



# University of Nebraska Medical Center Department of Neurological Sciences

*presents:*

## Parkinson's Disease in 2023

*A Conference for Parkinson's Disease  
Patients & their Family/Care Partners*

Wednesday, November 1, 2023 | 8 a.m. – 2:30 p.m.

Embassy Suites La Vista

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## Welcome!

Welcome to the Parkinson's Disease 2023 Patient and Care Partner Conference!

Today's symposium is an informational event that UNMC's Department of Neurological Sciences is holding as part of our service to the community. We have donated the many hours of staff and physician time that have gone into producing this event.

We would also like to offer our sincere thanks to our sponsors/exhibitors, who have made this symposium possible. We hope you'll visit them during program breaks.

Lastly, we would like to offer our deepest thanks to all of **you**, who have come from near and far to be here with us today. We hope that you will learn from us, but we are confident that we will also learn from you. We are honored to be a part of the PD Community and to have this opportunity to offer information that we hope will improve your health and wellbeing.

Sincerely,

The Movement Disorders Program  
Department of Neurological Sciences  
University of Nebraska Medical Center

## Neurological Sciences Movement Disorders Team



### **John Bertoni, MD, PhD**

Dr. Bertoni is Professor Emeritus in the Department of Neurological Sciences at the University of Nebraska Medical Center. His interests include Parkinson Disease, Epidemiology, Toxicology and New Clinical Therapies.



### **Mara Seier, MD**

Dr. Seier is an Assistant Professor in the Department of Neurological Sciences at the University of Nebraska Medical Center and Movement Disorders Division Chief. Her specialties and interests include Parkinson's Disease, Movement Disorders and Deep Brain Stimulation. Dr. Seier evaluates patients with movement disorders including Parkinson's Disease, chorea, dystonia, ataxia, tremor, spasticity, and gait abnormalities. She also performs Botulinum Toxin injections and Deep Brain Stimulation. Her research interests include Parkinson's Disease and essential tremor.



### **Amy Hellman, MD, FAAN**

Dr. Hellman is an Associate Professor in the Department of Neurological Sciences at the University of Nebraska Medical Center and Director of the Huntington Disease Society of America (HDSA) Center of Excellence at Nebraska Medicine. Her specialties and interests include Parkinson's Disease, Huntington's Disease, chorea, and dystonia. Dr. Hellman evaluates patients with movement disorders including Parkinson's Disease, chorea, dystonia, spasticity, gait abnormalities and ataxia. She also performs botulinum toxin injections and Deep Brain Stimulation. Her research interests include Parkinson's Disease and Huntington's Disease.



### **Miguel Situ-Kcomt, MD**

Dr. Situ-Kcomt is a board-certified neurologist and Assistant Professor in the Division of Movement Disorders, Department of Neurological Sciences at UNMC. He has a particular interest in Parkinson's management therapies which include Deep Brain Stimulation Surgery, as well as an interest in dystonia.

**Erin Cameron-Smith, MD**

Dr. Smith is a Movement Disorders neurologist at Nebraska Medicine, specializing in Parkinson's Disease and other types of tremor disorders. She is Co-Director of the Comprehensive Movement Disorders Clinic. She is a native Nebraskan and did all her medical training at UNMC in Omaha.

**Kiel Woodward, MD**

Dr. Woodward is an Assistant Professor of Movement Disorders in the Department of Neurological Sciences at the University of Nebraska Medical Center. His interests include Parkinson's Disease, tremor, dystonia, ataxia, and other forms of abnormal movements.

## Heartland Neurological Therapy and Wellness Center

**Cheri Prince, DPT**

Cheri is a Physical Therapist and Director of Heartland Neurological Therapy and Wellness Center in Waterloo, NE. She received her Doctorate degree in Physical Therapy from Creighton University in 1999. Her clinical interests include Parkinson's Disease and other neurologic conditions. Cheri holds certifications in LSVT BIG, PWR! (Parkinson's Wellness Recovery), and Rock Steady Boxing. She has taken advanced training in Dual Task Training and has completed the Allied Team Training for Parkinson through the Parkinson Foundation. She is also a member of the Heartland Advisory Board for the Heartland Chapter of Parkinson Foundation. She has presented locally and nationally on both the use of Dual Task Training for PD, Freezing of Gait (FOG), and the Physical Therapy Assessment and Treatment of the Parkinson Patient.

## AGENDA

- 8:00-9:15      **Registration/Breakfast/Exhibitor Tables Open**
- 9:15-9:30      **Opening Comments/Welcome**  
John Bertoni, MD, PhD, UNMC
- 9:30-10:00     **Diagnosis and Management of Parkinson's Disease**  
Mara Seier, MD, UNMC
- 10:00-10:30    **Sleep and Parkinson's Disease**  
Amy Hellman, MD, UNMC
- 10:30-11:00    **Break and Exhibitor Tables**
- 11:00-11:30    **Psychiatric Issues in Parkinson's Disease**  
Kiel Woodward, MD, UNMC
- 11:30-12:00    **Exercise in Parkinson's Disease: Importance of Aerobic, Skill Based and Dual Task Exercise**  
Cheri Prince, DPT Director Heartland Neurological Therapy and Wellness Center
- 12:00-1:00     **Lunch and Exhibitor Tables Open**
- 1:00-1:30      **Research Updates in Parkinson's Disease**  
Erin Cameron-Smith, MD, UNMC
- 1:30-1:45      **Movement Session**  
Heartland Neurological Therapy and Wellness Center Team
- 1:45-2:15      **Advanced Treatment: Focused Ultrasound and Deep Brain Stimulation**  
Miguel Situ-Kcomt, MD, UNMC
- 2:15-2:30      **Closing Remarks**

**This event will be recorded and available at a later date. For questions or for access to the recording, please email: [unmcneuroconf@unmc.edu](mailto:unmcneuroconf@unmc.edu)**



## 2023 Parkinson's Disease Conference Event Evaluation Form

Please leave this form on your table. We will collect them following the event.

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Please give us your feedback about this symposium to help us plan future meetings!

1. Presentation Speaking Quality:  Excellent  Good  Fair  Poor

Comments:

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2. Presentation Program Content:  Excellent  Good  Fair  Poor

Comments:

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3. Was the program presentation beneficial to you?  Yes  No

Comments:

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4. Did you receive the information you expected?  Yes  No

Comments:

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5. Was sufficient time provided for the presentation?  Yes  No

Comments:

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6. Meeting Location:  Excellent  Good  Fair  Poor

Comments:

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7. Suggestions for Future Topics:

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# **Thank you to our sponsors!**

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**Medtronic**

**Parkinson's Foundation**

**The Key**

**YMCA of the Greater Omaha Metro**

## Contact Information

We provide excellent and compassionate care to patients with Movement Disorders, advance research, educate future generations of physicians and support our communities. Our program is the only Movement Disorders program in Nebraska and the largest in the region.

Our program works closely with the Departments of Neurosurgery, Neuroradiology, Neuropsychology, Psychiatry, Orthopedic Surgery and Rehabilitation to provide comprehensive, state-of-the-art, multidisciplinary care for patients with Movement Disorders. The Movement Disorders Program focuses on diseases of the brain that produce alterations of motor control, including tremor, clumsiness, voluntary or involuntary abnormal movements. Areas of expertise include management of patients with Parkinson Disease, Essential Tremor, Dystonia, Tics, Chorea, Ataxia and Myoclonus. We have a very busy Deep Brain Stimulation program with expertise in challenging Movement Disorders cases. Our Center also manages the largest Dystonia and Spasticity Clinic in the region, providing a full complement of treatments for these conditions, including Botulinum toxin injections, Deep Brain Stimulation and intrathecal baclofen pump therapy.

Our Movement Disorders specialists teach medical, nursing and physician assistant students, as well as Neurology, Psychiatry and other residents, in how to recognize and treat these complex diseases. We also conduct research in Parkinson Disease, tremor, dystonia, chorea and other similar disorders.

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**To schedule an appointment with one of our Movement Disorders specialists, please contact us:** Nebraska Medicine Clinical Neurosciences Center - Movement Disorders Clinic  
4242 Farnam Street, Suite 650 | Phone: (402) 559-8600

Neurological Sciences Home Page:  
<http://www.unmc.edu/neurologicalsciences/>

A recording of today's event will be available following the conference. If you are interested in a link to the recording, please email: [unmcneuroconf@unmc.edu](mailto:unmcneuroconf@unmc.edu)

A digital copy of the booklets will be available following the conference.  
Please visit: <https://www.unmc.edu/neurologicalsciences/outreach/index.html>  
or email: [unmcneuroconf@unmc.edu](mailto:unmcneuroconf@unmc.edu) for a copy.

**University of Nebraska  
Medical Center**



**Nebraska  
Medicine**

Diagnosis and Treatment of Parkinson's Disease

MARA SEER, MD  
ASSISTANT PROFESSOR UNMC NEUROLOGICAL SCIENCES  
MOVEMENT DISORDER DIVISION

UNIVERSITY OF  
**Nebraska**  
Medical Center

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How is Parkinson's Disease Diagnosed?

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How is PD diagnosed?

