Parkinson Research Updates



PARKINSON FOUNDATION OF THE NATIONAL CAPITAL AREA



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Disclosures

- This lecture will summarize some of the recent and ongoing research in Parkinson's disease
- I will focus in more detail on some specific research directions
- Reference will be made to off-label use of therapies
- The information contained herein does not supersede any advice and care provided by your own physician
- I have no relevant financial disclosures









Updates in the Conceptual Understanding of PD

"There is no Parkinson Disease" (William Weiner) There are many subtypes and trajectories and under the "Parkinson" umbrella

A Disease of the Entire Body



Parkinson affects the whole body Parkinson may actually start far from the brain and work its way into the brain

Nature Reviews | Neuroscience

α-Syn PFF Injection

Neuron 2019 Aug 21;103(4):627-641 PMID: 31255487 PMCID: PMC6706297





Overview of the site of injection and vagotomy.

Representative double-immunostaining for pSer129-a-syn (green) and Tuj-1 (red) in the upper duodenum (UD) and pyloric stomach (PS) after 1 month postinjection.



Electron microscopic image of mouse PFF. Scale bar represents 100 nm.

Distribution of mouse α -Syn PFF length after sonication. Mean length of mouse PFF is 64.7 nm ± 1.7 nm (n=494).

Critical Elements: Size of the PFF Concentration of PFF injected Sites of injection

Courtesy of Dr Ted Dawson

Time Dependent Loss of DA Neurons



Unbiased stereological counting shows loss of DA neurons over time in α -Syn PFF injected mice.

DAT SPECT/CT scans





Outcome Measures, and the Importance of the PwP Voice

- NINDS CDE for Parkinson updated, and needs your input: <u>https://www.commondataelements.ninds.nih.gov/</u> <u>Parkinson%27s%20Disease</u>
- The critical role of PwP input into research increasingly recognized

Virtual and Remote Assessments: AT-HOME PD

• Virtual longitudinal, observational study of Parkinson's disease



Research in Prodromal Disease

 Widespread interest in the prodromal phase of the disease



Research in Prodromal Disease

MJFF is launching a prodromal treatment trial platform structure



Therapy Research

- Pharmacologic
- Gene therapy
- Neuromodulation
- Other (exercise!)



Prasad and Hung, Pharmaceuticals 2021

Clinical Trials

- NIH definition: "A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes."
- Phase I: first test in people; focused mainly on safety
- Phase II: initial effectiveness, further safety, answers questions of dose, type of patients responding best, outcome measures etc.
- Phase III: definitive efficacy and safety; typically used for regulatory approval
- Phase IV: post-approval, long term follow-up in many patients

Clinical Trials

- Why you should participate
- Help support scientific advances
- You can gain valuable knowledge about both the treatments and science and your condition
- Connection with the cutting edge of care and research
- Every single treatment available exists because of participants in trials!
- Why you should not participate
- As a substitute for your standard care or to access the latest medication (it may not work; you may be in the placebo arm)
- Understand the study and the risks clearly. Talk to your doctor!

Optimizing Motor Control and Control of Complications

- Advances in pharmacotherapy: opicapone; istradefylline; safinamide; gocovri; inhaled levodopa; sublingual apomorphine; (zonisamide)
- Better algorithms for use of dopaminergic medication
- Combined therapies: role of DBS in "smoothing out" motor control

Optimizing Motor Control and Control of Complications

Advances in neuromodulation (DBS): directional leads; new stimulation patterns; closed loop



Krauss et al, Nat Rev Neurol 2021

Non-Motor Symptoms Therapy

- Dominate the QOL impact in advanced disease
- Remain undertreated compared to motor features
- Recent progress:
 - Pimavanserin for psychosis
 - Treatment of sleep dysfunction

THE LANCET Neurology Volume 21, Issue 5, May 2022, Pages 428-437

ENLITE PD

(APOMORPHEE): a multicentre, randomised, controlled, double-blind crossover study

Safety and efficacy of subcutaneous night-time only apomorphine infusion to treat insomnia in

patients with Parkinson's disease

A Dose Selection Trial of Light Therapy for Impaired Sleep in Parkinson's Disease

Light Therapy for Non–Motor Symptoms: ENLITE-PD

 Phase 2 NeuroNEXT trial evaluating a novel light therapy intervention for non-motor PD symptoms. The goal of this trial is to determine the dose of light therapy that is most appropriate for improving impaired sleep in Parkinson's Disease patients.



