Outline

- ✓Overview of What Matters in a Dizzying Array of Novel Treatments
- ✓When Will We Have a Cure?
- ✓Please Remember "Old" Therapies Are Tried and Work Well When Used Appropriately (by a Movement Disorder Specialist)
- ✓Overview of 3 Important Areas of PD Therapeutic Advances:
  - ✓Recently Approved/Relatively New/Branded PD Medications
  - ✓A Few Important Clinical Trials
  - ✓The Future of PD Treatments

What Matters & Where to Get Reliable Information?

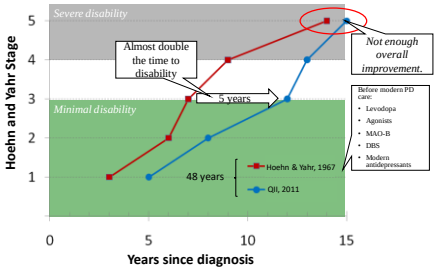
1. In our age of world-wide epistemological crisis it has become particularly challenging to know anything for certain.
   1. The epistemological crisis stems from the political arena[1]
   2. With the ubiquitous nature of the internet, there is abundance of information, but much less readily available ways to ascertain accuracy and reliability
   3. There are many hidden or non-obvious potential conflicts of interests associated with "free" information
2. What can you do?
   1. Verifiable expertise can often be anchored on objective information such as peer-reviewed publications and academic achievements
   2. Large patient advocacy organizations, such as Parkinson's Foundation, MJFF, PFNCA should be trusted more than other forums – investigate before you trust a support group online or a speaker arranged by a group with possible conflicts
   3. While fellow patients should most definitely be listened to, remember they are no doctors (unless they are) and no experts in Parkinson disease – your movement disorder specialist provider is – 2nd opinions & 3rd opinions are always a good idea

[1] https://www.nytimes.com/2020/11/26/opinion/republican-disinformation.html

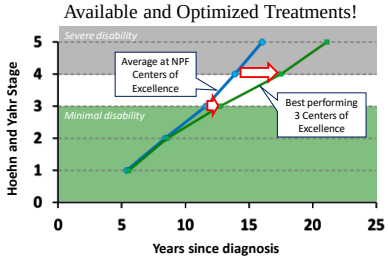
When Will We Have a Cure?

1. "Cure" implies a perfect and complete restoration to a state before a disease hit.
2. Such feat for PD will not be possible before we not only slow, stop or prevent, but actually reverse aging.
3. Lost brain tissue is not lost liver, kidney, bone, lung, etc tissue. The function of kidney is provided by the tissue, which is perfectly replaceable. Brain functions in terms of circuitry – the function, learned and stored information acquired over years and decades, cannot be replaced by adding naïve neurons and glia back.
4. However, in theory, it should be possible to slow, stop, or even prevent PD
5. That's called disease modifying or neuroprotective therapies

"Old" Therapies Should Not Be Ignored!



Further Gains Are Still Possible – With Currently Available and Optimized Treatments!

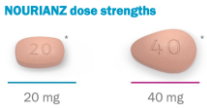


Recently Approved/Relatively New/Branded PD Medications

Levodopa	Dopamine agonists	MAO-B inhibitors	COMT inhibitors	Amantadine	A2A
Inbrija® (inhaled levodopa) Approved by the FDA in May 2019	Apomorphine (Kynmobi®) Approved by the FDA in May 2020	Safinamide (Xadago®) Approved by the FDA in March 2017	Opicapone (Ongentys®) Approved by the FDA in April 2020	Osmolex® Approved by the FDA in December 2018	Istradefylline (Nourianz™) Approved by the FDA in August 2019
C/L enteral suspension (Duopa®) FDA approval in January 2015	Rotigotine (Neupro® patch) FDA approval in July 2007 & April 2012	Rasagiline (Azilect®) FDA approval in July 2006	Stalevo® (carbidopa-levodopa and entacopone) FDA approval in June 2006	Gocovri® FDA approval in August 2017	
Rytary® FDA approval in January 2015	Apomorphine (Apokyn®) FDA approval in April 2004	Selegiline (Zelapar®) FDA approval in June 2006	Entacapone (Comtan®) FDA approval in December 1999		
Parcopa® (orally disintegrating tablet) FDA approval in August 2004					

Emergent Rx in PD

Nourianz



- Adenosine receptor antagonist to treat off episodes of PD as adjunctive treatment to carbidopa/levodopa
- 20-40 mg once daily
- With or without food

TEXT

Kynmobi

- Is sublingual film indicated for off times in PD
- Improvement in motor symptoms at 15 minutes and last up to 90 minutes

SUBLINGUAL APOMORPHINE CURRENTLY APPROVED .

