Research Update: How Can We Cure Parkinson’s Disease?

Danish Bhatti, MD
UNMC
Dr. Bhatti has disclosed the following financial relationships:

- Speaking and Consulting—*Teva Neuroscience, Merz, Adamas, Accadia Pharmaceuticals* and Allergan (Barret Hodgson) Pakistan
- Research funding – *Abbvie*
### 2193 Studies found for: Parkinson Disease

Also searched for Parkinson and Disorders. [See Search Details](#)

<table>
<thead>
<tr>
<th>Row</th>
<th>Saved</th>
<th>Status</th>
<th>Study Title</th>
<th>Conditions</th>
<th>Interventions</th>
<th>Locations</th>
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<tbody>
<tr>
<td>1</td>
<td></td>
<td>Active, not recruiting</td>
<td><a href="#">Examining Parkinson's Disease-Related Retirement: Results of Turkey</a></td>
<td>Parkinson Disease</td>
<td></td>
<td>University Cerrahpaşa Istanbul, Turkey</td>
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<td>2</td>
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<td>Unknown</td>
<td><a href="#">Parkinson's Disease Registry</a></td>
<td>Parkinson Disease</td>
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<td>Hualien Tzu Chi Hospital Hualien, Taiwan</td>
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<td>Withdrawn</td>
<td><a href="#">Gait Disorders in Parkinson's Disease</a></td>
<td>Parkinson's Disease</td>
<td>Device: vibratory cueing device</td>
<td>University of Minnesota Minneapolis, Minnesota, United States</td>
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<td>4</td>
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<td>Enrolling by invitation</td>
<td><a href="#">Circuit-Based Deep Brain Stimulation for Parkinson's Disease; Udal Clinical Core</a></td>
<td>Parkinson Disease</td>
<td>Other: Observational</td>
<td>University of Alabama at Birmingham Birmingham, Alabama, United States</td>
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<td>5</td>
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<td>Recruiting</td>
<td><a href="#">Biomarkers to Guide Directional DBS for Parkinson's Disease</a></td>
<td>Parkinson Disease</td>
<td>Device: Boston Scientific Vercise PC IPG with directional DBS lead</td>
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</table>
Parkinson’s related research reports

1865 - the naming of Parkinson’s

Levodopa (1960)
Research Parkinson Questions in Disease

Annual PD CME Symposium “Advances in PD”
October 19, 2018 – Omaha, NE, U.S.A.
KEY RESEARCH AREAS AT UNMC:

1. **Better Diagnosis** and Monitoring of PD
   1. Smartphone app for tremor
   2. Wearable device for PD
   3. Finger tapping application
   4. Driving assessment in PD

2. **Neuroprotection** Trials
   1. STEADY PD III
   2. SURE PD III
   3. NILO PD II

3. **Symptomatic Improvement**
Interquartile range of DK: Scaled measure of the variability in dyskinesia.

Interquartile range of BK: Scaled measure of the variability in bradykinesia.

75th %ile range of patient DK

Patients Median DK Plot

25th %ile range of patient DK

75th %ile range of patient BK

Patients Median BK Plot

25th %ile range of patient BK

Medication Reminder times
# Tremor Summary

<table>
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<th>Fri</th>
<th>Sat</th>
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Beyond average metrics

Can the distribution of activity predict changes in disease severity?
Linking Changing Disease to Real-World Driver Performance in Parkinson's Disease
- Black Box Systems
- SENSEI Driving Simulator
- VENUS on-road drive
- Wearable Activity monitor
- At Home Study procedures
HOW CAN WE SLOW DOWN PARKINSON DISEASE

ANNUAL PD CME SYMPOSIUM “ADVANCES IN PD”
October 19, 2018 – Omaha, NE, U.S.A.
Loss of Pigmented Neurons
LEWY BODIES
LEWY BODIES IN GUT
HOLY GRAIL

