

What's new in PD therapeutics?

Jane Wright Symposium

2017

Overview

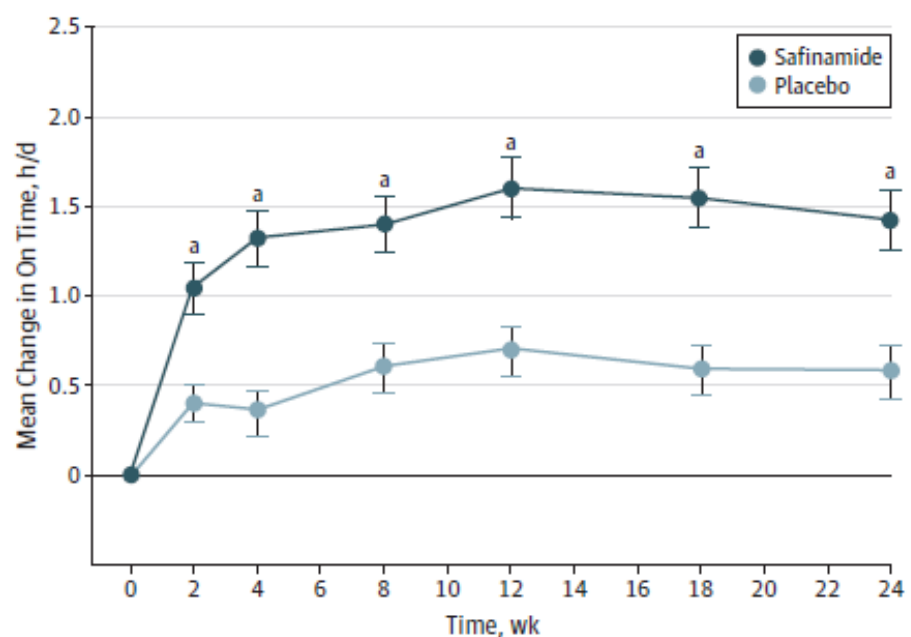
- Recently approved medications
 - Motor symptoms
 - Non-motor symptoms
- New Surgical Procedures
- Treatments in the pipeline

Safinamide (xadago)

- Approved 2017 as an add-on treatment for people with Parkinson's disease (PD) who are taking levodopa/carbidopa and experiencing "off" episodes.
- Safinimide is a reversible MAO-B inhibitor. It is taken once a day
- Advantages: convenient, low side effects
- Disadvantages: modest effect similar to rasagline and selegiline

Results from Settle trial (JAMA Neurology 2017)

Figure 2. Change in "On" Time Without Troublesome Dyskinesia During Double-blind Treatment in the Intention-to-Treat Population (Last Observation Carried Forward)



No. at risk						
Safinamide	263	268	268	269	269	274
Placebo	270	273	273	273	275	275

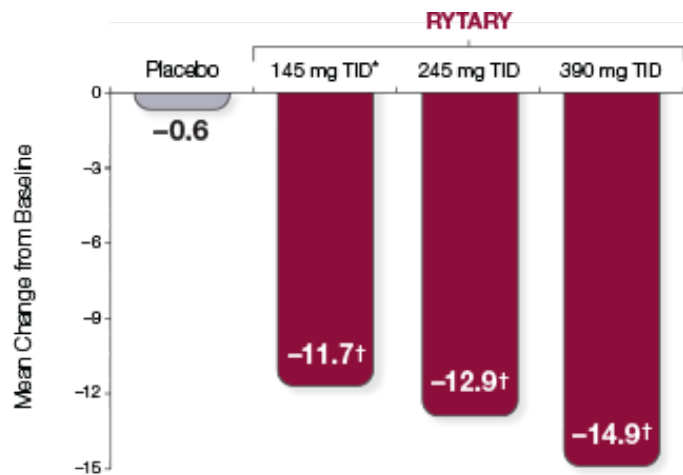
Results are based on patient diary data. "On" time indicates when patients experience relief of parkinsonian motor features. Error bars indicate SE.

^a $P < .001$ (unpaired, 2-sample t test).