SUBLINGUAL APOMORPHINE

- Many people do not like injections; moreover, sublingual route is easier to administer,
- Sublingual apomorphine (APL-130277) tested in phase 2/phase 3 studies, FDA approval pending
- Dose: 10-30 mg during OFF phase,
- ON state achieved in 15-30 min of dose in about 80% of patients,
- Mean duration of ON phase is 50 min and 60% remain ON for >90 min
- Common side effects are dizziness, somnolence and nausea.

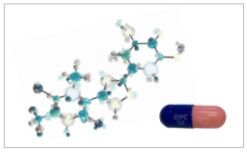
KYNMOBI™
(apomorphine HCl) sublingual film
10 mg • 15 mg • 20 mg • 25 mg • 30 mg

Emergent Rx in PD

TEXT

Ongentys

- Approved in 2016 in EU
- Once daily at bedtime
- Not be taken with food
- 50 mg daily



OPICAPONE – COMT INHIBITOR

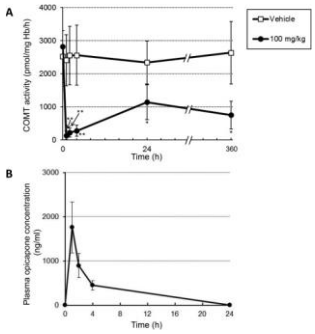
Data were combined for both studies and results for 50 mg doses were presented.

The data presentation revealed statistically significant increases in absolute "ON" time without reports of dyskinesia from baseline to week 14 or 15 endpoints.

All patients treated with opicapone in the open-label extension studies experienced improvements in "ON" time without dyskinesia.

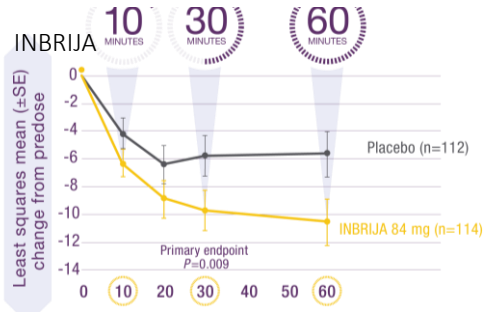
- From baseline, the average increase in "ON" time was 2.0 ± 2.6 hours in BIPARK-1 and 1.8 ± 3.2 hours in BIPARK-2.
- Also, a significantly higher percentage of patients who received 50 mg doses of opicapone had an increase in total "ON" time of an hour or longer at week 14 or 15 in both BIPARK-1 and BIPARK-2

Emergent Rx in PD



INBRIJA

- Inhaled Levodopa
- Indicated for intermittent treatment of OFF episodes in patients with Parkinson disease treated with carbidopa/levodopa
- Initiate when OFF period symptoms start to return



Clinical trials

- Disease modifying approach
- Symptomatic therapies
  - Motor symptoms
  - Non-motor symptoms

PD drug therapies in the clinical trial pipeline: 2020

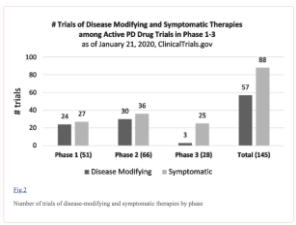
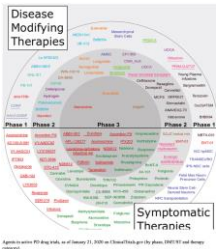


Fig 2
Number of trials of disease-modifying and symptomatic therapies by phase

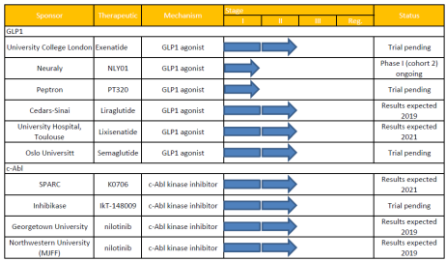
McFarthing et al. J Parkinson Dis. 2020; 10(3): 757-774.