________________________
Neuroprotection
## Neuroprotection trials in PD

<table>
<thead>
<tr>
<th>Study</th>
<th>Active Agents</th>
<th>N</th>
<th>Primary outcome</th>
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<tbody>
<tr>
<td>DATATOP</td>
<td>selegiline, tocopherol</td>
<td>801</td>
<td>need for dopa</td>
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<tr>
<td>Tetrud, Langston</td>
<td>selegiline</td>
<td>54</td>
<td>need for dopa</td>
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<tr>
<td>SINDEPAR</td>
<td>selegiline</td>
<td>101</td>
<td>UPDRS</td>
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<td>ROADS</td>
<td>lazabemide</td>
<td>321</td>
<td>need for dopa</td>
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<tr>
<td>Swedish selegiline</td>
<td>selegiline</td>
<td>79</td>
<td>need for dopa</td>
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<td>Norwegian-Danish</td>
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<td>79</td>
<td>UPDRS</td>
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<tr>
<td>TEMPO</td>
<td>rasagiline</td>
<td>371</td>
<td>UPDRS</td>
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## Neuroprotection trials in PD

<table>
<thead>
<tr>
<th>Study</th>
<th>Active Agents</th>
<th>N</th>
<th>Primary outcome</th>
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<tbody>
<tr>
<td>NIL-A</td>
<td>neuroimmunophilin A</td>
<td>300</td>
<td>UPDRS motor</td>
</tr>
<tr>
<td>QE-2</td>
<td>coenzyme Q10</td>
<td>80</td>
<td>UPDRS</td>
</tr>
<tr>
<td>CALM-PD</td>
<td>pramipexole vs. l-dopa</td>
<td>82</td>
<td>beta-CIT SPECT</td>
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<tr>
<td>REAL-PET</td>
<td>ropinirole vs. l-dopa</td>
<td>186</td>
<td>fluorodopa PET</td>
</tr>
<tr>
<td>Jankovic &amp; Hunter</td>
<td>riluzole</td>
<td>20</td>
<td>UPDRS</td>
</tr>
<tr>
<td>ELLDOPA</td>
<td>l-dopa</td>
<td>360</td>
<td>UPDRS</td>
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<tr>
<td>Riluzole</td>
<td>riluzole</td>
<td>1084</td>
<td>need for l-dopa</td>
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</table>
# Neuroprotection trials in PD

<table>
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<tr>
<th>Study</th>
<th>Active Agents</th>
<th>N</th>
<th>Primary outcome</th>
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<tr>
<td>NINDS NET-PD</td>
<td>minocycline, creatine, CoQ10, GPI-1485</td>
<td>390</td>
<td>UPDRS</td>
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<tr>
<td>PRECEPT</td>
<td>CEP-1347</td>
<td>800</td>
<td>need for dopa</td>
</tr>
<tr>
<td>Guilford</td>
<td>GPI-1485</td>
<td>82</td>
<td>UPDRS</td>
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</table>

- *more than 5000 research subjects*
- *no definite neuroprotective agent*
Pathophysiology of Parkinson Disease is now beginning to unfold.
Calcium is currently a big deal in PD
Abundant fish protein inhibits α-synuclein amyloid formation

Tony Werner, Ranjeet Kumar, Istvan Horvath, Nathalie Scheers & Pernilla Wittung-Stafshede

https://www.spiedigitallibrary.org/journals/Neurophotonics/volume-3/issue-04/041807/Probing-amyloid-protein-aggregation-with-optical-superresolution-methods--from/10.1117/1.NPh.3.4.041807.full?SSO=1
STEADY-PD III

Efficacy of Isradipine in early Parkinson’s Disease
Alpha-synuclein aggregates activate calcium pump SERCA leading to calcium dysregulation