- ▶ A **clinical diagnosis** by a Neurologist or a Movement Disorder Neurologist
- ▶ There is not one specific test to diagnose PD
- ▶ Your doctor should ask you about your symptoms
- ▶ Your doctor should do a thorough neurological exam
  - ▶ Including watching movements of face, upper and lower extremities, strength, reflexes, sensation and walking

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## Parkinsonism

- ▶ **Bradykinesia** – slowness of movement, decreased amplitude, hesitation and halted movement
- ▶ Rigidity – stiffness felt when major joints are moved passively
- ▶ Rest Tremor – a tremor seen when hand/leg are fully at rest

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▶ An "umbrella" term describing certain signs on exam

▶ Can have many causes

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## Ways that Parkinson's motor symptoms can manifest

- ▶ Smaller handwriting
- ▶ Reduced volume of voice
- ▶ Less facial expression
- ▶ Slowing down of everyday activities
- ▶ Issues with dexterity
- ▶ More difficulty rolling over in bed; getting up from a chair
- ▶ Reduced arm swing with walking
- ▶ Shuffling gait and stooped posture
- ▶ Tremors – both resting and during action
- ▶ Drooling
- ▶ Stiffness in the joints
- ▶ Cramping/curling of feet/toes getting up from a chair

Not everyone will have the same type of symptoms; for example, 30% of PD patients do not have tremor.

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## Symptoms that may also occur in PD

- ▶ Loss of sense of smell
- ▶ Autonomic symptoms: Constipation, Drop in blood pressure upon standing (dizziness), Urinary urgency or frequency, Sexual dysfunction
- ▶ Sleep issues: Insomnia, Daytime sleepiness, Rapid Eye Movement (REM) sleep behavior disorder
- ▶ Psychiatric issues: Depression, Anxiety, Hallucinations or Paranoid thoughts
- ▶ Cognitive changes: Slowness in thinking, Memory changes, Difficulty with multi-tasking
- ▶ Drooling
- ▶ Fatigue
- ▶ Pain

**Non-Motor Symptoms of PD**

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## Tests your doctor may order



- ▶ Routine blood tests
  - ▶ Complete blood count
  - ▶ Metabolic panel
  - ▶ Thyroid function tests
  - ▶ Vitamins levels: B1 (thiamine), B9 (folate), B12, Vit D
- ▶ Inflammatory/Rheumatologic markers
- ▶ Infectious causes: Syphilis
- ▶ Copper and copper storage markers

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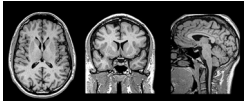
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## Tests your doctor may order

- ▶ MRI of the brain
- ▶ These tests are not necessarily done to "detect" Parkinson's Disease but to rule out other mimics or conditions that could be contributing to symptoms

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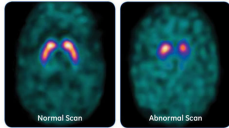
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Tests your doctor may order

▶ **DaTscan**

- ▶ A radioactive tracer is given that labels dopamine transporters which are found in a part of the brain called the "striatum"
- ▶ A healthy dopamine system has normal uptake of signal; whereas the signal in a brain with neurodegenerative parkinsonism is abnormal



**NOT essential for making the diagnosis of Parkinson's disease**  
False positives and false negatives can occur!

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What causes Parkinson's Disease?

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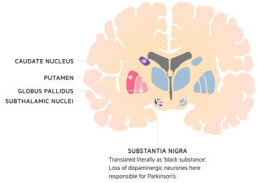
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What causes Parkinson's Disease?

- ▶ Chronic, progressive condition that occurs secondary to loss of brain cells (neurons) that produce **dopamine**
  - ▶ These neurons are found within the substantia nigra
- ▶ **Dopamine** is a chemical (neurotransmitter) that the brain uses to regulate movement



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## Loss of dopamine...

Results in loss of movement

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## What causes PD?

- ▶ **Alpha-synuclein** is a protein normally found in neurons (brain cells)
- ▶ For reasons we do not yet understand, in brains of people with PD it accumulates and forms clumps in neurons
- ▶ These abnormal clumps within neurons are called **Lewy Bodies**
- ▶ **Abnormal  $\alpha$ -syn** is also found in other parts of the body

Lewy Body

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## Blood test for PD?

- ▶ We are getting closer to having a blood test that may be capable of identifying alpha-synuclein
  - ▶ Seed amplification assay
- ▶ This testing has also been studied on cerebral spinal fluid, but does require getting a spinal tap (lumbar puncture)
- ▶ **Not currently available** – still needs more studies until it is available
  - ▶ Still not good enough to detect in EVERYONE that has PD (false negative)
  - ▶ Still not reliable enough to be the only way to diagnose PD (false positives)

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
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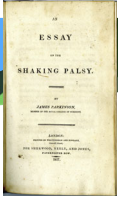

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## What causes PD?



- ▶ The cause of Parkinson's disease is **unknown**
- ▶ **James Parkinson** described the disease in 1817; 200 years later we are still not sure
- ▶ Likely a combination of factors involved

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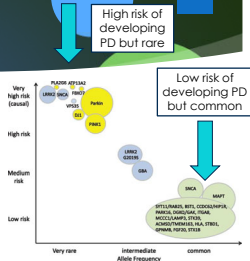
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## What causes PD?



**Genetics**

- ▶ Still in the "early stages" of our understanding
  - ▶ Genetic causes of PD only discovered within the past 20 years
- ▶ 90% of patients do not have gene mutation known to cause PD
  - ▶ In the 10% of patients with a gene mutation; their children and other family members have an increased risk of developing Parkinson's Disease

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## PD GENERation: Mapping the Future of Parkinson's Disease



- ▶ **PD GENERation** – a national initiative that offers genetic testing for clinically relevant Parkinson's related genes and genetic counseling at **NO** cost for people with PD
  - ▶ Can be done at home through a telemedicine appointment and at-home check swab collection kit
  - ▶ Tests for 7 most common causes of genetic-PD

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**PD GENERation:**  
Mapping the Future of Parkinson's Disease



- ▶ As of this summer >10,000 people have been enrolled for genetic testing
- ▶ The study has identified that 12.7% of people have a genetic form of PD
- ▶ Goals of this study:
  - ▶ Accelerate clinical trials for PD
  - ▶ Improve PD care and research
  - ▶ Empower people with PD (and their families)

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What causes PD?



- ▶ **Older age:** 1 out of 100 people over the age of 60, average age of onset is 60
- ▶ **Male Gender:** Male to Female ratio is 1.5-2x higher
- ▶ **Environmental/Chemical exposures**
  - ▶ Pesticides/Herbicides (including permethrin, beta-hexachlorocyclohexane, rotenone, paraquat, "Agent Orange" )
  - ▶ Solvents/Cleaning chemicals (tetrachloroethylene)
- ▶ **Head injuries**
- ▶ **Smoking and Coffee consumption = protective**

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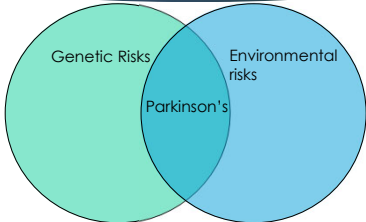
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What causes PD?



The diagram consists of two overlapping circles. The left circle is light green and labeled 'Genetic Risks'. The right circle is light blue and labeled 'Environmental risks'. The overlapping area in the center is a darker teal color and labeled 'Parkinson's'.

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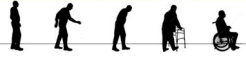
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## Progression of PD

### HOEHN AND YAHR SCALE

STAGE 1	STAGE 2	STAGE 3	STAGE 4	STAGE 5
Only one side of the body is affected	Symptoms affect both sides of the body	Balance and stability become affected	Symptoms increase, however still able to stand and walk	Assistance is required for everyday activities



- ▶ Progression of PD is difficult to predict
- ▶ The experience of living with Parkinson's over the course of a lifetime is unique to each person
- ▶ As symptoms and progression vary from person to person, neither you nor your doctor can predict which symptoms you will get, when you will get them or how severe they will be

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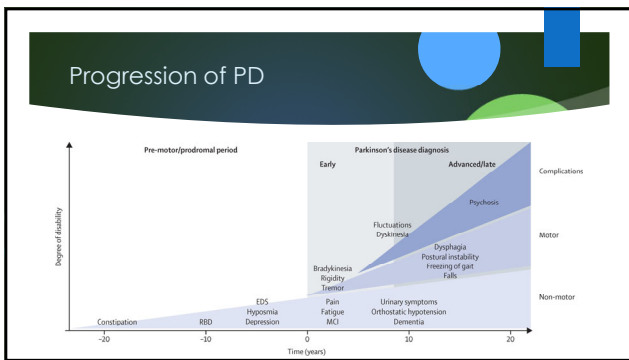
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## How is Parkinson's Disease Treated?

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## Treatment of PD

- ▶ **Motor symptoms**
  - ▶ Bradykinesia/akinesia
  - ▶ Tremor
  - ▶ Rigidity/stiffness
  - ▶ Gait/balance changes
- ▶ **Non-motor symptoms**
  - ▶ Depression/anxiety
  - ▶ Sleep disturbance
  - ▶ Cognitive changes
  - ▶ Urinary dysfunction
  - ▶ Constipation
  - ▶ Dizziness and hypotension
  - ▶ Hyperhidrosis
  - ▶ Sexual dysfunction
  - ▶ Fatigue
  - ▶ Pain



An iceberg floating in the ocean. The small tip above the water represents motor symptoms, while the much larger part submerged below the water represents non-motor symptoms.