PD drug therapies in the clinical trial pipeline: 2020



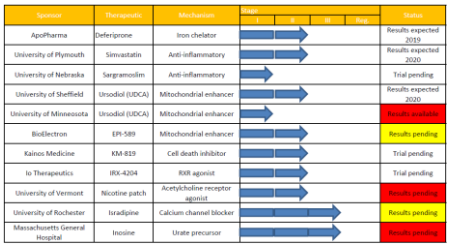
McFarthing et al. J Parkinson Dis. 2020; 10(3): 757-774.

Disease Modifying/Neuroprotective Trials



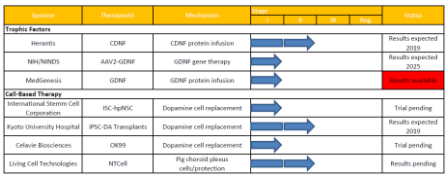
Sponsor	Therapeutic	Mechanism	Stage	Status
GLP1				
University College London	Exenatide	GLP1 agonist		Trial pending
Neuraly	NLY01	GLP1 agonist		Phase I (cohort 2) ongoing
Peptron	PT320	GLP1 agonist		Trial pending
Cedars-Sinai	Liraglutide	GLP1 agonist		Results expected 2019
University Hospital, Toulouse	Lixisenatide	GLP1 agonist		Results expected 2021
Oslo Universitt	Semaglutide	GLP1 agonist		Trial pending
c-Abl				
SPARC	K0706	c-Abl kinase inhibitor		Results expected 2021
Inhibikase	IKT-148009	c-Abl kinase inhibitor		Trial pending
Georgetown University	nilotinib	c-Abl kinase inhibitor		Results expected 2019
Northwestern University (MJFF)	nilotinib	c-Abl kinase inhibitor		Results expected 2019

Disease Modifying/Neuroprotective Trials (Cont.)



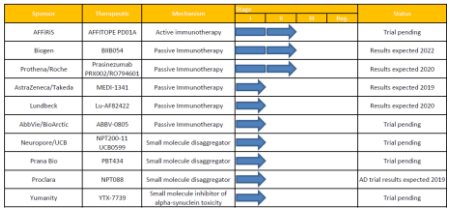
Sponsor	Therapeutic	Mechanism	Stage	Status
ApoPharma	Deferiprone	Iron chelator		Results expected 2019
University of Plymouth	Simvastatin	Anti-inflammatory		Results expected 2020
University of Nebraska	Sargramostim	Anti-inflammatory		Trial pending
University of Sheffield	Ursodiol (UDCA)	Mitochondrial enhancer		Results expected 2020
University of Minnesota	Ursodiol (UDCA)	Mitochondrial enhancer		Results available
BioElectron	EPI-589	Mitochondrial enhancer		Results pending
Kainos Medicine	KM-819	Cell death inhibitor		Trial pending
Io Therapeutics	IRX-4204	RXR agonist		Trial pending
University of Vermont	Nicotine patch	Acetylcholine receptor agonist		Results pending
University of Rochester	Isradipine	Calcium channel blocker		Results pending
Massachusetts General Hospital	Inosine	Urate precursor		Results pending

Cell Replacement and Repair



Sponsor	Therapeutic	Mechanism	Stage	Status
Trophic Factors				
Herantis	CDNF	CDNF protein infusion		Results expected 2019
NIH/NINDS	AAV2-GDNF	GDNF gene therapy		Results expected 2025
MediGenesis	GDNF	GDNF protein infusion		Results available
Cell-Based Therapy				
International Stemm Cell Corporation	ISC-hpNSC	Dopamine cell replacement		Trial pending
Kyoto University Hospital	iPSC-DA Transplants	Dopamine cell replacement		Results expected 2019
Celavie Biosciences	OK99	Dopamine cell replacement		Trial pending
Living Cell Technologies	NTCell	Pig choroid plexus cells/protection		Results pending

