



Updates in 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

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



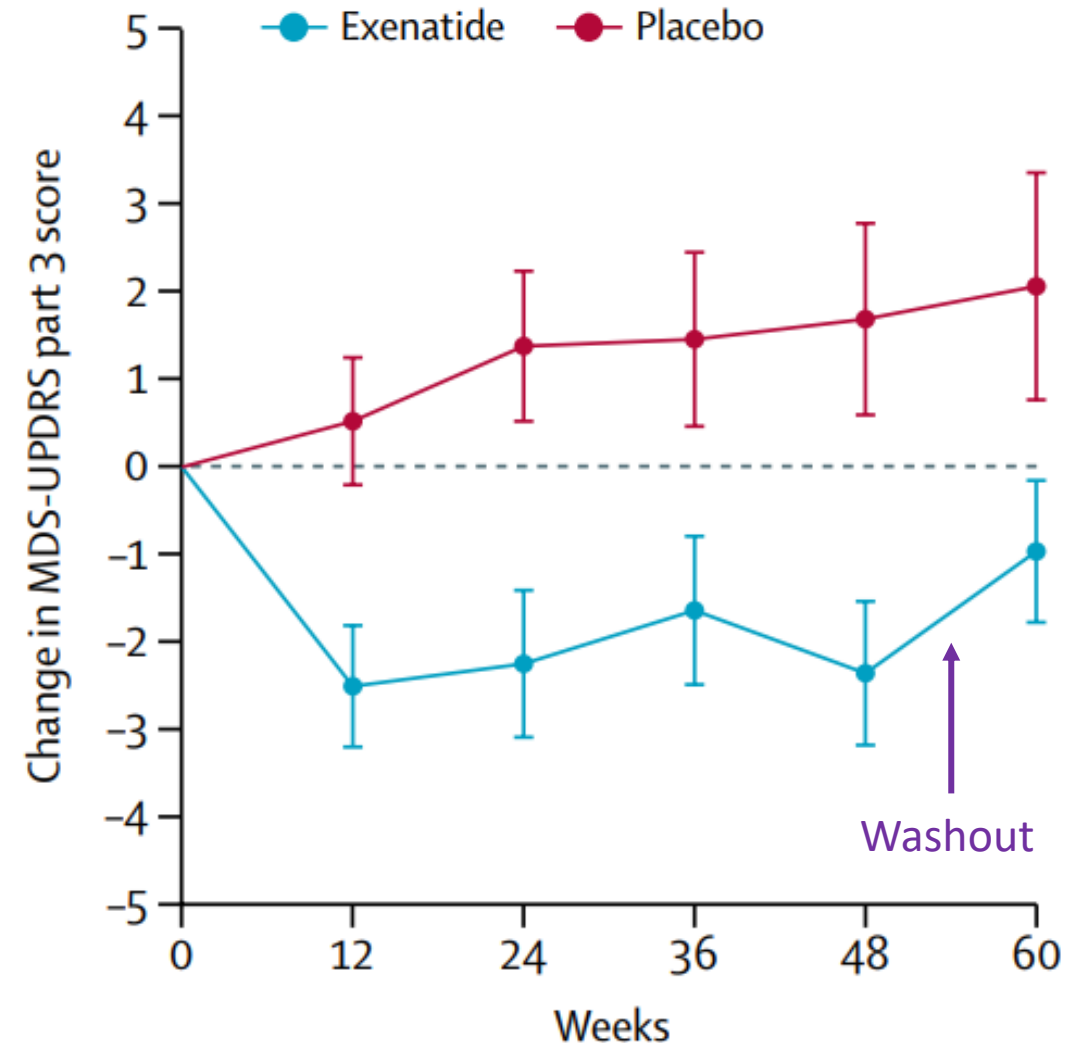
GLP-1R Agonist (Exenatide) Phase 2 Trial