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## Treatment of PD



A male physician in a white coat is looking at a tablet held by an elderly female patient who is using a cane.

- ▶ Treatment is individualized
- ▶ Education is critical
  - ▶ Expectations, potential side effects, need for dose increase in the future, additional medications in the future
- ▶ "Team" decision
  - ▶ Patient and physician making choices together
- ▶ Combination of medication and exercise
- ▶ Guiding principal about treatment decision → Quality of life

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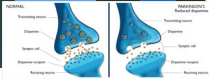
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## Medication Options in PD



Two diagrams showing dopamine signaling. The left diagram shows a neuron with dopamine being released into the synapse, where it binds to receptors on another neuron. The right diagram shows an enzyme (MAO-B) breaking down dopamine in the synapse.

- ▶ PD is from lack of dopamine in the brain → our goal is to increase dopamine signaling in the brain
- ▶ Many different ways to approach this:
  - ▶ Raise dopamine levels (carbidopa/levodopa)
  - ▶ Block enzymes in the brain that breakdown dopamine (rasagiline, entacapone)
  - ▶ Stimulate dopamine receptors
    - ▶ Dopamine agonists (ropinirole, pramipexole, rotigotine)
    - ▶ Other (amantadine)

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## Carbidopa/Levodopa (Sinemet)

- ▶ Levodopa is converted into dopamine in the brain
  - ▶ Fits like a "key in a lock"
- ▶ Since it is a "replacement" therapy it is the most effective and potent at treating motor symptom
  - ▶ **Gold standard** in treating PD
- ▶ Given with carbidopa to decrease risk of side effects and improve its effectiveness
- ▶ Typically, people with PD should notice an improvement in symptoms within 1-2 weeks

Blood-brain barrier

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## Carbidopa/Levodopa (Sinemet)

- ▶ Possible common side effects: nausea/upset stomach, lowered blood pressure, sedation, abnormal dreams, hallucinations
- ▶ Effects that can occur later in disease:
  - ▶ **Motor Fluctuations** – early wearing off before next dose is due causing reemergence of parkinsonian symptoms
    - ▶ Nearly half of all patients will experience this by 2-5 years after disease onset
  - ▶ **Levodopa Induced Dyskinesia** – involuntary movements that can affect head, trunk or extremities
    - ▶ Typically occurring at peak levodopa levels, but can also occur when medication levels rising/falling

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## Carbidopa/Levodopa Formulations

25 mg/100 mg  
Carbidopa/Levodopa IR tablets

Carbidopa/Levodopa ER capsules (Rytary)

Carbidopa/Levodopa Inhaled (Inbrija)

Carbidopa/Levodopa CR tablets

Carbidopa/Levodopa intestinal infusion (Duopa)

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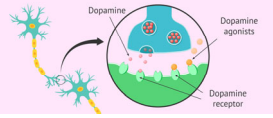
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## Dopamine Agonists

- ▶ Act on dopamine receptor but not as efficiently as dopamine
- ▶ Not as potent as levodopa; but lower rates of dyskinesia
- ▶ Oral formulations
  - ▶ Ropinirole (Requip) – IR and ER forms
  - ▶ Pramipexole (Mirapex) – IR and ER forms
- ▶ Transdermal patch
  - ▶ Rotigotine (Neupro) – long-acting form
- ▶ Subcutaneous (injection)
  - ▶ Apomorphine – used as a “rescue”



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## Dopamine Agonists

**Advantages**

- No dietary concerns with protein for absorption into the gut and brain
- Have a longer half life than IR levodopa

**Disadvantages**

- Similar side effects to Levodopa: nausea, vomiting, hypotension
- Hallucinations** (especially in older patients)
- Excessive daytime sleepiness (“sleep attacks”)
- Lower leg edema
- Impulse Control Disorders(ICD); pathologic gambling, hypersexuality, and compulsive eating and shopping

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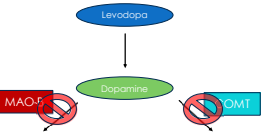
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## Blocking enzymes that breakdown dopamine

- ▶ **Monoamine oxidase-B inhibitors** (MAO-B inhibitors)
  - ▶ Rasagiline
  - ▶ Selegiline
  - ▶ Safinamide
- ▶ **Catechol-O-methyl Transferase inhibitors** (COMT inhibitors):
  - ▶ Entacapone
  - ▶ Opicapone
  - ▶ Tolcapone



These medications have **modest** benefit in reducing symptoms; can increase “On” time

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## Amantadine

- ▶ Antiviral agent that also has antiparkinsonian effects
  - ▶ Increases dopamine release and inhibits dopamine reuptake
  - ▶ Reduces glutamate hyperactivity which may contribute to both **Improved Off time** and **reduction of Dyskinesia**
- ▶ Used as a treatment for parkinsonian symptoms, **decrease dyskinesia**, also can be helpful for dystonia and gait/freezing
- ▶ Side effects: **Hallucinations**, confusion, nightmares, blurred vision, "lacy" appearing rash, edema

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## Treatment of PD

- ▶ Various therapies, treatments, medications for the Non-Motor symptoms of PD that I did not cover today
  - ▶ **Non-motor symptoms:** Depression/anxiety, Sleep disturbance, Cognitive changes, Urinary dysfunction, Constipation, Dizziness and hypotension, Hyperhidrosis, Sexual dysfunction, Fatigue, Pain
- ▶ EXERCISE!!!
  - ▶ We do not have any medication that can slow the progression of PD but studies have shown that exercise is the closest thing we have!



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# Thank you!

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# Sleep in Parkinson's Disease

Amy Hellman, MD, FAAN  
Associate Professor  
Department of Neurological Sciences

University of Nebraska Medical Center Nebraska Medicine

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## Importance of sleep

Insufficient sleep may contribute to many negative outcomes

- Daytime somnolence
- Decreased alertness → poor performance, increased risk of accidents, injury, and death
- Detrimental effects of psychological and physical health
  - Depression/anxiety
  - Cognitive impairment
  - Poor cardiac health
  - Immunosuppression
  - Obesity
- Decreased quality of life

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## Sufficient sleep

Two dimensions

- Duration (quantity)
- Depth (quality)

Sufficient sleep depends on the number of arousals from sleep, percentage, duration, and type of sleep stages

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## Sleep and Parkinson's Disease

- Sleep is commonly impacted by Parkinson's Disease (PD)
- PD can cause many different disorders of sleep
  - May start many years before the movement symptoms of PD start
  - Worsen as the disease worsens
- The same sleep disorders occur in people without PD, but they occur more frequently in people with PD

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## Sleep Disorders in PD

- Insomnia
- Nocturnal akinesia
- Restless leg syndrome (RLS) and Periodic leg movements in sleep (PLMS)
- REM sleep behavior disorder
- Sleep apnea
- Excessive daytime sleepiness

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## Insomnia

- Effects 80% of people with PD
- Problems falling asleep, staying asleep, or both
- Poor sleep quality
  - Fragmented sleep
  - Less deep, restful sleep
  - Nocturnal tremor
- Can be aggravated by medications to treat motor symptoms of PD

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## Factors contributing to insomnia

- Nocturnal motor symptoms
- Depression, anxiety, and panic disorder
  - All very common in PD
  - All effect sleep
- Urinary frequency during the night
- Nocturnal leg cramps
- Medications
  - Dopaminergic medications
  - Non-PD medications

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## Management of Insomnia

- Discuss any contributing factors with your doctor
- Maintain good sleep hygiene
- Cognitive Behavioral Therapy
- Medication options (discuss with your doctor)
  - Melatonin
  - Prescription medications
  - Do NOT take over the counter sleep aids without approval from your doctor

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## Sleep hygiene

- Regular sleep schedule
  - Go to bed at the same time each night
  - Get the same amount of sleep
  - Wake at the same time each morning
- Exercise daily and regularly but not in the late evening
- Get plenty of exposure to light during the day
- Sleep in a quiet, dark environment
- Avoid looking at screens nearing bedtime
- Avoid caffeine after lunch
- Don't eat a big meal just before bed
- Avoid alcohol within 3 hours of bedtime
- Do not smoke, especially in the evening/night
- Do something relaxing before bedtime
- Associate your bed with sleep

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## Stretch to prevent leg cramps



Stand facing the wall, feet together, about 24 inches from the wall. With the heels firmly on the floor and the body aligned straight at the hips and knees, lean forward to the wall, stretching the back of the leg. Hold this position for 10 to 30 seconds. Repeat five times per session, at least two sessions daily.

uptodate.com

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## Nocturnal Akinesia

- Trouble turning over in bed or getting up to go to the bathroom
- Most often seen in later stages of PD
- Often associated with nocturnal tremor
- Management
  - Increase nighttime dose of PD medication
    - Long-acting carbidopa/levodopa or dopamine agonist
- If this is not effective, continuous medication may be useful
- Deep brain stimulation may have favorable impact on sleep

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## Restless Leg Syndrome

- Unpleasant crawling or deep aching sensation in the legs or arms
- Relieved temporarily by moving the legs, sometimes requiring a person to get up and walk around
  - Differentiates from leg restlessness which is a common "wearing off" phenomenon
- Worse in the evening, interfering with sleep
- Can be treated with PD medications if motor symptoms are also occurring
- Other medications may be a better choice

