n=65)	Active control group (n=65)	Aerobic intervention group (n=65)	Active control goup (n=65)	Aerobic intervention group (n=65)	Active control group (n=65)	Available data	p value
Primary outcome								
MDS-UPDRS III, motor score in the off state*	29·5 (2·7)	27·2 (2·7)	29·0 (2·5)	31·4 (2·5)	1·3 (1·8)	5·6 (1·9)	−4·2 (1·3; −6·9 to −1·6)	0·0020

- HR_max = 206.9 – 0.67 * age
- 0.5 to 0.7 * (HR_max – HR_resting) + HR_resting = moderate intensity heart rate
- 30 min, 3 times a week
- Limitation: Not possible to blind patients

Start an exercise regimen!

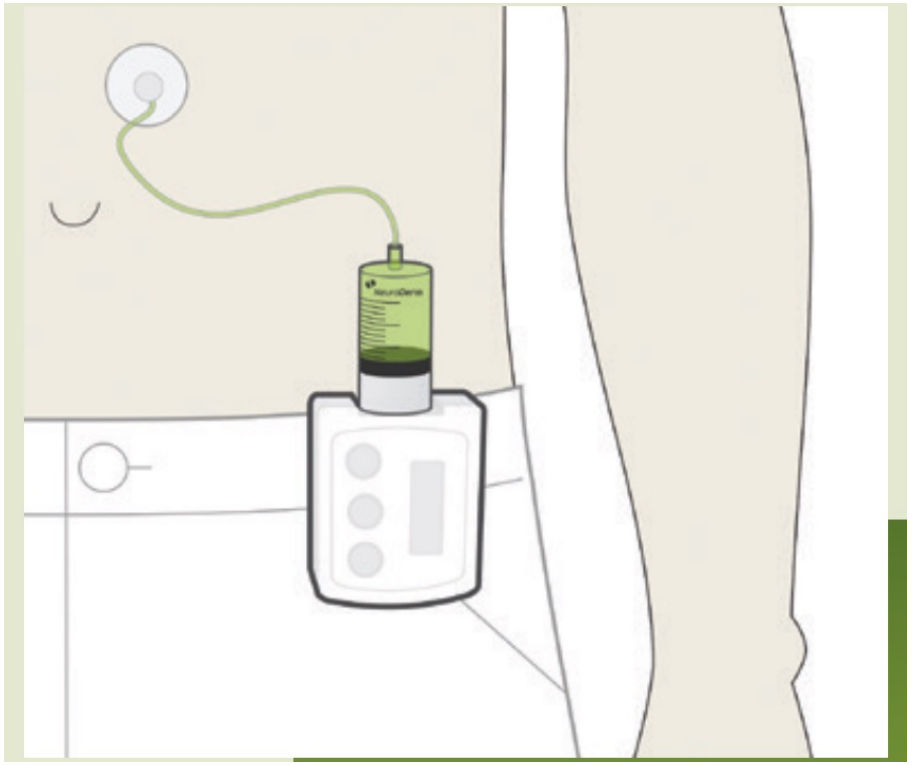
Symptomatic Therapies

New formulations of old drugs:	Opicapone, Safinamide, Levodopa inhalation powder, Apomorphine sublingual film, long-acting Amantadine, subcutaneous Levodopa
	Useful in special cases, but does not change treatment for most patients at this time
New interventional approaches:	Focused ultrasound
	Dopamine neuron stem cell implantation

Subcutaneous Levodopa-Carbidopa

Two companies with similar approaches (Abbvie, NeuroDerm) for a 24-hour/day continuous subcutaneous carbidopa/levodopa infusion

Both have completed Phase 3 trials showing improvement in ON time without troublesome dyskinesias