Levodopa/carbidopa (Rytary)

- Approved 2015 for the management of Parkinson's motor symptoms
- Rytary is a capsule that contains both immediate release and extended release carbidopa/levodopa
- Advantages: Rytary may allow few daily doses and less "off" time
- Disadvantages: Has the same side effects as levodopa/carbidopa

Impact of Rytary in early PD



Mean change from baseline[‡] in sum of UPDRS[§] Parts II and III scores at Week 30 or early termination.¹

- In clinical trials, patients did not take additional carbidopa-levodopa products.¹

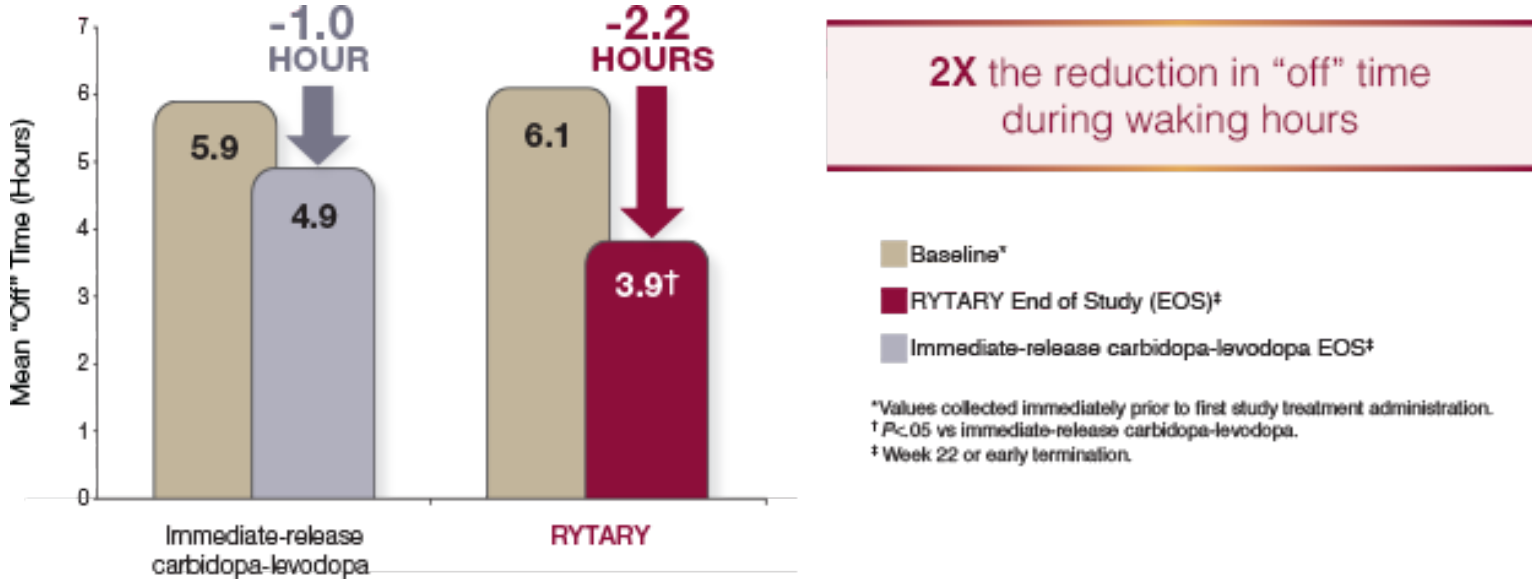
*3 times daily.

† $P < .05$ vs placebo.

‡Values collected immediately prior to first study treatment administration.

§Unified Parkinson's Disease Rating Scale.