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## REM Sleep Behavior Disorder

- Acting out of dreams
- Movements
  - Thrashing, hitting, kicking, falling out of bed
- Vocalizations
  - Screaming, laughing, singing
- May cause harm to themselves or others
- Not remembered

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## Management of RBD

- Safe sleeping environment
  - Remove breakable, sharp, or dangerous objects from the bedside
  - Mattress on the floor
- Medications (discuss with your doctor)
  - Melatonin
    - Naturally secreted by the brain to induce sleep
  - Clonazepam
    - Sedating, may worsen sleep apnea, gait, cognition
    - Little, if any, tendency to develop tolerance, dependence, abuse, or adverse sleep effects

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## Sleep Apnea

- Caused by collapse of the airway during sleep
- Snoring, gasping, choking, interrupted breathing
- Poor sleep quality resulting in excessive daytime sleepiness
- Can worsen cognitive function, cause irritability, depression, psychosis
- Associated with other health risks
  - Increased risk of high blood pressure, coronary artery disease, arrhythmias, heart failure, and stroke, among others
- May be worsened by treatment of other sleep disorders

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## Management of Sleep Apnea

- Diagnosed with a sleep study
- Managed by a primary care provider or sleep specialist
  - Treated the same in people with and without PD
  - Behavior modifications for OSA
    - Weight loss and exercise
    - Avoid alcohol, even during the day
- Continuous positive airway pressure (CPAP)
- Alternative therapies including oral appliances and surgical procedures are available and may be appropriate for some people

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## Excessive Daytime Somnolence

- Caused by Parkinson's Disease itself and contributed to by medications and the sleep disturbances discussed earlier
- Management
  - Identify treatable causes
  - Improve sleep hygiene
  - Reduce sedative medication
  - Bright light therapy
  - Physical activity and exercise
- If more conservative measures are not effective, stimulating medications may be tried but have variable effects
- Adjust activity to minimize risk

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## In Summary

- Sleep disorders are common non-motor PD symptoms that have a big impact on a person's life
- Identification and appropriate management of these symptoms is important and has impact on health, safety, and quality of life

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# Psychiatric Issues in Parkinson's Disease

Parkinson's Disease 2023  
Patient and Caregiver Symposium  
Kiel Woodward, MD  
University of Nebraska Medical Center – 11/01/2023



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## Objectives

Discuss importance of mental health in Parkinson's Disease  
Explain how to recognize depression, anxiety, and apathy  
Discuss potential treatment options and other tips for improving mental health

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**MENTAL HEALTH**

IS...	ISN'T...
<ul style="list-style-type: none"> <li>• Important</li> <li>• Something everyone has</li> <li>• Inherently linked to (or probably inseparable from) physical health</li> <li>• On a continuum</li> <li>• Worth making time for</li> <li>• Part of being human</li> <li>• Something we need to look after</li> <li>• Positive + Negative</li> <li>• Changeable</li> <li>• Complex</li> <li>• Real</li> </ul>	<ul style="list-style-type: none"> <li>• A sign of weakness</li> <li>• Shameful</li> <li>• All in your mind</li> <li>• Always something negative</li> <li>• Something you decide to have</li> <li>• Something to tuck away only when it feels broken</li> <li>• An unchangeable term when mental illness</li> <li>• Feeling good all the time</li> <li>• Something you can snap out of</li> <li>• Fixed</li> <li>• Fake news</li> </ul>

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Depression

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### Why is mental health important?

Mental health greatly affects quality of life

- It affects how we think, feel, and act
- It can exacerbate other Parkinsonian symptoms
- Depression and anxiety can affect overall health and quality of life **at least as much** the motor symptoms of PD

Depression can be deadly – increases risk of suicide

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### Why is mental health important?

Mental health disorders are very common in PD

Depression: 30% SG #v#88 ( #rup do

Dsdwk | #7 3 ( #SG #v#88 ( #rup do

Anxiety: 40% PD vs. 33% normal

Despite being common, they are underrecognized and undertreated

Aarland D, et al. Depression in Parkinson disease—epidemiology, mechanisms and management. *Neu Rev Neurol*. 2011 Dec 36(6):35-47.  
den Brok MG, et al. Apathy in Parkinson's disease: A systematic review and meta-analysis. *Mov Disord*. 2015 May;30(6):769-69.

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## Why are mental health issues so common in PD?

### Reactionary

- Limited activities
- Reduced independence
- Chronically progressive disease without a cure

### Intrinsic to Parkinson's Disease

- Loss of brain cells producing dopamine, serotonin, and norepinephrine
- These chemicals are responsible for regulating mood, energy, motivation, appetite, and sleep

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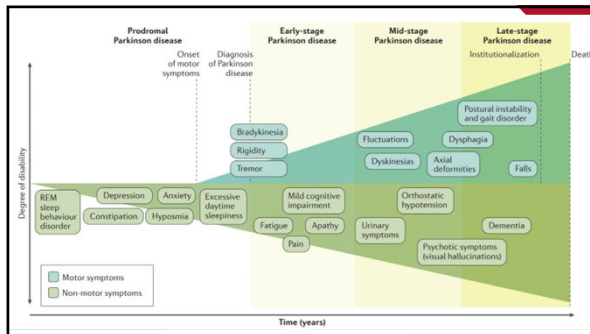
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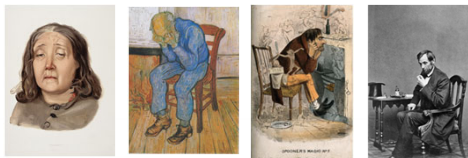
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## What is Depression?

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## What is Depression?

Major Depressive Disorder (MDD)  
DSM-V criteria (Diagnostic and Statistical Manual of Mental Disorders):

- 2 weeks of at least 5 of the following:
  - Depressed mood\*\*
  - Loss of interest in activities/pleasure (anhedonia)\*\*
  - Fatigue/low energy
  - Changes in weight (gain or loss)
  - Sleep changes (insomnia or excessive sleep)
  - Motor slowness or agitation
  - Feelings of worthlessness/guilt
  - Decreased concentration
  - Thoughts of death/suicide
- Symptoms must cause significant distress or impairment

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## Risk Factors for Depression

Female gender  
Young onset of motor symptoms (<40 years old)  
Severe cognitive impairment  
Other medical problems (e.g., heart disease, arthritis, diabetes)  
Family history of depression

Baquero, M, Martin, N. Depressive symptoms in neurodegenerative diseases. World J Clin Cases. 2015;3(8):682-693

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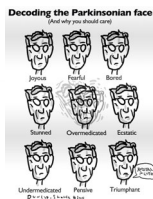
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## Difficulties in diagnosing depression in PD

Many symptoms of depression overlap with symptoms of PD  
Reduced facial expression in PD makes it more difficult to express emotion  
Depression in PD often involves frequent, shorter changes in mood versus a constant state of sadness daily  
Many people with Parkinson's do not recognize they have a mood problem or are unable to explain symptoms



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### What is Apathy?

A lack of motivation, failure to initiate goal-directed behavior

Examples of apathetic behavior

- Difficulty initiating activities
- Needing prompting or reminding
- Low activity levels
- Lack of effort/reduced productivity
- Not completing tasks that were started
- Not concerned about issues that used to be important

Often seen with depression, but commonly can present as pure apathy

Category	Percentage
Apathy	51%
Depression	26%
Pure apathy	29%
Pure depression	4%
Apathy and depression (Overlap)	22%

Smith-Baron, L. et al. Apathy and depression: distinct factors in Parkinson's disease. *Front Neurology* 10: 201 (2019). doi:10.3389/fnol.2019.00201

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### Depression vs. Apathy

<p><b>Depression – Mood disorder</b></p> <ul style="list-style-type: none"> <li>Sadness</li> <li>Worthlessness</li> <li>Guilt</li> <li>Hopelessness</li> <li>Helplessness</li> <li>Pessimism</li> <li>Suicidal ideation</li> </ul>	<p><b>Apathy – Motivation disorder</b></p> <ul style="list-style-type: none"> <li>Decreased initiative</li> <li>Less interest in starting new activities</li> <li>Less interest in the world</li> <li>Emotional indifference</li> <li>Decreased emotional reactivity</li> </ul>
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**Overlap**

- Anhedonia (inability to feel pleasure)
- Less interest in usual activities
- Increased slowness

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## Why is Apathy Harmful?

Reduced daily functioning and activity  
Increased caregiver stress/distress  
Poor treatment compliance  
Worse rehabilitation outcome

## Higher Morbidity and Mortality

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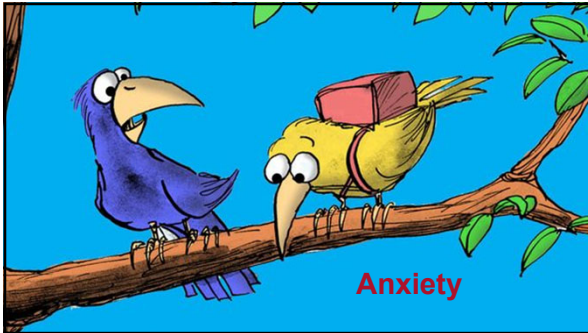
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## What is an Anxiety Disorder?