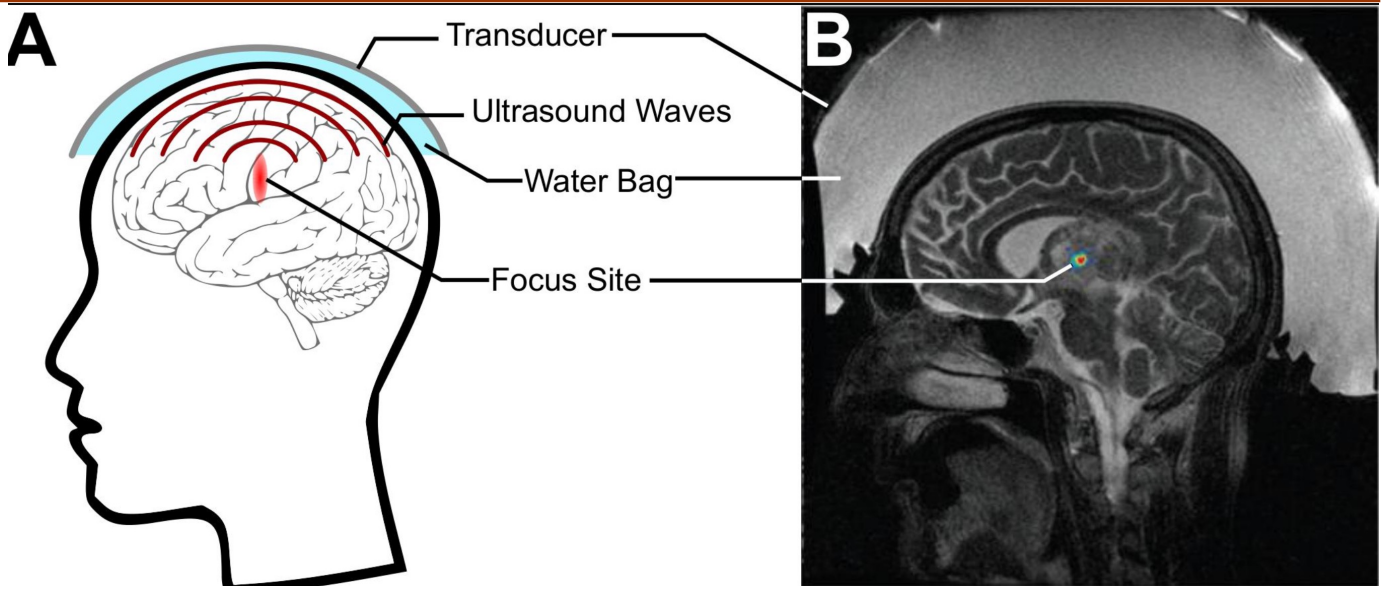
No major issues except for infusion site reactions (mostly mild /moderate, but a couple skin infections requiring antibiotics)

AbbVie's product (PRODUODOPA) already approved in Europe

Focused Ultrasound

Focused non-ionizing ultrasonic waves to lesion tissue

- Targets in the brain:
  - Thalamus (for tremor only) – approved by FDA
  - Globus Pallidus (primarily for dyskinesias) – approved by FDA
  - Subthalamic Nucleus
  - Pallidothalamic tract



STN Focused Ultrasound Trial (2020)

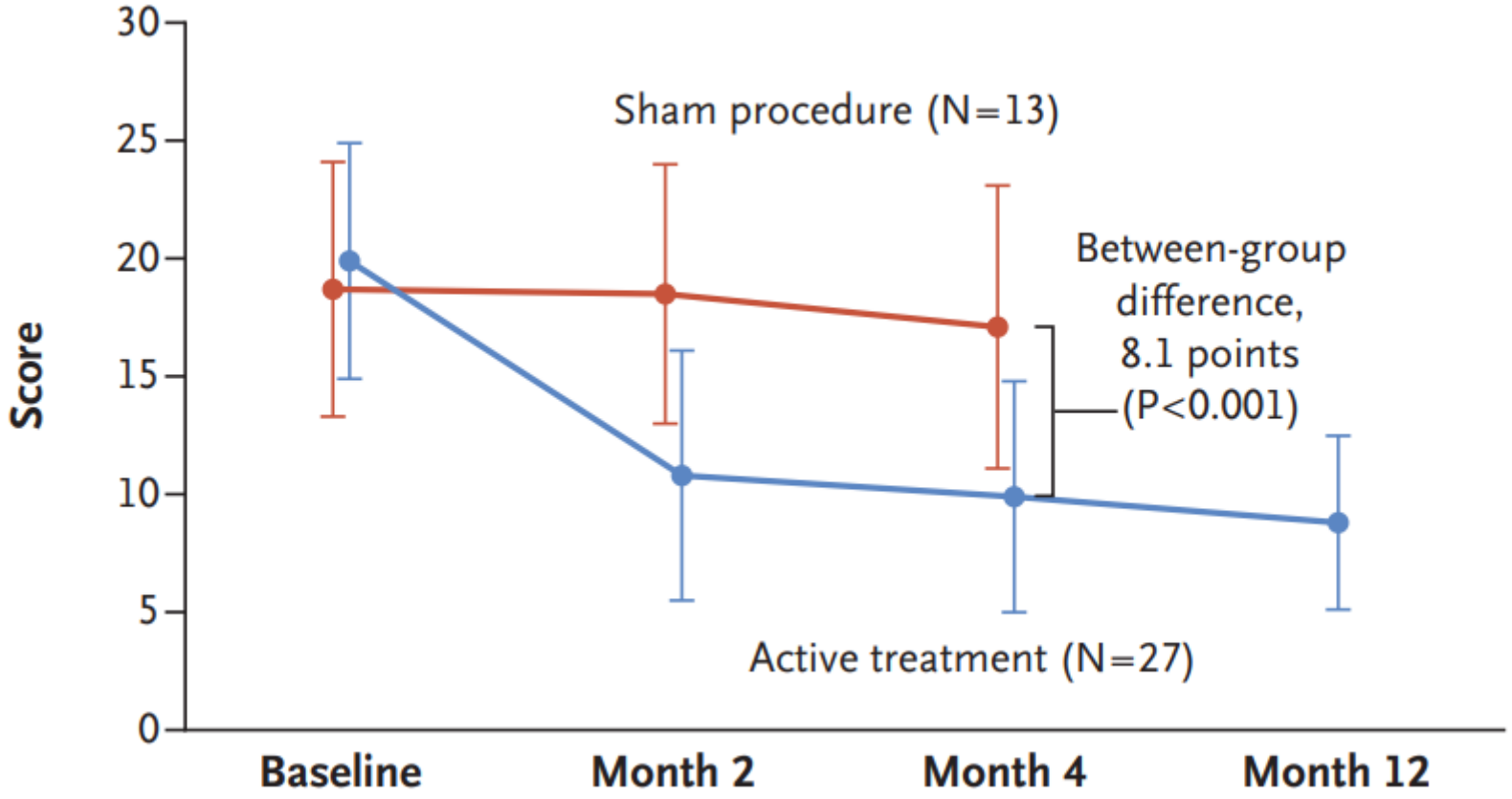
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 24, 2020 VOL. 383 NO. 26

