Fitting the brain-body connection and other complexities of Parkinson's disease into the current drug development ecosystem.

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Is Parkinson's disease a "brain disease"?

PD-pathology shows up before symptoms in skin, colon, kidney

can we catch it and treat it early?

Severe ulcer patients who have had vagus nerve completely severed ***seem to be*** protected against PD (partial vagotomy does not provide protection)

T2D increases PD risk, but T2D patient who have taken GLP1 agonists do not have elevated risk (other comparable meds do not change risk)

do GLP1 agonists change the progression of PD?

Following history and failing to acknowledge intrinsic complexity has gotten us into trouble.

I left academic science in 2004, to seek a treatment to ***slow progression*** of Parkinson's disease.

First mistake: Parkinson's disease is not a single entity, and most cases cannot be effectively treated by a single intervention. WE NEED TO SUBDIVIDE MORE!

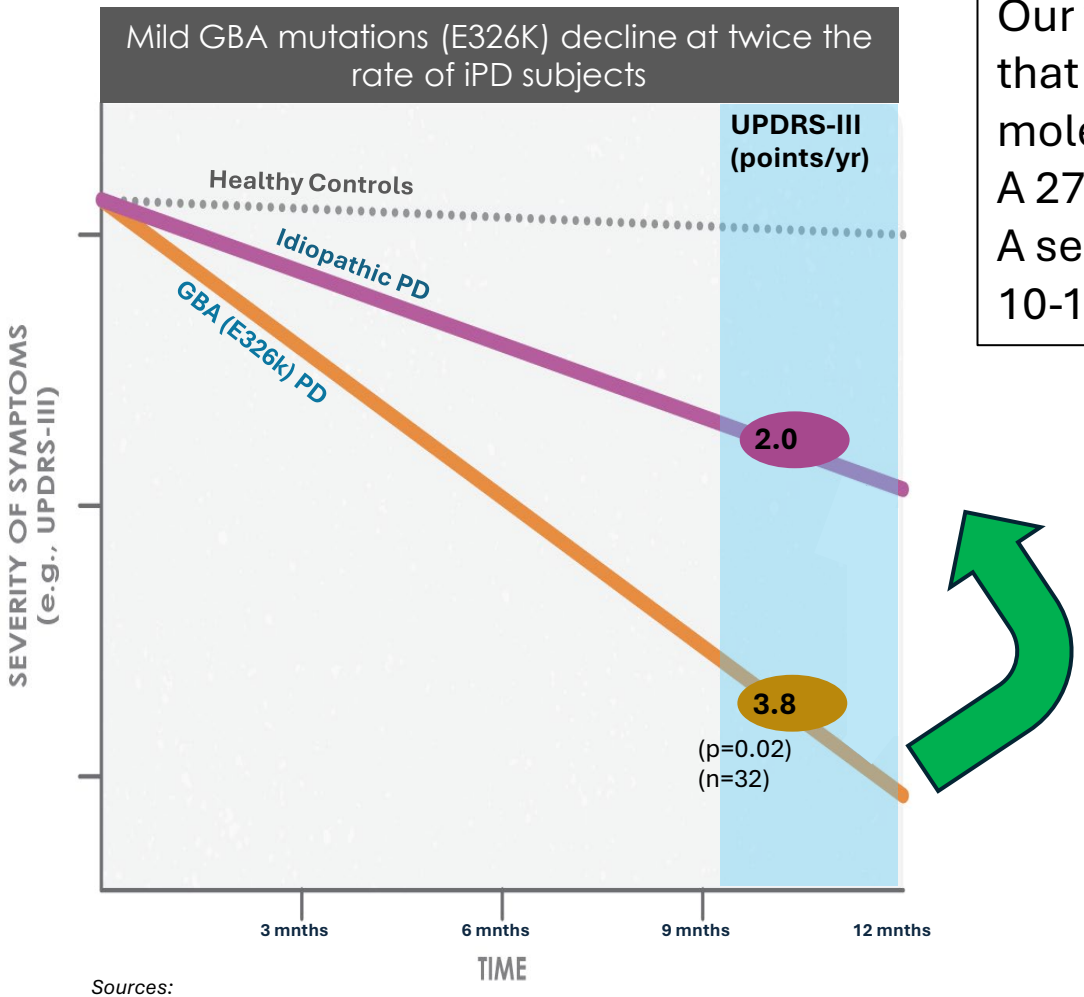
Second mistake: Measure PD progression by a ***combination rating scale*** that ignores disease heterogeneity. WE NEED TO SUBDIVIDE MORE!

Third mistake: What we call PD may have more in common with Lewy body dementia than LBD with AD. Many groups now favor treating underlying biology (or biomarker). WE NEED TO GROUP MORE!!

CAN WE SUBDIVIDE AND GROUP AT THE SAME TIME?

AI, ***if we let it***, can change things by eliminating the biases that have accumulated over 200 years…

Mutations in the GBA1 gene increase the risk of Parkinson's and *increase the progression of disease*.



Sources:
R Alcalay et al (Brain 2015); MY Davis et al (JAMA Neurology Sep2016); Zabetian et al; Scherzer et al Annals of Neurology 2016

Our work started in 2013 and produced a molecule that we showed, in 2018-19, to be safe in GBA-PD. This molecule was sold to Bial Pharma. They will complete A 270-patient trial (3 arms, 18m dosing) in early 2026. A second trial will likely be required for approval. 10-15% of the US PD population carries a GBA mutation.

Our goal was to "remove" the GBA component of progression and slow to the non-genetic PD rate. This would provide a significant benefit in one year, and a growing benefit over time. If treated ***before*** symptoms became acute, effect could approach a formal "cure".

Radical suggestion for change; focus on NNT, not only average efficacy:

Recognize that “efficacy”, as defined by the FDA, is measured in an ***average*** PD patient (in the trial population). We should insist that Pharma provides data from their trials that allow identification of responders. That data should guide physicians, payers, and patients.

> Incentivize development of drugs that have low ***non***-response rate (***reduce the NNT***)