Effect of Rytary in advanced PD



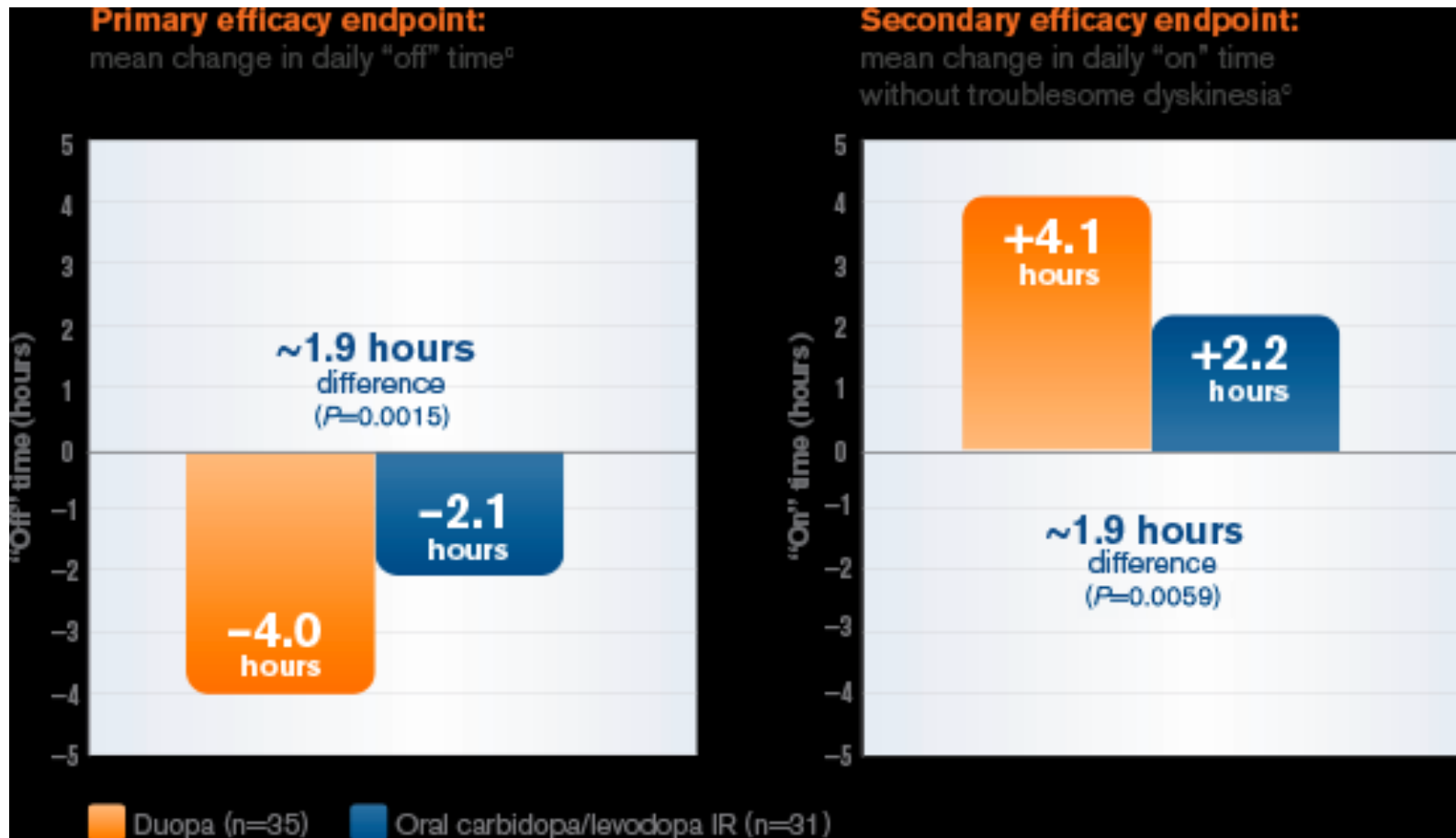
Levodopa/carbidopa (Duopa)

- Approved in 2015 for treatment of PD motor symptoms
- It is a gel formulation of carbidopa/levodopa that is designed for continuous infusion into the small intestine, usually infused for 16 hours per day
- Advantages: may be an alternative to deep brain stimulation
- Disadvantages: similar side effects to levodopa; tube and pack can be cumbersome