Alpha-Synuclein Therapies



Sponsor	Therapeutic	Mechanism	Stage	Status
AFFiRiS	AFFITOPE PD01A	Active immunotherapy		Trial pending
Biogen	BIIB054	Passive Immunotherapy		Results expected 2022
Prothena/Roche	Prasinezumab PRX002/RO7046601	Passive Immunotherapy		Results expected 2020
AstraZeneca/Takeda	MEDI-1341	Passive Immunotherapy		Results expected 2019
Lundbeck	Lu-AF82422	Passive Immunotherapy		Results expected 2020
AbbVie/BioArctic	ABBV-0805	Passive Immunotherapy		Trial pending
Neuropore/UCB	NPT200-11 UCB0599	Small molecule disaggregator		Trial pending
Prana Bio	PBT434	Small molecule disaggregator		Trial pending
Proclara	NPT088	Small molecule disaggregator		AD trial results expected 2019
Yumanity	YTX-7739	Small molecule inhibitor of alpha-synuclein toxicity		Trial pending

Pasadena study (immunotherapy)

- Prasinezumab stimulates a passive immunity against alfa-synuclein.
- Prasinezumab shows signs of slowing motor symptoms decline in early stage PD in phase 2 study
- Double blind Intravenous infusion every 4 weeks for 52 weeks.
- At the end of the first phase (52 weeks) all subjects are receiving the medication q4 weeks
- 316 subjects were enrolled and part 2 of the study is ongoing

Spark trial (Immunotherapy for PD)

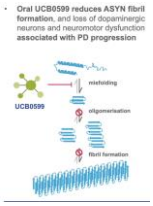
- Utilization of BIIB054, a selective antibody against misfolded form of alpha synuclein (immunotherapy)
- Q4week IV infusion
- Prior studies showed the continues infusion of BIIB054 reduces the misfolding protein and loss of dopamine transporters (DAT)
- Study is undergoing but completed the recruitment, enrolled 311 subjects

Affitope pd01a

- An injectable vaccine that targets alpha-synuclein protein is being developed by a biotech company Affiris (active immunization)
- The Phase 1a and 1 b were conducted and showed the compound is safe and well-tolerated.
- Affiris intends to conduct a Phase 2 trial in the US

Alfa synuclein (asyn) misfiling inhibitor

- An orally available brain-penetrant inhibitor of ASYN misfolding
- Oral UCB0599 reduces ASYN fibril formation and loss of dopaminergic neurons and neuromotor dysfunction associated with PD progression



- *Late braking abstracts MDS virtual 2020*

Repair-pd

- A phase 2 single-center pilot study in Texas to assess the safety and tolerability of CNM-Au8 in 24 subjects.
- CNM-Au8 is a concentrated suspension of gold (AU) and can protect cells from oxidative stress due to ints antioxidant properties.
- CNM-Au8 might help to protect dopaminergic neurons and slowing he progression of PD
- There is a plan to conduct another Phase 2 trial, RESCUE-PD

Ambroxol(boosting of waste disposal processes)

- Ambroxol is a respiratory medication reduces levels of harmful alpha synuclein.
- Encouraging results from the open label trial in 18 patients with PD
- Ambroxol was well tolerated and it penetrated into the brain. A larger phase three study would be the next step.

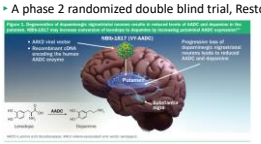
Interaputamenal cdn

- CDNF is a neurotrophic factor shown to protect neurons.
- 17 subjects with PD were randomized to receive placebo or study medication every 4 weeks via an intraputamenal drug delivery device in Sweden and Finland.
- The phase I-2 in human was safe and well tolerated.
- The data for the extension phase of the study is expected to be available by the end of the year.

Sigrid Booms et al. MDS Virtual meeting 2020

Aadc gene therapy

- AAV2 gene therapy encoding human aromatic L-amino acid decarboxylase (AADC)
- VY-AADC01 administered surgically was well tolerated.
- Phase I studies showed clinical benefit with significant reduction on PD medications
- No SAE were reported today
- A phase 2 randomized double blind trial, Restore-1 is ongoing.