Feelings of constant worry or nervousness that are present more than what would be considered normal and result in a significant impact on daily functioning and quality of life

An infographic comparing Anxiety and Anxiety Disorders. It features a central purple heart containing a brain illustration. To the left, under the heading "ANXIETY", are several text boxes describing it as a normal reaction to stress, triggered by specific stressors, having a start and end point, being helpful or motivational, lessening in stressful situations, and being a response to toxic situations. To the right, under the heading "ANXIETY DISORDERS", are text boxes describing it as an intense or disproportionate emotional response, ongoing and lasting weeks or months, interfering with daily life, and having physical symptoms like sweating, trembling, and a racing heart. A URL is provided at the bottom: <http://invermeresummitouthcentre.org/anxiety/>

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## What is an Anxiety Disorder?

Common manifestations:

- Excessive worry
- Avoidance
- Seeking reassurance
- Easily upset
- Insomnia
- Eating disorders
- Physical complaints
- Panic attacks

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## What is an Anxiety Disorder?

The 3 most common types of anxiety in PD are

- Generalized anxiety disorder
- Social anxiety
- Anxiety/panic attacks

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## How does anxiety cause problems?

Exacerbates motor symptoms of PD  
Impaired concentration and memory  
Interferes with sleep  
Medication side effects  
Friction with friends and family

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## Suicide

Approximately 30% of PD patients have had thoughts about suicide  
Danish study found that people diagnosed with PD were 2.2x more likely to commit suicide than the general population

When you or a loved one has suicidal thoughts:

- Use your social support network – find a support group, stay socially engaged
- Seek professional help: psychiatrist, psychologist, neurologist, social worker
- Prioritize self-care
- Use emergency support services. Call 911 there is immediate need

Erlangsen A, et al. Association Between Neurological Disorders and Death by Suicide in Denmark. JAMA. 2020;323(5):444-454.  
Lee T, et al. Increased suicide risk and clinical correlates of suicide among patients with Parkinson's disease. Parkinsonism Relat Disord. 2016 Nov;32:102-107.

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## Suicide Resources

### National Suicide Prevention Lifeline

**1-800-273-8255**  
The Lifeline provides 24-hour-a-day, free and confidential support for people in distress, prevention and crisis resources for you or your loved ones and best practices for professionals  
<https://suicidepreventionlifeline.org/>

### The Substance Abuse and Mental Health Services Administration National Helpline

**800-662-HELP (4357)**  
Confidential, free, 24-hour-a-day, 365-day-a-year, information service, in English and Spanish, for individuals and family members facing mental and/or substance use disorders  
<https://www.samhsa.gov/>

### Crisis Text Line

**Text HOME to 741741**  
Crisis Text Line provides free, 24/7 mental health support via text message  
<https://www.crisistextline.org/>

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## How can we treat mental health?



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## Medications for Depression

Very few controlled trials of medications for depression in PD

### First line therapies:

- SSRIs: citalopram (Celexa), paroxetine (Paxil), sertraline (Zoloft), others

### Second line therapies

- SNRIs: venlafaxine (Effexor), duloxetine (Cymbalta)
- TCAs: amitriptyline (Elavil), nortriptyline (Pamelor)
- MAOIs/COMTs: selegiline (Eldepryl), rasagiline (Azilect), entacapone
- \*\*Antipsychotics: quetiapine (Seroquel), clozapine (Clozaril)
- Others: mirtazapine (Remeron), trazodone (Desyrel), bupropion (Wellbutrin)

Bomang-Layno E, Fialho L, Murray AN, Hindlecock S. Antidepressive treatments for Parkinson's disease: a systematic review and meta-analysis. *Parkinsonism Relat Disord.* 2015;21(9):833.

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## Medications for Anxiety

No controlled trials specifically for anxiety in PD

### First line therapies

- SSRIs & SNRIs

### Second line therapies

- TCAs
- Others: buspirone (Buspar), gabapentin (Neurontin), pregabalin (Lyrica)
- Antipsychotics: quetiapine (Seroquel), clozapine (Clozaril)
- Benzodiazepines: clonazepam (Klonopin), lorazepam (Ativan), diazepam (Valium)

Seppi K, Ray Chaudhuri K, Coelho M, et al. Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review. *MovDisord* 2019;34(5):765.

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## Medications for Apathy

Currently no approved treatments specifically for apathy

### First line

- Optimizing Parkinson's medication regimen
  - Carbidopa/levodopa
  - Ropinirole (Requip), pramipexole (Mirapex), rotigotine (Neupro)

### Second line

- Cholinesterase inhibitors: donepezil (Aricept), rivastigmine (Exelon)
- SNRIs
- Stimulants: Methylphenidate

Mohs B, et al. Diagnosis, treatment and management of apathy in Parkinson's disease: a scoping review. *BMI Open.* 2020 Sep 9;1(09)

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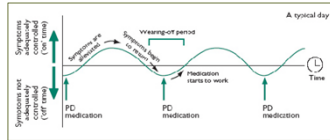
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## Special Considerations for PD

As PD progresses, fluctuations in symptoms can occur with changing levels of medication in your body  
 Not only motor symptoms! Mental health can fluctuate, as well  
 Adjustment of PD medications may be required for optimal treatment



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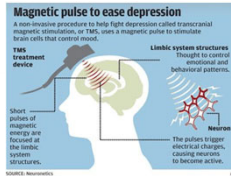
## Other Medical Interventions

Deep brain stimulation (DBS)  
 Electroconvulsive therapy (ECT)

- Longstanding therapy for severe, intractable depression. No trials specifically for PD
- Safe and effective – may cause temporary confusion/delirium
- Incompatible with DBS

Transcranial magnetic stimulation (TMS)

- Recently FDA-approved for depression
- Under investigation for effects on mood and motor symptoms in PD



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## Psychotherapy

Cognitive behavioral therapy (CBT)

- A therapy technique aimed at changing negative thinking and behavior patterns. Helps establishing coping techniques and thinking positively
- The most studied intervention for depression and anxiety in PD. Shown to be at least as effective than use of medication alone

Resource to find a local therapist: [psychologytoday.com](http://psychologytoday.com)



Dobbins RD, et al. Cognitive-behavioral therapy for depression in Parkinson's disease: a randomized, controlled trial. Am J Psychiatry. 2011;168(10):1066-1074

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## Exercise

Exercise improves physical and psychiatric symptoms of Parkinson's Disease

Examples:

- Walking
- Stretching
- Yoga
- Tai-Chi
- Lifting weights
- Whatever gets you moving!



Wu PL, Lee M, Huang TT. Effectiveness of physical activity on patients with depression and Parkinson's disease: a systematic review. PLoS One. 2017;12(7)

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## Complementary and Non-Conventional Therapies

- Light therapy
- Relaxation techniques
- Massage therapy
- Acupuncture
- Aromatherapy
- Meditation
- Music therapy



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## Social Support

Your network of people that you can turn to in times of need (and vice-versa)

Family, friends, work, support group, religious community, etc.

Helps build healthy habits, cope with stress, and improve motivation

Types of social support

- Emotional support
- Instrumental support – physical support (e.g., hot meal, rides)
- Informational support – guidance, advice, mentoring



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## Support Groups

Helpful for both PD patients and caregivers!  
Information on local support groups can be found at:

- [www.ParkinsonsNebraska.org](http://www.ParkinsonsNebraska.org) 
- [www.Parkinson.org](http://www.Parkinson.org) 
- [www.APDAParkinson.org](http://www.APDAParkinson.org) 
- [www.MichaelJFox.org](http://www.MichaelJFox.org) 

Also, many on-line support groups

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## Take-Home Points

- Depression, anxiety, and apathy are very common in PD
- Not a personal failing/weakness, it is a part of PD and a chemical imbalance in the brain
- Affects quality of life as much as motor symptoms
- Depression increases risk of suicide
- Underdiagnosed: recognition of the symptoms is key!
- Can be difficult to recognize, they mimic motor symptoms of PD and may present in different patterns than non-PD patients
- Discuss your mental health with your doctor annually. If possible, bring along a family member or friend

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## Exercise in Parkinson's Disease: Importance of Aerobic, Skill Based and Dual Task Exercise



*Presented by:*  
Cheri Prince, PT, DPT

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## Exercise in Parkinson Disease

Today's Discussion:

- Why is exercise important in Parkinson Disease and what can it do for you?
- How do we need to exercise to achieve these outcomes?
- Role of Aerobic, Skill Based and Dual task Exercise



FIRST UP.....

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*Exercise is  
Medicine!!*



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## Benefits of EXERCISE

Exercise is important because it improves **BRAIN FUNCTION!**

- Improved heart and lung function= improved motor function, attention and cognitive speed
- Improves attention, executive function and memory in healthy older adults
- Improves memory, executive function and balance

Physical activity such as exercise increases brain derived neurotrophic factors (BDNF), therefore promoting neuroplasticity (regeneration of neurons/neuronal pathways) within the brain. This promotion of neuroplasticity provides benefits such as improved motor functioning, brain functioning, and slowing of the progression of PD.

Brain- Derived Neurotrophic Factors (BDNF): A protein in the brain that is in charge of creating and controlling the growth of neurons.