Duopa tubing and dispensing pump



Effect of Duopa on motor fluctuations



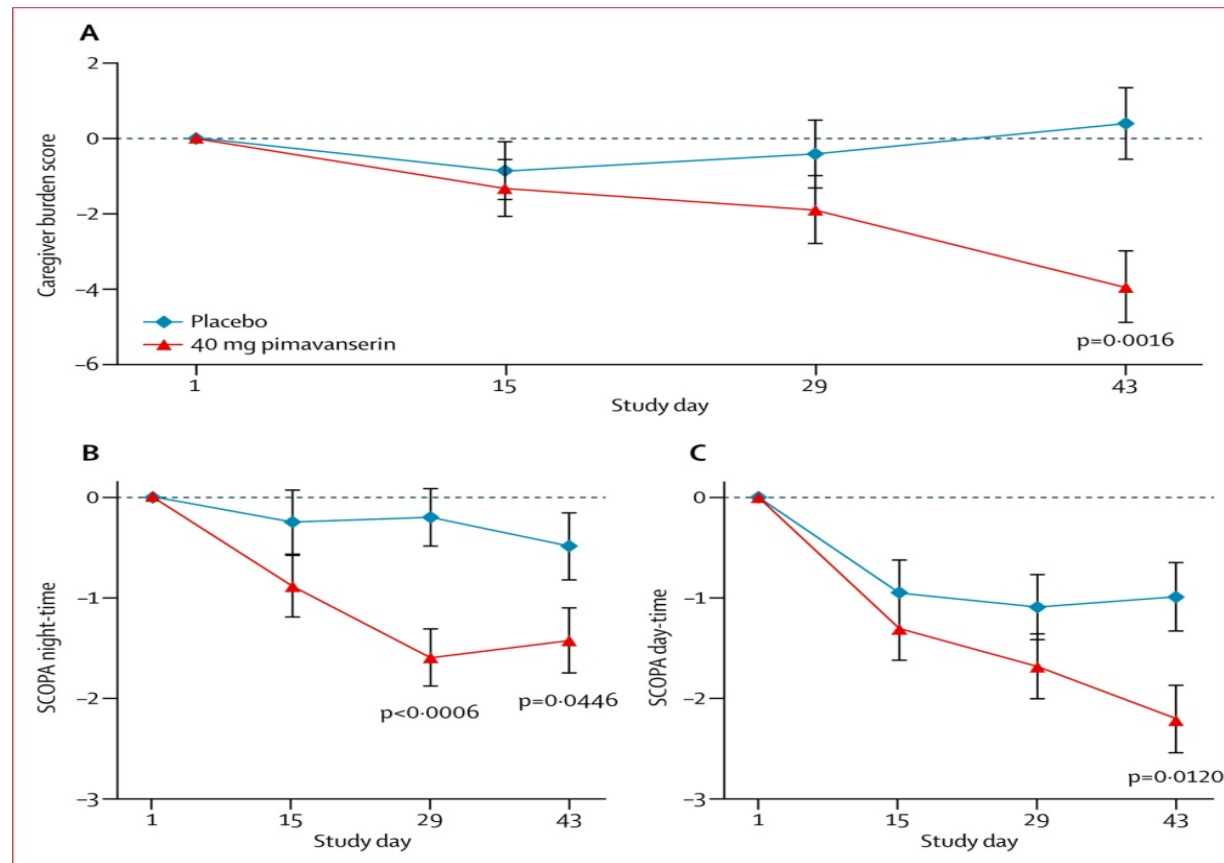
Droxidopa (Northera)

- Was approved in 2014 to treat orthostatic hypotension
- Droxidopa is converted to norepinephrine (nor-adrenaline) which works to raise blood pressure
- Advantages: may lessen lightheadedness that results from low blood pressure
- Disadvantages: can cause high blood pressure, particularly when lying down

Pimavanserin (Nuplazid)

- Pimavanserin was approved in 2016 for the treatment of hallucinations due to Parkinson's disease psychosis
- Pimavanserin does not work on the dopamine system and therefore should not worsen Parkinson's motor symptoms
- Advantages: May also improve sleep
- Disadvantages: most common side effects are leg swelling, nausea and confusion. May not work as well as clozaril

Pimavanserin for PD Psychosis (Pimavanserin - 5HT-2A inverse agonist)



Cummings et al. *The Lancet* 2013;383:533-540.