Cristine Betzer1,2, Louise Berkhoudt Lassen1,2, Anders Olsen1, Rikke Hahn Kofoed1,2, Lasse Reimer1,2, Emil Gregersen1,2, Jin Zheng1,2, Tito Cai1, Wei-Ping Cai1, Tong Chen1, Arne Moeller1,2, Marisa Brini1, Yuhong Fu1, Gienda Halliday1, Tomasz Brudet1,2, Susana Aznar1,2, Bente Falckenberg1,2, Jens Peter Andersen1 & Poul Henning Jensen1,2
microscopic worms (called *C. elegans*) genetically engineered to produce high levels of alpha synuclein
Striosomes and Interneurons

A schematic representation of a medium-sized spiny neuron (MSN) with inputs on the neuron are indicated: excitatory cortical or amygdalopaminergic terminals from the substantia nigra pars compacta terminate in close association with the corticostriatal inputs on the neighboring medium-sized spiny neurons and striatal interneurons dendrites. Adapted from Smith and Bolam (1990).
GABAergic inhibition in dual-transmission cholinergic and GABAergic striatal interneurons is abolished in Parkinson disease

N. Lozovaya¹, S. Eftekharì², R. Cloarec², L.A. Gouty-Colomer², A. Dufour², B. Riffault², M. Billon-Grand², A. Pons-Bennaceur³, N. Oumar¹, N. Burnashev³, Y. Ben-Ari¹,² & C. Hammond¹,³
**Bumetanide** functions as an NKCC1 chloride importer antagonist.
## CASE REPORT

**Bumetanide to Treat Parkinson Disease: A Report of 4 Cases**

*Philippe Damier, MD, PhD, MBA,* Constance Hammond, PhD,† and Yehezkel Ben-Ari, PhD†

<table>
<thead>
<tr>
<th>Cases</th>
<th>UPDRS III (OFF)</th>
<th>UPDRS II (OFF)</th>
<th>Patient’s main clinical effect</th>
<th>Potassium Baseline</th>
<th>Potassium After 2 mo of bumetanide</th>
<th>Side effects</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After 2 mo of bumetanide</td>
<td>Baseline</td>
<td>After 2 mo of bumetanide</td>
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<tr>
<td>1</td>
<td>44</td>
<td>29</td>
<td>30</td>
<td>18</td>
<td>Improvement of parkinsonism</td>
<td>3.9</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>11</td>
<td>15</td>
<td>10</td>
<td>No change</td>
<td>4.1</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>26</td>
<td>39</td>
<td>33</td>
<td>Improvement of gait</td>
<td>4.4</td>
</tr>
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<td></td>
<td></td>
<td>Improvement of balance</td>
<td>3.8</td>
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</table>

They were treated for 2 months with the diuretic. Reproduced from (Damier et al., 2016).

*Patient 3 was assessed during subthalamic DBS ON. UPDRS indicates Unified Parkinson’s Disease Rating Scale; UPDRS III, motor scale in OFF-drug condition; UPDRS II, activities of daily living in the worst conditions (OFF).
Cellular Senescence Is Induced by the Environmental Neurotoxin Paraquat and Contributes to Neuropathology Linked to Parkinson’s Disease

Shankar J. Chinta,1,6,8 Georgia Woods,1,8 Marco Demaria,1,8 Anand Rane,1 Ying Zou,1 Amanda McQuade,1 Subramanian Rajagopalain,1 Chandani Limbad,1,8 David T. Madden,1,8 Judith Campisi,1,8 and Julie K. Andersen1,7,
Immunotherapy is the future horizon for Parkinson Disease
• 2 Vaccines understudy (Phase I completed)
• Long term safety, immunological and clinical parameters.
• Study AFF011 for vaccine AFFITOPE® PD03A in early Parkinson's disease.
• Currently planning a Phase II efficacy trial.
In 2016, Prothena reported the Phase I safety clinical trial results. Double blind placebo controlled, 6 doses, 80 subjects. 6 months long with 3 injections (once a month) of respective dose. Observed for 3 more months. Drug was well tolerated with mild side effects. PRX002 antibodies were crossing blood brain barrier and entering the brain. This resulted in a rapid reduction of alpha-synuclein levels (in some cases by up to 97 percent after a single dose!).
• The PASADENA study will assess the safety and efficacy of prasinezumab. (Phase II)
• Phase 2 study will be a randomized, double-blind, placebo-controlled, three-arm study
• 300 patients (less than 2 years since diagnosis), 52 weeks.
• intravenous infusion once every 4 weeks. must not be on any dopaminergic therapy, and not start one for next 52 weeks.
Immunotherapy