Levels of BDNF are decreased in many neurodegenerative diseases such as Parkinson's Disease

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## Exercise in Parkinson Disease— General Guidelines

**Parkinson's Exercise Recommendations**

**Exercise and physical activity can improve many motor and non-motor Parkinson's symptoms.**

Aerobic Activity	Strength Training	Balance, Agility & Multitasking	Stretching
<ul style="list-style-type: none"><li>• Improves cardiovascular health</li><li>• Improves lung capacity</li><li>• Improves motor function</li><li>• Improves attention and cognitive speed</li><li>• Improves memory, executive function and balance</li></ul>	<ul style="list-style-type: none"><li>• Improves muscle strength</li><li>• Improves balance</li><li>• Improves posture</li><li>• Improves motor function</li><li>• Improves attention and cognitive speed</li><li>• Improves memory, executive function and balance</li></ul>	<ul style="list-style-type: none"><li>• Improves balance</li><li>• Improves posture</li><li>• Improves motor function</li><li>• Improves attention and cognitive speed</li><li>• Improves memory, executive function and balance</li></ul>	<ul style="list-style-type: none"><li>• Improves flexibility</li><li>• Improves posture</li><li>• Improves motor function</li><li>• Improves attention and cognitive speed</li><li>• Improves memory, executive function and balance</li></ul>

Source: [www.parkinson.org](http://www.parkinson.org)

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HOW we Exercise is KEY!! We NEED to Achieve Neuroplasticity!



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## Research/Exercise Recommendations

**NEUROPLASTICITY!!!**  
 • Our brains CAN Change! BUT,  
 It matters HOW we exercise!

- We achieve neuroplasticity by:
  - Physical Effort - work hard
  - Attentional Focus – self monitor
  - Cognitive Engagement – like it
    - Based upon Parkinson's Well Recovery (PWR!) concepts



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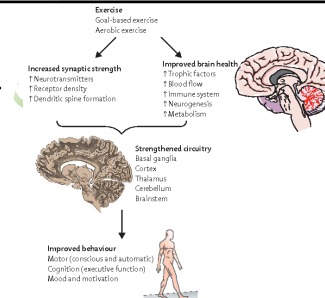
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## Research/Exercise Recommendations



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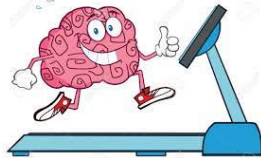
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## Aerobic Exercise: Key Components

- **Duration:**
  - As little as 10 min has shown benefit
  - Most studies do 45-60 min per session
  - 150 min /week minimum
- **Intensity:**
  - 60-80% of HR Max
  - 8/10 RPE
  - Start with what you can do, use intervals
- **Frequency:**
  - Most studies show at least 3-4 days a week



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## Aerobic Exercise: Key Components

- Heart Rate Calculations and use of Heart Monitors
  - Max HR= 220-age, then 60-80% of that
  - May need to use RPE vs Heart rate monitor
  - Using Heart rate Monitor or RPE increases ATTENTION to how hard you are working – and this alone helps you work harder!
- Safety Considerations
  - May have altered heart rate response in PD as well as due to medications
  - Functional level may dictate safest aerobic equipment, i.e. seated vs standing



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## Rating Of Perceived Exertion Scale (RPE)

RPE SCALE	SPORT DESCRIPTION	ACTIVITY LEVEL	HEART RATE
10	Very heavy effort, such as competitive sports	Very heavy	170-190
9	Heavy effort, such as competitive sports	Heavy	155-170
8	Very hard effort, such as competitive sports	Very hard	140-155
7	Hard effort, such as competitive sports	Hard	125-140
6	Some effort, such as competitive sports	Some	110-125
5	Light effort, such as competitive sports	Light	95-110
4	Very light effort, such as competitive sports	Very light	80-95
3	Light effort, such as competitive sports	Light	65-80
2	Very light effort, such as competitive sports	Very light	50-65
1	Very light effort, such as competitive sports	Very light	35-50
0	No effort, such as competitive sports	No effort	20-35

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## Skill Based Training: Key Components

- Working on Parkinson's specific skills (posture, balance, trunk rotation, stepping)
- Mobility Practice (moving in each position)
- Transitions between positions
- Adding Strengthening, extra balance and stretching!

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## Skill Based Training: Key Components

**HOW DO WE WORK ON IT?**

- With skilled exercise we can work on all these skills and directly counteract the effects of Parkinson's
- **Spontaneous** - Movement flow
- **Bradykinesia** - Work on Movement speed
- **Rigidity** - Muscle flexibility, activating the right muscles!
- **Functional Mobility** - Practice the movements you need for life!
- **Posture** - (PWR) (S) in all positions and add advanced challenges
- **Balancing** - Practice 10 "tricks" (stable, in focus - with the best walking you can already do)
- **Walking** - Practice it!
- **Balance** - Practice it!
- **Coordination** - Practice activities with specific timing, upper and lower body coordination
- **Strength** - we do functional strengthening - lifting our own body weight in all positions, and add weights!
- **Flexibility** - Stretch - WITH MOVEMENTS!

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## Treating the Whole Person: Dual Task Training!

### Is Dual Tasking Better than Physical Exercise Alone?

Zhu et al (2016) combined data from 20 randomized controlled studies with 2667 participants and found:

- Dual Tasking improved cognition greater than no intervention
- Dual Tasking improved cognition better than physical exercise by itself
- Dual Tasking improves cognition more in older participants
- Dual Tasking effects appear to last longer than single tasking effects

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### Purpose of using Dual Task approach

- Our daily life demands us to dual-task such as:
  - Getting dressed and watching the news
  - Drinking a cup of coffee and reading the newspaper
  - Walking, carrying a bag, and talking to a friend or spouse
- Our ability to dual task as we age declines due to decreased motor and cognitive abilities as well as executive function decline



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**Dual Task Exercise: Key Components**

- Dual Tasking is recommended for PwPD early after diagnosis
- There are many way to incorporate Dual task training in your exercise including simple things like: counting repetitions in various ways, naming items in a category, keeping your pace while completing a cognitive activity or even while voicing, spelling etc
- Some types of exercise lend themselves to being Dual Task such as Boxing, Dancing but Dual Task should be incorporated into your Parkinson's Exercise program
- Dual Task is FUN, more complex/difficult, requires increased attention – all components needed for NEUROPLASTICITY!
- Goal is to practice dual tasking until it becomes more automatic, and we can keep moving well even when distracted by other things...
- Safe, efficient mobility REQUIRES COGNITION!

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**HOW TO START?**  
*Don't do it alone!*

- Exercise IS Medicine and you need someone to help prescribe it for you!
- If you haven't had PARKINSONS SPECIFIC Physical, Occupational and Speech Therapy, YOU NEED TO!
- You should partner with an experienced therapist to help you design a program specific to you that meets the requirements to ACHIEVE NEUROPLASTICITY!
- You can GET BETTER!
- You can CHANGE YOUR COURSE of Parkinsons!
- GET STARTED NOW!

Don't look for someone who will solve all your problems. Look for someone who won't let you face them alone.

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# Research Updates in Parkinson's Disease

**Erin L. Smith**  
Assistant Professor  
Movement Disorders Division



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## “When will we find a cure?”



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## Foundations of Current Research

**Disease-Modifying** Treatments (DMTs)

- Targeting the Pathology of Parkinson's
- Accumulation of alpha-synuclein protein in the brain

Targeting **Genetic** Types of Parkinson's

Finding Ways to **Detect** Parkinson's Even Before it Starts

Treating Symptoms to **Improve Long-Term Outcomes**



Parkinson's Foundation Better Lives. Together.

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## Today's Topics

1. Developing Therapeutics
2. Genetic Discoveries
3. Advancing Biomarkers
4. Databases
5. UNMC Studies
6. How to Get Involved



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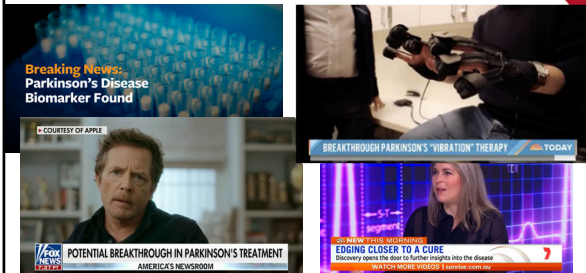
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## News-Worthy Breakthroughs



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## Other Areas (Not Covered Today)

- Surgical and advanced therapy updates
    - Deep Brain Stimulation (DBS)
    - Focused Ultrasound
    - Levodopa Infusions (Intestinal & Subcutaneous Pumps)
  - Symptom-specific treatments
    - Cognitive Decline
    - Freezing of Gait
    - Sleep
  - Nutrition and the Gut Biome
  - Quality improvement & outcomes-based projects
    - Hospitalization metrics
    - Fall prevention
  - Therapy comparisons
    - Exercise
- ...and more!