Focused ultrasound

Man's hands stop shaking for first time in 15 years after doctors zap his brain with pioneering ultrasound treatment

- Doctors used MRI scans to find rogue brain cells causing the tremor
- Ultrasound killed cells by heating them
- Patient was awake and aware throughout the five-hour procedure and didn't need anaesthetic
- Experts say it could help patients with other conditions such as Parkinson's or brain tumours
- By [Claire Bates](#)
- **PUBLISHED:** 10:44 EDT, 19 December 2012 | **UPDATED:** 11:45 EDT, 19 December 2012
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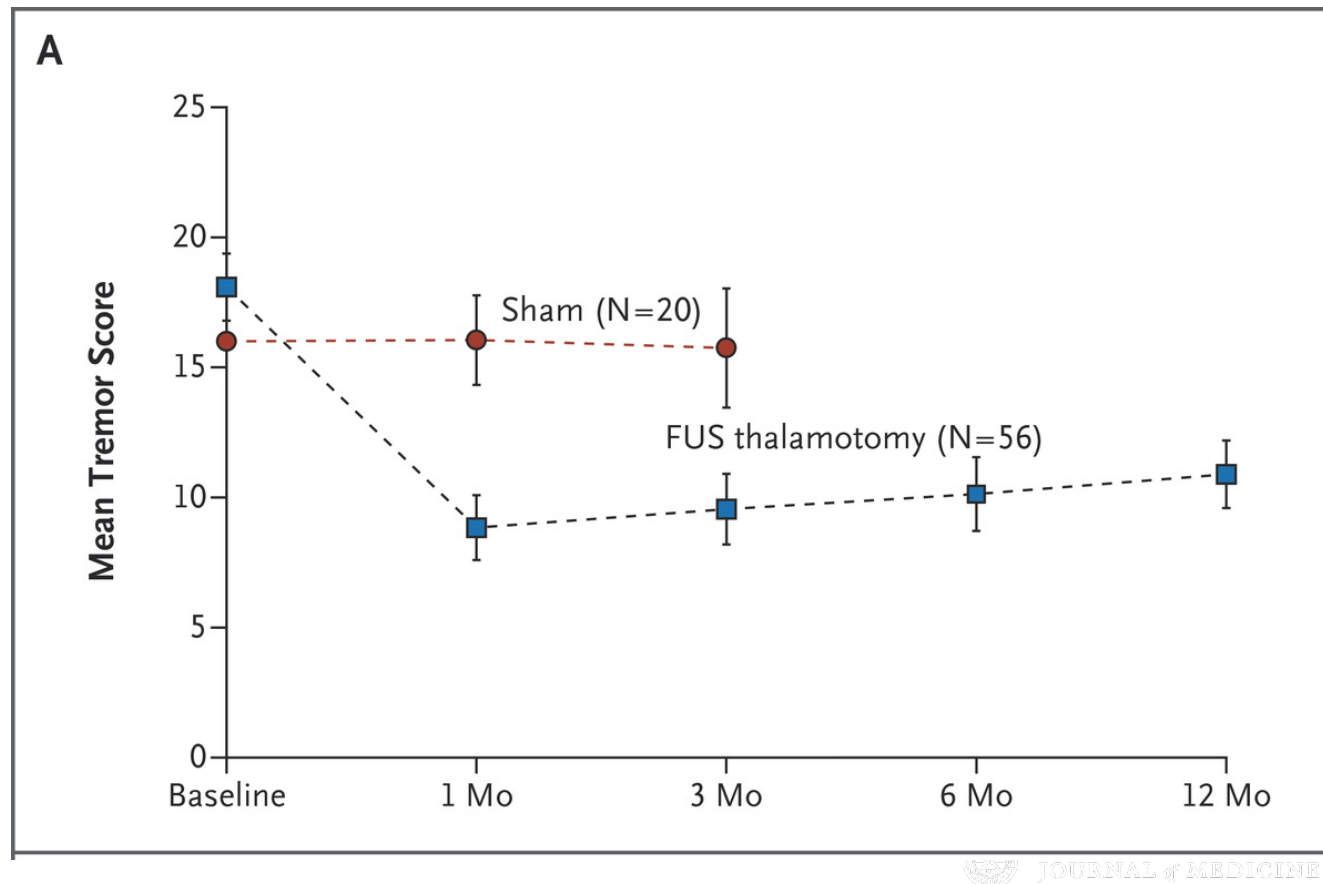
Read more:

<http://www.dailymail.co.uk/health/article-2250513/Man-stops-shaking-time-15-years-brain-zapped-ultrasound-pioneering-surgery-free-treatment.html#ixzz4k1y2je40>

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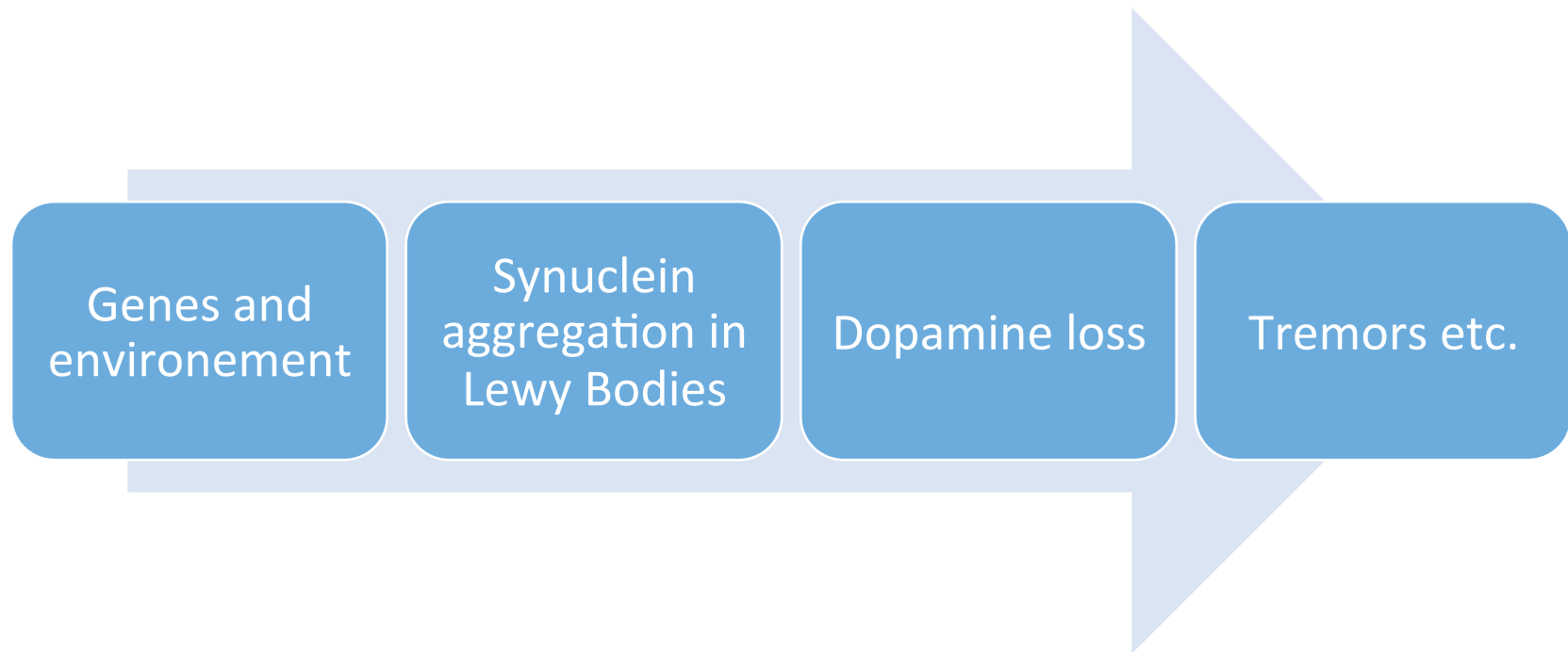