Information can also be found on the NeuroNEXT website: http://www.neuronext



.org

Disease-Modifying Therapy Research

 "Holy grail" of PD research, subject of intense focus and effort, but with little or no success to date.



The Disease Modification Conundrum in Parkinson's Disease: Failures and Hopes

👰 Zoltan Mari1* and 🌉 Tiago A. Mestre2

Disease-Modifying Therapy Research



Disease-Modifying Therapy Research

- Targeting alpha-synuclein (main abnormal protein in PD)
- Enhancing autophagy (destruction of abnormal proteins)
- Correcting mitochondrial dysfunction
- Neuroprotection
- Cell therapies

Gene Therapy in PD

 GDNF: trophic factor shown to have beneficial properties on cells affected by PD



Brief Report

Trial of magnetic resonance–guided putaminal gene therapy for advanced Parkinson's disease

John D. Heiss MD 🔀 Codrin Lungu MD, Dima A. Hammoud MD, Peter Herscovitch MD, Debra J. Ehrlich MD, Davis P. Argersinger BS, Sanhita Sinharay PhD, Gretchen Scott BSN, RN ... See all authors $\,\,\,\vee\,\,$

First published: 30 May 2019 | https://doi.org/10.1002/mds.27724 | Citations: 45



Journal of Parkinson's Disease 10 (2020) 875-891 DOI 10.3233/JPD-202004 IOS Press

Review Article

GDNF and Parkinson's Disease: Where Next? A Summary from a Recent Workshop

Roger A. Barker^{a,*}, Anders Björklund^b, Don M. Gash^c, Alan Whone^d, Amber Van Laar^e, Jeffrey H. Kordower^f, Krystof Bankiewicz^g, Karl Kieburtz^h, Mart Saarmaⁱ, Sigrid Boomsⁱ, Henri J. Huttunen^{j,k}, Adrian P. Kells^e, Massimo S. Fiandaca^e, A. Jon Stoessl¹, David Eidelberg^m, Howard Federoffⁿ, Merja H. Voutilainenⁱ, David T. Dexter^o, Jamie Eberling^p, Patrik Brundin^q, Lyndsey Isaacs^r, Leah Mursaleen^{r,s}, Eros Bresolin^r, Camille Carroll^t, Alasdair Coles^u, Brian Fiske^p, Helen Matthews^r, Codrin Lungu^v, Richard K. Wyse^r, Simon Stott^r and Anthony E. Lang^w

GLP-1 Agonists in PD

Diabetes drugs reported to have neuroprotective effects in PD





Articles

Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial

Dilan Athauda MRCP^a, Kate Maclagan PhD^b, Simon S Skene PhD^b, Martha Bajwa-Joseph PhD^b, Dawn Letchford ^b, Kashfia Chowdhury MSc^b, Steve Hibbert MBA^b, Natalia Budnik Vrach^c, Luca Zampedri MSc^c, John Dickson PhD ^d, Yazhou Li PhD^e, Iciar Aviles-Olmos PhD^a, Prof Thomas T Warner FRCP^f, Prof Patricia Limousin MD^a, Prof Andrew J Lees FRCP^a, Nigel H Greig PhD^e, Susan Tebbs MSc^b, Prof Thomas Foltynie PhD^a, R

 Study Type 1:
 Interventional

 Actual Enrollment 2:
 63 participants

 Allocation
 Randomized

 Allocation
 Parallel Assignment

 Intervention Model
 Parallel Assignment

 Vaudruple (Participant, Care Provider, Investigator, Outcomes Assessor)
 reatment

 Official Tittle
 A Phase II, Randomized, Double-blinded, Placebo-controlled Trial of Liraglutide in Parkinson's Disease

 Actual Study Start Date 3:
 April 3, 2017

 Estimated Primary Completion Date 4:
 Japril 3, 2022

Exercise in PD

• It is now widely accepted that exercise is beneficial in PD

- There are several ways in which exercise impacts the disease:
 - General health benefits
 - Improving or reducing decline in walking, balance, general mobility (and reducing falls)
 - Actual disease modification

Exercise for Gait and Balance Improvement

ORIGINAL ARTICLE

Tai Chi and Postural Stability in Patients with Parkinson's Disease

Fuzhong Li, Ph.D., Peter Harmer, Ph.D., M.P.H., Kathleen Fitzgerald, M.D., Elizabeth Eckstrom, M.D., M.P.H., Ronald Stock, M.D., Johnny Galver, P.T., Gianni Maddalozzo, Ph.D., and Sara S. Batya, M.D.