Published in 2017

32 PD patients received Exenatide,
30 PD patients received placebo

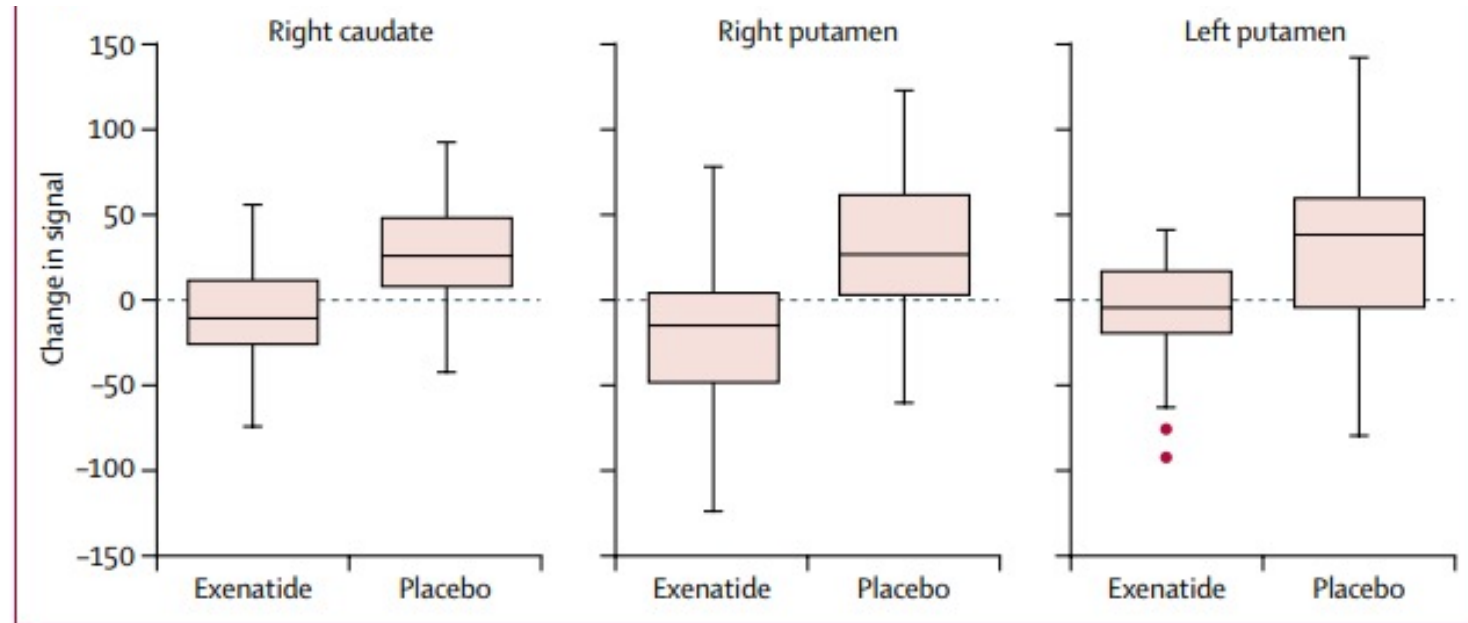
- 48 weeks on medication, 12-week washout period

Mild adverse effects, not worse than placebo

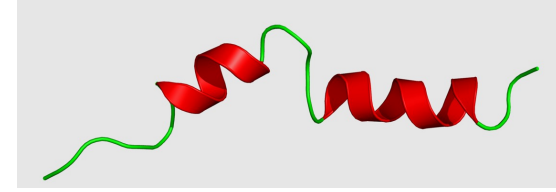


GLP-1R Agonist (Exenatide) Phase 2 Trial

Reduced rate of decline in
DAT Scan



GLP-1R Agonists – What's Next



- **2019 to 2024: Exenatide Phase III (UK)**
 - **200 patients, each patient followed over 24 months**
- 2020 to 2023: Pegylated Exenatide Phase II (US)
 - 240 patients, each patient followed for 9 months
- 2020 to 2022: Exenatide in new PD – Phase II (Sweden)
 - 60 patients, each patient followed over 18 months
- 2018 to 2022: Lixisenatide Phase II (France)
 - 156 patients, each patient followed over 12 months
- 2017 to 2022: Liraglutide Phase II (US – Cedars Sinai)
 - 63 patients, each patient followed over 12 months
- Studies in Norway and S. Korea as well

The primary analysis of the results included 37 people with Parkinson's on liraglutide and 18 on the placebo drug. **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, meaning the participants, even though none was aware they were taking the placebo drug, believed they were experiencing therapeutic results.