Randomized Trial of Focused Ultrasound Subthalamotomy for Parkinson's Disease

R. Martínez-Fernández, J.U. Máñez-Miró, R. Rodríguez-Rojas, M. del Álamo, B.B. Shah, F. Hernández-Fernández, J.A. Pineda-Pardo, M.H.G. Monje, B. Fernández-Rodríguez, S.A. Sperling, D. Mata-Marín, P. Guida, F. Alonso-Frech, I. Obeso, C. Gasca-Salas, L. Vela-Desojo, W.J. Elias, and J.A. Obeso

40 patients

- 27 treated
- 13 'sham' treatment (control)



STN Focused Ultrasound Adverse Effects

7% chance of weakness is relatively high for a unilateral lesions

Will be higher for bilateral lesions

Adverse Event	Focused Ultrasound Subthalamotomy (N=27)					Sham Procedure (N=13)
	Total	At 24 Hr	At 2 Mo	At 4 Mo	At 12 Mo	At 4 Mo
Dyskinesia on the more affected side, in the off-medication state — no. of patients (%)						
Any event, regardless of severity	6 (22)	0	6 (22)	3 (11)	0	0
Chorea	5 (19)	0	5 (19)	3 (11)	0	0
Ballism	1 (4)	0	1 (4)	0	0	0
New-onset dyskinesia on the more affected side, in the on-medication state — no. of patients (%)	6 (22)	0	6 (22)	1 (4)	2 (7)	0
Weakness on the more affected side — no. of patients (%)	5 (19)	5 (19)	2 (7)	2 (7)	2 (7)**	0
Isolated facial asymmetry — no. of patients (%)	3 (11)	3 (11)	3 (11)	1 (4)	0	0
Speech disturbance — no. of patients (%)						
Any objective or subjective event†	15 (56)	6 (22)	12 (44)	3 (11)	1 (4)	0
Dysarthria, assessed objectively on examination	7 (26)	6 (22)	5 (19)	3 (11)	1 (4)	0
Slurred speech, as reported by the patient	8 (30)	0	7 (26)	0	0	0
Gait disturbance — no. of patients (%)						
Any objective or subjective event‡	13 (48)	8 (30)	7 (26)	2 (7)	1 (4)	0
Ataxia, assessed objectively on examination	3 (11)	2 (7)	1 (4)	0	0	0
Unsteady gait, as reported by the patient	10 (37)	6 (22)	6 (22)	2 (7)	1 (4)	0

Focused Ultrasound - What's next

- Centers are continuing to test out unilateral Focused Ultrasound and report their experiences
  - Side effect profile will likely improve as centers get experienced

- We'll hopefully see more results for other Focused Ultrasound targeted brain regions soon (e.g. pallidothalamic tract)

Thoughts:

- May be useful for patients who cannot get DBS, but at this time unlikely to be superior to DBS for most patients. It is currently only used for 1 side of the body (unilateral), and has higher chance of adverse effects

Stem Cells for PD

Unfortunately, symptomatic only

- *Not* being used as a cure
- Replaces dopamine, does not prevent spread of disease

Logic:

- Dopamine cells are dying, let's replace them

Trials done in 1980s and 1990s with mixed effects

- Some benefited, some had no effect, and some worsened due to uncontrollable dyskinesias

Trying again with argument that we have better quality stem cells and surgical techniques

Stem Cells for PD – What's Next

- BlueRock therapeutics announced positive phase 1 results of its stem cell product (bemdaneprocel) and will move to phase 2

- Australia, Japan, UK/Sweden, China all have started or will start soon early phase clinical trials for Dopamine Neuron Stem Cell implantation

Thoughts:

- Very likely to be succesful initially, allowing patients to come off their Dopamine medications.
- However, at 5 to 10 years post implantation, I suspect we will see difficult to control dyskinesias

Summary

- Disease Modifying Therapies
  - α-synuclein reduction
  - GLP-1R agonists
  - Ambroxol
  - Buntanetap
  - LRRK2 inhibition

- Symptomatic Therapies
  - Subcutaneous Carbidopa / Levodopa infusion
  - Focused Ultrasound
  - Stem Cell Implantation

Q&A