There are other companies with early-stage programs in this area, including

- **Biogen** (BIIB054),
- **AC Immune** (ACI-870),
- **Proclara** (NPT088),
- **NeuroPore** (NPT200-11; in collaboration with **UCB**)
- **BioArctic Neuroscience** (BAN0805; in collaboration with **AbbVie**).
Multi-center, randomized, double-blind, placebo-controlled study of nilotinib in individuals with Parkinson’s disease (PD).
Phosphorylation by the c-Abl protein tyrosine kinase inhibits parkin’s ubiquitination and protective function.
Gene augmentation therapy

- Cell with non-functioning gene
- Functioning gene
- Cell functioning normally

- Dopamine synthesis genes
- LentiVector
- Dopamine production in striatum
• Phase 1b trial with 8 participants, 57 years average age, PD for average of nine years.
Long-term safety and tolerability of ProSavin, a lentiviral vector-based gene therapy for Parkinson’s disease: a dose escalation, open-label, phase 1/2 trial

750,000
48 genes targeted by 57 FDA-approved drug families disease-modifying drugs for PD. Neuroprotective effects reported in 17 of the 57 drugs.

750,000
Dabrafenib – an anti-melanoma drug. The investigators then demonstrated that Dabrafenib could rescue both cell & mouse models of Parkinson’s.
But an interesting aspect of the results was the ‘positive control’ compound they used: *Epigallocatechin Gallate* (or simply EGCG) leading to the PROMESA clinical study.
NEWLY APPROVED THERAPIES FOR PD

26th ANNUAL PD SYMPOSIUM “RISK FACTORS OF PD”
October 21, 2016 – Omaha, NE
NEWLY APPROVED THERAPIES:

1. **Motor Fluctuation** of PD
   1. Rytary (carbidopa-levodopa)
   2. Opicapone (safinamide)
   3. DUOPA (carbidopa-levodopa)
   4. Gocovori (Amantadine ER)

2. **Non-Motor** symptoms of PD
   1. Nuplazid (Pimavanserin)
   2. Northera (Droxtidopa)

3. **DBS Therapies** for PD
   1. St Jude Infinity (Abbott)
   2. Vercise (Boston Scientific)
INBRIJA – Inhaled Levodopa
DUOPA: CARBIDOPA/LEVODOPA ENTERAL SUSPENSION PUMP
Programming Directional Leads with MICC
SIGNIFICANT EMERGING THERAPIES FOR PD

26th ANNUAL PD SYMPOSIUM "RISK FACTORS OF PD"
October 21, 2016 – Omaha, NE
UPCOMING THERAPIES:

1. Motor Fluctuation of PD
   1. Rytary PLUS IPX 203 (carbidopa-levodopa)
   2. Accordion Pill (carbidopa-levodopa)
   3. SQ DUOPA (carbidopa-levodopa)
   4. SL Apomorphine
   5. Inhaled carbidopa-Levodopa

2. Non-Motor symptoms of PD

3. DBS Therapies for PD
   1. Responsive Stimulation
   2. Adaptive Stimulation
   3. Non-invasive Stimulation
The Accordion Pill™ - A Drug Delivery Solution for Key Unmet Needs

General Structure of the Accordion Pill

[Diagram showing the process of layering and folding to create an encapsulated capsule]
Subcutaneous Sinemet Pump
Subcutaneous Apomorphine Pump
THANK YOU!

Advances and Emerging Therapies in Parkinson Disease

DANISH BHATTI MD
dbhatti@unmc.edu
Assistant Professor, Neurology
Co-Director PD Comprehensive clinic
Director, International Neurology program
Associate Director, Movement Disorders Fellowship