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

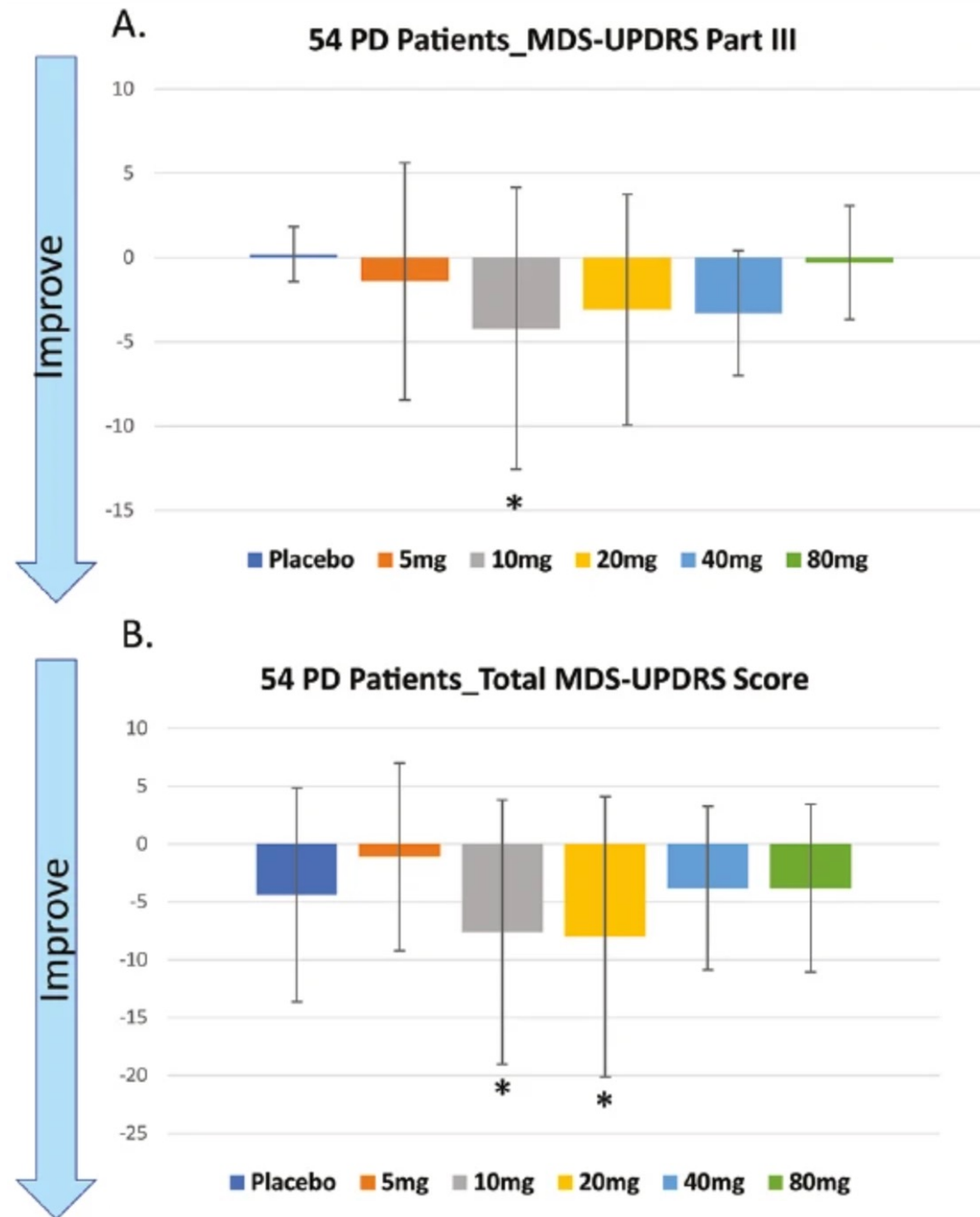
- A Phase 3 study will start in the UK this year
- 330 patients total
 - Some patients will take Ambroxol and some will take placebo, for 2 years
 - Their quality of life and movement ability will be compared at the 2-year mark

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 started
 - UCSF is currently recruiting patients for this study
- Patients will take Buntanetap 10mg, Buntanetap 20mg, or Placebo for 6 months then be 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)

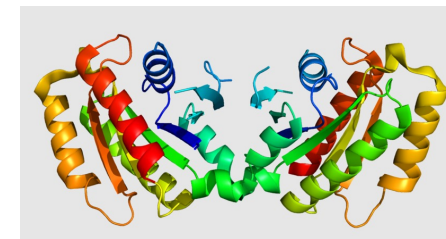
Goal:

- 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 3 trial in patients with LRRK2 mutations
 - Results expected in 2031
 - Phase 2 trial in all PD patients
 - Results expected in 2025

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

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:

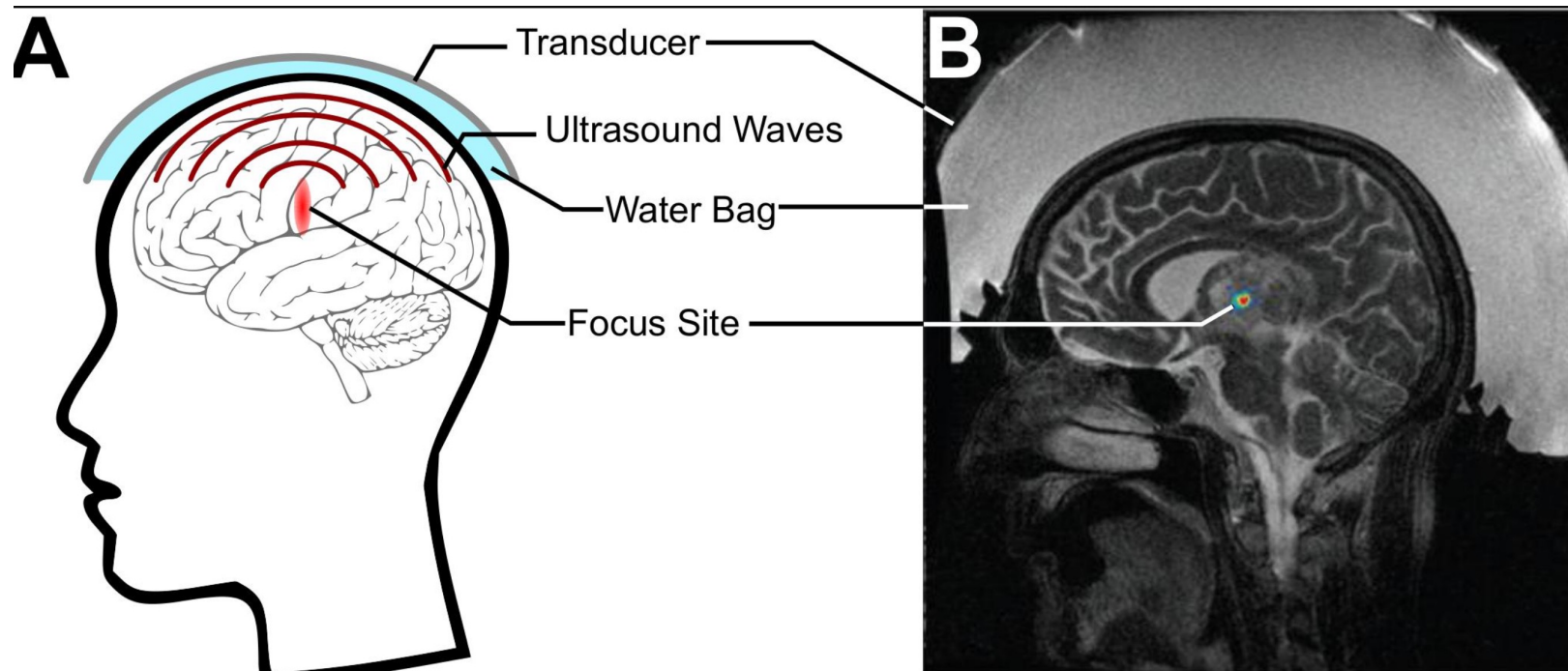
Ultrasound lesion of the Subthalamic Nucleus (STN) (approved, further trials ongoing)

Dopamine neuron stem cell implantation (in trials)

STN Focused Ultrasound

Focused non-ionizing ultrasonic waves to lesion tissue

- In this case, the subthalamic nucleus in the brain



STN Focused Ultrasound Trial (2020)