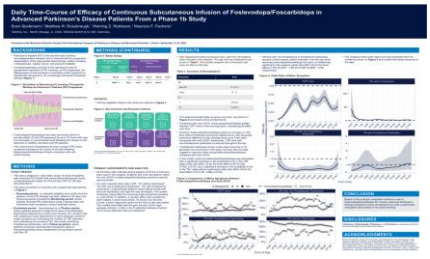


VY-AADC01 administered using a single posterior trajectory per putamen was well tolerated.

Stewart Factor et al. MDS Virtual meeting 2020

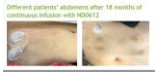
Subcutaneously infusion of levodopa/carbidopa

- Abbvie trial, 24 h/day CSCI.
- Single arm, open label, Phase Ib study with 20 subjects.
- The study showed improvement of PD symptoms across all waking days especially in the early morning.



Subcutaneously infusion of levodopa/carbidopa

- Neuroderm trial with CSCI of ND0612
- Phase 2b, international, open label study over one year
- 24 h/day and 16 h/day infusion tested total daily dose of 720 mg of levodopa
- Mild to moderate infusion site reactions were common
- A phase 3 double-blind pivotal efficacy trial (BouNDless) is being initiated



Continuous subcutaneous apomorphine infusion (CSAI)

- CSAI has been used world wide to treat motor fluctuation in PD
- Not available in the USA yet
- The recent open label multi center trial in us in 99 patients with PD showed that the CSAI was safe and well-tolerated during one year follow up
- The New Drug Application was submitted to FDA for review

https://doi.org/10.1038/npjparkd.2016.23

Inhaled Apomorphine

- Randomized, placebo-controlled study in 24 PD patients
- Absorbed rapidly tmax less than 3.5 min
- It showed improvement of the symptoms and relatively well tolerated
- AE: throat irritation, orthostatic hypotension, yawning, nausea, somnolence an and dyskinesia.

MDS virtual congress 2020

TEXT

Mild cognitive impairment

- NYX-458 is an oral compound that regulates the NMDA receptors in brain.
- The Phase 2 double blind clinical trial is undergo now and was supported by positive preclinical date.
- Aptinyx has paused patient enrollment due to the current COVID-19 pandemic.

Constipation

- Targeting alpha synuclein
  - ENT-01 which doesn't enter the brain and only targets alpha synuclein inside cells.
  - A phase 2 open label study showed this drug was safe and well controlled and reduced the constipation.
  - This finding suggest that the nervous system of the gut is not irreversibly damaged and if a drug penetrates to the brain may be able to restore neurons function.

Excessive daytime sleepiness

- THN (Modafinil 200 mg and low dose flecainide 2 mg) in the treatment of EDS with PD, a double-blind, placebo controlled study.
- The effect probably is by modifying the interaction between neuronal and glial networks in the brain.
- THN was well tolerated and significantly improved EDS in patients with PD
- No serious adverse effect was reported

Neurogenic orthostatic hypotension (NOH)

- Ampreloxetine is a long acting, norepinephrine reuptake inhibitor
- A phase 3 double blind, placebo controlled study is currently undergoing
- Target enrollment: 188

Stem cell research

- TRANSENURO: Open label European-Union-funded allograft trial. Subjects receive transplants of hfVM (human fetal ventral mesencephalic tissue)
  - Complete the recruitment of 11 subjects
  - Grafting fetal tissue into the brain of PD subjects
  - Continue observing the subjects for 36 months
  - Study will be completed in 2021

Stem cell research

- Allogenic bone marrow-derived mesenchymal stem cells
- 20 subjects received a single intravenous infusion
- Single infusion was safe and well-tolerated in mild to moderate PD patients.
- There was a potential signal for clinical improvement.
- Moving forward to phase II randomized placebo-controlled efficacy trial

Schiness M et al. The University of Texas Health Science Center at Houston. The City College of New York. MDS virtual congress 2020

Future directions

- CRISPR: A gene editing technology, potential in better understanding the disease and treatment
- mRNA technology
- Pharmacogenetics
- Precision medicine
- Objective, ecologically valid, accurate, clinically meaningful measures to guide treatment