Patients doing tai chi had 67% fewer falls than those doing stretching

Treadmill training for patients with Parkinson's disease

Cochrane Systematic Review - Intervention Version published: 13 September 2015 see what's new

https://doi.org/10.1002/14651858.CD007830.pub4 🗗

Conclusions changed Am score 6 Used in 2 guidelines View article information

🜌 Jan Mehrholz | Joachim Kugler | Alexander Storch | Marcus Pohl | Kathleen Hirsch | Bernhard Elsner

Treadmill training improved gait speed by ~0.1 m/s, and stride length by ~ 5cm In-patient multidisciplinary rehabilitation for Parkinson's disease: A randomized controlled trial

Marco Monticone MD, PhD 🕿, Emilia Ambrosini PhD, Alessandro Laurini MD ... See all authors

First published:11 June 2015 | https://doi.org/10.1002/mds.26256 | Citations: 33 Improved balance, lasting at least a year

Exercise and Disease Modification



Courtesy of Dr Daniel Corcos PhD

Exercise and Disease Modification: CYCLE

- Cyclical Lower Extremity Exercise (CYCLE) trial for Parkinson's disease
- Uses cycling aerobic exercise at home for 12 months as the intervention
- Will test motor and non-motor outcomes in patients with PD
- Clinicaltrials.gov: NCT04000360

Exercise and Disease Modification: SPARX

- High-intensity aerobic exercise
- Phase II trial showed feasibility and interesting preliminary effects



Schenkman M et al, JAMA Neurol 2017

Exercise and Disease Modification: SPARX

 Phase 3 multi-site, randomized, evaluator-masked, study of endurance treadmill exercise on changes in the Movement Disorder Society-Unified Parkinson Disease Rating Scale (MDS-UPDRS) Part III score at 12 months among persons with early stage Parkinson disease

NCT04000360



US SITES	
1. Boston University	7. Louisiana Sta
2. Cleveland Clinic	Baton Rouge N
3. Case Western Reserve University/	8. Mayo Clinic
Kent State University	9. Northwester
4. Columbia University Medical Center	10. OhioHealth
5. Emory University	11. Oregon hea
6. Iowa State University & MacFarland	University
Clinic-Neurology	12. Rush Unive

te University & 13. University of Alabama at euroMedical Center Birmingham 14. University of California - Sar n University in 15. University of Cincinati 15. University of Cincinati 16. University of Fordia rsity Medical Center 18. University of Florida
 19. University of Minnesota
 25. Un

 20. University of Pennsylvania
 26. Wi

 21. University of Pittsburgh
 St. Loi

 22. University of Southern
 27. NY

 California
 23. University of Texas

 28. Un
 48. Un

 Medical Branch
 29. Wi

 41. University of Littaburgh
 51. Loi

25. University of Virginia 26. Washington University in St. Louis 27. NYU Langone <u>CANADIAN SITES</u> 28. University of Alberta 29. Wilfred Laurier University

Research Projects in Intramural NINDS (Clinical Center)

- Phenotype-genotype correlations in movement disorders: Aims to identify genetic contributors to PD and other diseases and their interplay with environmental factors
- Deep Brain Stimulations therapy in movement disorders: DBS for PD, ET, dystonia
- Acute effects of medium chain triglyceride
 nutritional ketosis in Parkinson: Studying the effects of
 ketogenic diet on PD

Where to Find Information

- <u>https://clinicaltrials.gov/</u> lists all trials conducted in the United States
- NINDS PD research landing page: <u>https://www.ninds.nih.gov/Disorders/Patient-</u> <u>Caregiver-Education/Hope-Through-</u> <u>Research/Parkinsons-Disease-Hope-Through-</u> <u>Research</u>
- MJFF trial finder: <u>https://www.michaeljfox.org/trial-finder</u>

THANK YOU