The **NEW ENGLAND**
JOURNAL of MEDICINE

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DECEMBER 24, 2020

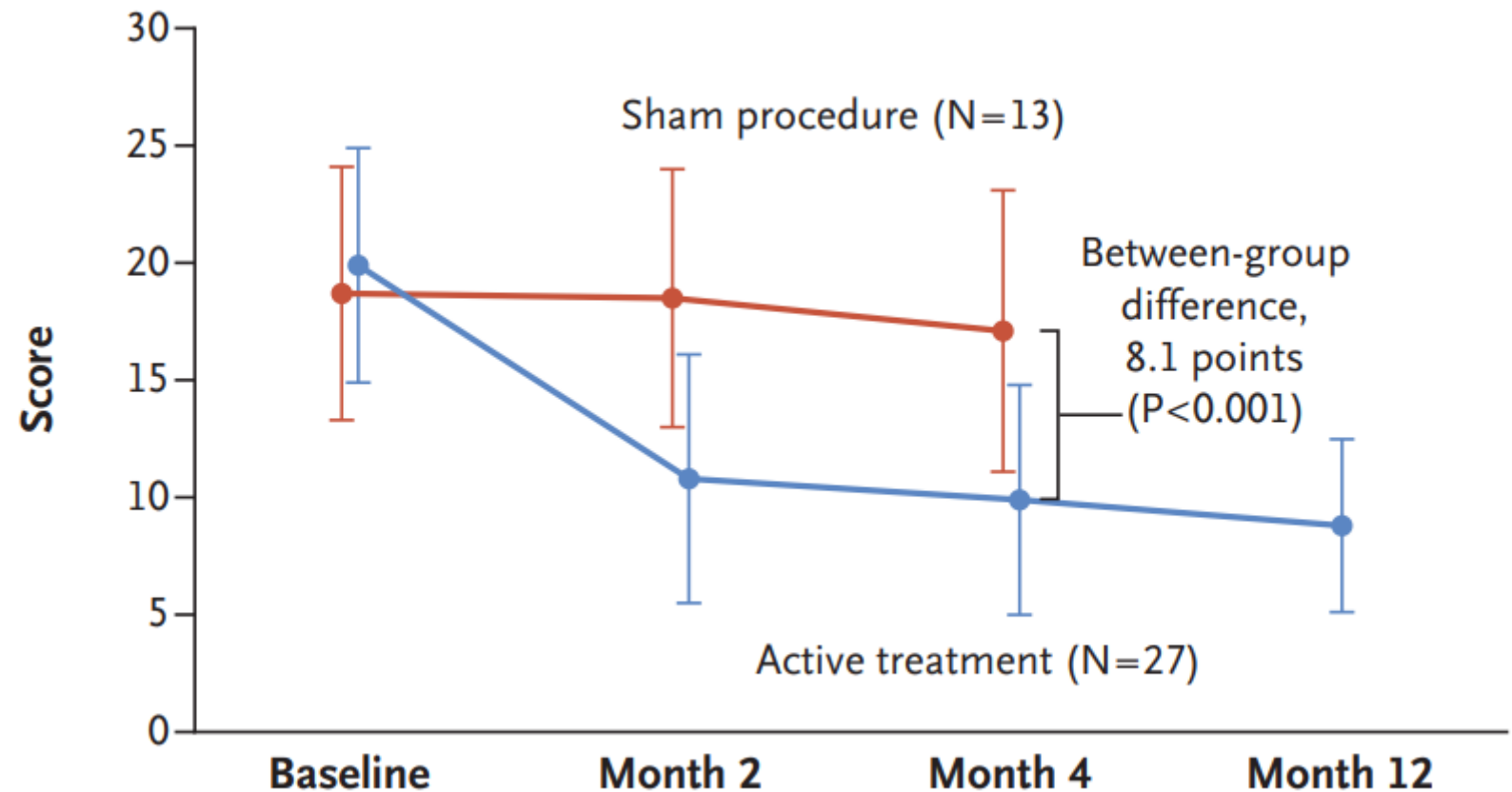
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Randomized Trial of Focused Ultrasound Subthalamotomy
for Parkinson's Disease

R. Martínez-Fernández, J.U. Mániz-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

STN Focused Ultrasound - What's next

- Centers will test out unilateral STN Focused Ultrasound and report their experiences
 - Side effect profile will likely improve as centers get experienced
- 2019 to 2022: STN Focused Ultrasound – Both sides of brain
 - 10 patients

Thoughts:

- May be useful for patients who cannot get DBS (e.g. patients > 80 years of age), but at this time unlikely to be superior to DBS for most patients

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

- 2021 to 2024: iPSC Dopamine Neurons implantation into Putamen – **Advanced** PD – Phase 1 (US, Memorial Sloan Kettering)
 - 12 patients
- Australia, Japan, UK/Sweden, China all have started or will start soon Phase 1 clinical trials for Dopamine Neuron Stem Cell implantation


Thoughts:

- Very likely to be successful 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
 - GLP-1R agonists
 - Ambroxol
 - Buntanetap
 - LRRK2 inhibition
- Symptomatic Therapies
 - Focused Ultrasound of STN (likely to be beneficial in cases where DBS is not an option)
 - Stem Cells (early stages - will be beneficial initially, but risk of dyskinesias eventually)



Q&A

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 group (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

- $HR_{max} = 206.9 - 0.67 * age$
- $0.5 \text{ to } 0.7 * (HR_{max} - HR_{resting}) + HR_{resting}$ = moderate intensity heart rate
- 30 min, 3 times a week
- Limitation: Not possible to blind patients