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## Developing Therapeutics

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## Types of Therapeutics

### Disease Modifying Therapies

- **Slow** or **halt** the progression of neuron dysfunction / neuron death (i.e. therapies that prevent further neurons from being impacted by the disease)

### Symptomatic Therapies

- **Improve** / **restore function** for the patient (i.e. therapies that improve motor function, cognitive function, etc)

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Journal of Parkinson's Disease 13 (2023) 427–439  
DOI 10.3233/JPD-239901  
IOS Press 427

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### Clinical Trial Highlights

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## Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2023 Update

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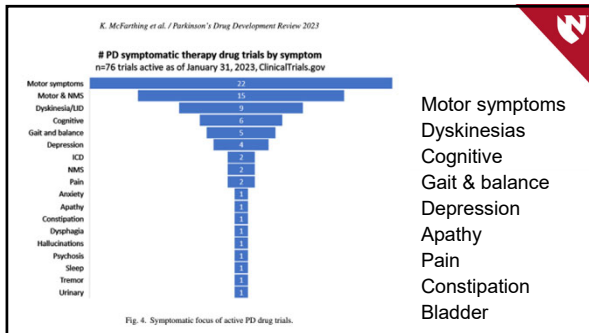
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### Mechanisms of DMTs

- Alpha synuclein targets
- Glucagon-like peptide (GLP-1) agonists
- Antioxidants
- Anti-inflammatories
- Gene-specific
  - GBA
  - LRRK2

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### Quick Review: Pathological Processes in PD

#### Hypothesis of alpha-synuclein protein

Misfolds while being made  
→ Builds up in the brain and becomes **toxic**  
→ Leading to **dopamine cell death** and Parkinson's Disease

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## Alpha Synuclein Therapies

**Goal:**  
Stop misfolding and aggregation

Sheila M. Fleming, Ashley Davis, Emily Simons, Targeting alpha-synuclein via the immune system in Parkinson's disease. Current vaccine therapies. Neuropharmacology, Volume 202, 2022, 108870. Nature Reviews | Drug Discovery

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## Alpha Synuclein Therapies

- Give or create **antibodies against**  $\alpha$ -synuclein
  - Through IV
  - As a vaccine
- Block  $\alpha$ -synuclein
- Break misfolded  $\alpha$ -synuclein

**Studies ongoing**  
**Seem well-tolerated so far**  
*Caveat: Not every PD has an alpha-synuclein problem*

Front. Mol. Neurosci., 05 December 2019 | doi: 10.3389/fnmol.2019.00209 | Volume 12 - 2019 | https://doi.org/10.3389/fnmol.2019.00209

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## Diabetes Medications: GLP-1 Agonists

- Study suggested 30% risk of PD in pts with type 2 diabetes
- GLP-1 agonists = used to trigger insulin release
  - Used for diabetes and weight loss
  - Receptors also present in the brain

**GLP-1 agonists may block brain's "inflammatory response"**

**GLP-1 Agonists**

- Pancreas:** Insulin, Glucagon
- Stomach:** Gastrin, Ghrelin, Motilin
- Brain:** Ghrelin, Orexin

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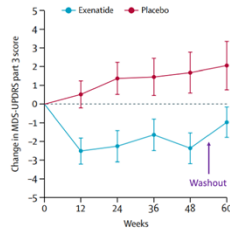
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## Diabetes Medications: GLP-1 Agonists

### Exenatide

- 2017 Phase 2 Trial
- Hopeful results for slowing PD down
- More studies ongoing in Norway and South Korea



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## What about those Parkinson's Gloves ???

Featured on Good Morning America (December 2022)

Stanford Medicine  
Peter Tass Labs



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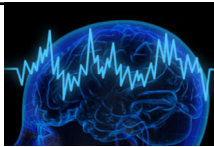
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## The Parkinson's Gloves

- 2021 Study (Tass)
  - 6 participants helped tremors, stiffness
- Vibration in fingertips
  - "Resets" abhorrent electrical activity in the brain
  - Similar tools tested for swallowing and freezing of gait
- FDA approval may not be for a few years



**Status:**  
NOT currently recruiting.  
Website survey to sign up for future studies.

Similar glove study recruiting in Eugene, Oregon

Tass PA. Vibratile coordinated reset stimulation for the treatment of Parkinson's disease. *Neural Regen Res*. 2022 Jul(7):1495-1497. doi: 10.4103/1673-274.320201. PMID: 34914531; PMCID: PMC9377398.

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## Can a Cough Medicine Cure PD?

### Ambroxol

- Cough medicine used on 50+ countries
  - NOT FDA approved in the US
- Enzyme tied to specific genetic mutation (GBA)
  - Clears alpha-synuclein



Mullin S, Smith L, Lee K, et al. Ambroxol for the Treatment of Patients With Parkinson Disease With and Without Glucosylated Glutamate Mutations: A Nonrandomized, Noncontrolled Trial. *JAMA Neurol*. 2020;77(4):427-434. doi:10.1001/jamaneurol.2019.4611

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## Can a Cough Medicine Cure PD?

### Ambroxol

- JAMA (2020)
- 18 patients
  - Safe and well-tolerated

- ASPro-PD
- 2023 Phase III Clinical Trial Enrolling in the UK
  - Patients with and without the GBA genetic mutation



Mullin S, Smith L, Lee K, et al. Ambroxol for the Treatment of Patients With Parkinson Disease With and Without Glucosylated Glutamate Mutations: A Nonrandomized, Noncontrolled Trial. *JAMA Neurol*. 2020;77(4):427-434. doi:10.1001/jamaneurol.2019.4611

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## Fibroblast Growth Factor 1 (FGF1)

### Hypothesis:

Disrupting small blood vessels in the brain causes damage to dopamine-producing cells that are dying off in Parkinson's

FGF-1 aims to **stimulate new blood vessel growth** to slow down PD or even reverse it



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## Fibroblast Growth Factor 1 (FGF1)

- 2022 study in Bahamas
- Gave FGF-1 through nasal route



December 2022 Update:  
Drug was safe and well-tolerated

ZHITTYA GENESIS MEDICINE INC.



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## Marijuana

- 2023 Parkinsonism & Related Disorders
  - Retrospective review
  - 152 patients
    1. Treatment Group (Medical Cannabis)
    2. Control Group
  - 2008-2022

LONG-TERM SAFETY OF MEDICAL CANNABIS IN PARKINSON'S DISEASE:



A RETROSPECTIVE CASE-CONTROL STUDY

Goldberg T, Raftich Y, Yager D, Fay-Kamron T, Hossain-Bar S, Anis B. Long-term safety of medical cannabis in Parkinson's disease: A retrospective case-control study. *Parkinsonism Relat Disord.* 2023 Jul;112:105498. doi: 10.1016/j.parkre.2023.105498. Epub 2023 May 6. PMID: 37211466.

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## Marijuana

### RESULTS

#### MOTOR OUTCOMES

LEDD H&Y

There were no significant differences between the MC and the control groups for LEDD or H&Y stage progression ( $p=0.90$ ,  $0.77$ , respectively).

#### NON-MOTOR OUTCOMES

Based on self-reports by patients to their treating physicians, a Kaplan-Meier analysis revealed no evidence of relative worsening in psychotic, depressive, or cognitive symptoms over time in the MC-treated group ( $p=0.16$ - $0.50$ ).

- **No effect** on motor symptoms or disease progression (good or bad)
- Did not worsen psychiatric or cognitive symptoms

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## Stem Cells for PD

Unfortunately, symptomatic only

- Not being used as a cure
- Replaces dopamine, does not prevent spread of disease

Logic:

- Dopamine cells are dying, let's replace them

Trials done in 1980s and 1990s with mixed effects

- Some benefited, some had no effect, and some worsened due to uncontrollable dyskinesias

Trying again with argument that we have better quality stem cells and surgical techniques

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## Sargramostim (Leukine)

Open Access

Translational Neurodegeneration

RESEARCH

Open Access

An open-label multiyear study of sargramostim-treated Parkinson's disease patients examining drug safety, tolerability, and immune biomarkers from limited case numbers

Katherine E. Olson<sup>1</sup>, Ma M. Abdelmassih<sup>1</sup>, Krista L. Nannenga<sup>1</sup>, Yeman Lu<sup>1</sup>, Helen Olszewski<sup>1</sup>, Pamela Santamaria<sup>1</sup>, J. Lee Molloy<sup>1</sup>, and Howard E. Gendelman<sup>1</sup>

Olson, K.E., Abdelmassih, M.M., Nannenga, K.L., et al. An open-label multiyear study of sargramostim-treated Parkinson's disease patients examining drug safety, tolerability, and immune biomarkers from limited case numbers. *Transl Neurodegeneration* 12, 26 (2023). <https://doi.org/10.1186/s41234-023-00361-1>

### UNMC Study

- Anti-inflammatory medication
- Given as skin injection
- 5 patients over 33 months
- Motor scores remained stable

Could this slow down PD progression?

### Future Directions:

Need a larger number with control group

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## Genetic Discoveries

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**Genetics & PD**

- **Age** is still our greatest known PD risk factor
- We've identified many **environmental risks (or protectors)**
  - Head injuries
  - Smoking
  - Coffee
  - Medications
- **Genetic** links to PD are rapidly expanding
  - 10-15% of PD pts have a genetic variant
  - Genetic variants may contribute to 25% PD risk
    - (+) Family History = 3-4x risk of developing PD

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**Why do genes in PD matter?**

*→ It's all treated the same anyway, right??*

Knowing genetic variants in PD can help us:

1. Validate theories for what causes PD
2. Customize predictions for disease progression
3. Guide clinical trial design
4. Individualize treatment for specific patients

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**Two Main Genetic Mutations**

<p><b>Leucine-rich repeat kinase 2 (LRRK2):</b></p> <ul style="list-style-type: none"> <li>• Regulates alpha-synuclein protein</li> <li>• Role in removing waste from the cell</li> </ul>	<p><b>Glucocerebrosidase (GBA):</b></p> <p>Works in the cell to break down waste</p> <p><b>Example: Ambroxol</b></p> <ul style="list-style-type: none"> <li>• Approved in Europe as a cold medicine</li> <li>• Improves function of GBA in brain cells (neurons)</li> </ul>
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## Advancing Biomarkers

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## What is a Biomarker?