Results of focused ultrasound compared to sham procedure

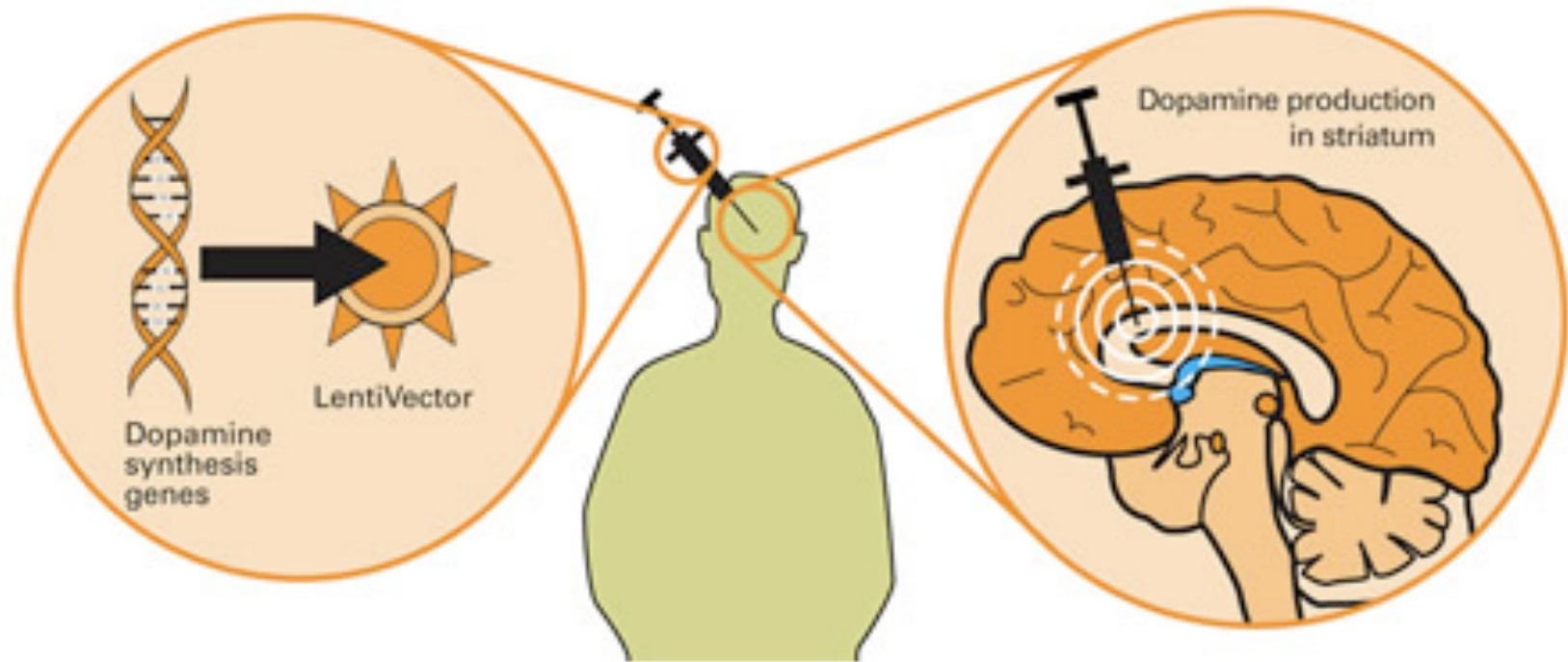


Elias WJ et al. N Engl J Med 2016;375:730-739.

What causes Parkinson's disease?



Gene therapy to improve the effects of levodopa



Treatments to remove alpha-synuclein

- Affiris: alpha synuclein vaccine
- Roache/Prothena: anti-alpha-synuclein antibody
- Biogen: anti-alpha synuclein antibody

Treatments aimed at specific genetic abnormalities

- GBA mutations: Sanofi phase 2 trial of a drug designed to replace missing GCase activity
- LRRK2 mutations: multiple companies with kinase inhibitors

Nilotinib

- Repurposed cancer drug
- A lot of excitement around early results
- MJFF sponsored study planned for late 2018

Others

- Isradipine

- Inosine

CVT-301 (levodopa)

- Self-administered, inhaled formulation of levodopa
- Developed by Acorda Pharmaceuticals
- Positive results from Phase III trial announced June 2017. Improved UPDRS III by approximately 4 points during “off” episodes
- Planned NDA (New Drug Application to FDA) later in 2017. Indication will probably be for rescue from “off” episodes (like apomorphine) If approved, would be available 2018-2019

Summary

- Newly approved medications focus on better delivery of old drugs and treatment of non-motor features
- Focused ultrasound is new, but not necessarily better than traditional DBS for Parkinson disease
- The pipeline of experimental medicines offers real promise for disease modification than