*“A measurable substance in an organism whose presence is indicative of some phenomenon such as disease, infection, or environmental exposure.”*

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## How Can We Use Biomarkers?

*Clinical diagnosis still only has 80-90% accurate*

Biomarkers can be used to:

- **Detect** PD before it starts (“Prodromal”)
- **Confirm** or support your diagnosis
- **Guide** disease disease or prognosis
- **Differentiate** between clinically similar diseases
- **Identify** best candidates for clinical trials and specific therapies

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**News-Worthy Biomarkers**



**Breaking News: Parkinson's Disease Biomarker Found**

# Omaha World-Herald

**CHI, Creighton researchers seek marker for Parkinson's blood test**

Julia Anderson May 26, 2023 Updated May 27, 2023

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Assessment of heterogeneity among participants in the Parkinson's Progression Markers Initiative cohort using  $\alpha$ -synuclein seed amplification: a cross-sectional study

Andrew Sidranski<sup>1</sup>, Luis Sanchez-Maranin<sup>2</sup>, David F. Cook-Lefevre<sup>3</sup>, Carly M. Farris<sup>4</sup>, Yikrazoua Ma<sup>5</sup>, Pratik A. Datta<sup>6</sup>, Hsin Hsiang<sup>7</sup>, Roy N. Maitland<sup>8</sup>, Lara M. Chalfont<sup>9</sup>, Tahira Farooq<sup>10</sup>, Douglas Galasko<sup>11</sup>, Karl Kieburtz<sup>12</sup>, Rajendra Mehta<sup>13</sup>, Erik M. Reichenauer<sup>14</sup>, Karl Mattner<sup>15</sup>, Florian Jahn<sup>16</sup>, Sabya<sup>17</sup>, Deepa Sivadas<sup>18</sup>, Caroline M. Tanner<sup>19</sup>, David Wilkinson<sup>20</sup>, Aleksandra Vekrellis<sup>21</sup>, Seung-Ho Choi<sup>22</sup>, Scott Kozlowski<sup>23</sup>, Chulhee Choe<sup>24</sup>, Ganga Choudhury<sup>25</sup>, Mark Francis<sup>26</sup>, Luis M. A. Oliveira<sup>27</sup>, Sumanth J. Matturi<sup>28</sup>, Todd Stone<sup>29</sup>, Kenneth Marek<sup>30</sup>, Claudio Soto, on behalf of the Parkinson's Progression Markers Initiative<sup>31</sup>

**Breaking News: Parkinson's Disease Biomarker Found**

**Lancet (May 2023)**

- 1123 subjects from PD Progression Markers Initiative database (PPMI)
  - Symptomatic, Pre-PD, Genetic Carriers, Healthy Controls
  - Consented to a **spinal tap**



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**Lancet Article Results**



**Goal** = Detect Alpha Synuclein in the Spinal Fluid (CSF)

**87.7% of those reporting PD symptoms had a positive test**  
("Rule In PD")

**96.3% of Healthy Controls had a negative test**  
("Rule Out PD")

Even better for PD patients with change in sense of smell:  
**Picked up 98.6% of cases**

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**CHI, Creighton researchers seek marker for Parkinson's blood test**

CHI, Creighton researchers seek marker for Parkinson's blood test

Looking for a "messenger" in the blood that passes on bad alpha synuclein proteins

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**CHI, Creighton researchers seek marker for Parkinson's blood test**

CHI, Creighton researchers seek marker for Parkinson's blood test

Currently Enrolling:

- 10 Parkinson's patients already participating
- Seeking at least 25 Parkinson's patients and 50 controls

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**Databases**

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**PPMI**

- Michael J. Fox Foundation
- No PD diagnosis needed
- Fill out info online
  - Local: KC, Chicago, Denver
- Data accessible upon request



**Parkinson's Progression Markers Initiative**

**PPMI Clinical**  
 Enhance understanding of early treatment of PD  
 N=4,000

**PPMI Remote**  
 Remote study activities using small test, genotyping, digital sensor technologies  
 N=50,000

**PPMI Online**  
 Online assessments using patient reported outcomes  
 N=100,000

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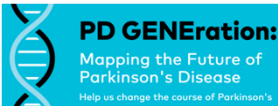
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**PD GENERation**

- Michael J. Fox Foundation
- Need PD diagnosis
- In-person or remote options

1. Screening visit (15-30 min)
2. PD GENERation appointment (2 hours)
  1. Clinical assessments and cheek swab
3. Genetic counselor consultation (15-30 min)
  1. Receive and review test results



**PD GENERation:**  
 Mapping the Future of Parkinson's Disease  
 Help us change the course of Parkinson's

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**“How Do I Get Involved?”**

Visit [clinicaltrials.gov](https://clinicaltrials.gov)

Call or email the **UNMC Research Advocate Office**  
[unmcrsa@unmc.edu](mailto:unmcrsa@unmc.edu)  
 402-559-6941

Reference the **UNMC Clinical Trial Database:**  
[https://net.unmc.edu/ctsearch/index\\_unmc.php](https://net.unmc.edu/ctsearch/index_unmc.php)

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## Useful Websites

- [www.pdtrialtracker.info](http://www.pdtrialtracker.info)
- [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
- [www.apdaparkinson.org](http://www.apdaparkinson.org)
- [www.michaeljfox.org](http://www.michaeljfox.org)
- World Health Organization (WHO) Registry

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## References

Included in specific slides  
Comprehensive list available upon request

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**Advanced Treatment: Deep Brain Stimulation & Focused Ultrasound**

Miguel Situ-Kcomt, MD  
Assistant Professor  
Department of Neurological Sciences



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**Disclosures**

None



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**When should it be discussed?**

Advanced Treatments should be discussed since **the first visit!**



- Keeps patients informed about their options.
- Emphasizes shared decision-making.
- Allows for future planning

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## What parts of the brain are targeted?

### Subthalamic Nucleus (STN)

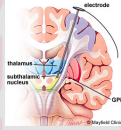
- Decreases levodopa dose
- Improves motor fluctuations

### Globus Pallidus Pars Interna (GPI)

- Improves dystonia symptoms
- Improves motor fluctuations
- Less programming sessions

### Ventral Interomedial Thalamus (ViM)

- Improves tremor
- Less chance of worsening psychiatric diseases



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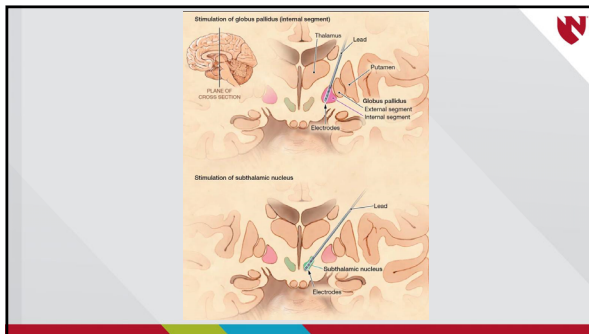
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## Deep Brain Stimulation (DBS)

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### What is it?

Surgical procedure whereby electrodes are implanted in specific brain targets to provide symptomatic benefit.

**It is not a cure**

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### How do we evaluate candidacy?

- Discuss interest with patient.
- Schedule inpatient ON/OFF testing
- Schedule a Brain MRI with specific sequences
- Perform a neuropsychological evaluation

Discuss patient's results of steps 2, 3, 4 in a multidisciplinary conference with neurosurgery and neuropsychology.

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### What is inpatient ON/OFF testing?

- Stop Parkinson's medications (levodopa, dopamine agonists, etc.) the night before.
- Stay in the hospital overnight.
- Evaluation of motor symptoms in the morning while OFF.
- 1.5x-2x the usual dose of levodopa is given.
- Evaluation of motor symptoms when ON.

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### How to know if it's right for you?

-  Excellent response to PD medications
-  Intolerable PD medication side effects (nausea, vomiting, dyskinesias)
-  High dose burden (too many pills!)
-  Unbearable motor fluctuations (medication runs out too fast)

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### How to know if it's not for you?

-  Decompensated psychiatric conditions
-  Surgical high risk (evaluated by surgeon or anesthesia)
-  Structural brain lesions where intended targets are (tumors, strokes, malformations)
-  Severe dementia

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### After surgery, what's next?

- Initial programming session – may take several hours.
- Subsequent sessions to fine tune appropriate response.
- Will medications be stopped?
  - Realistically\*, medications will always be needed, though burden may decrease.

**\* EACH PATIENT IS DIFFERENT**

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# Focused Ultrasound (FUS)

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## What is it?

Non-surgical technique

MRI guided high-frequency waves create a lesion in a specific target of the brain to provide symptomatic benefit.



**It is not a cure**

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**THIS IS STILL BEING RESEARCHED FOR PARKINSON'S DISEASE**

**UNMC CURRENTLY DOES NOT PERFORM THIS PROCEDURE.**

**YOU WOULD BE REFERRED TO ANOTHER FACILITY**

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### How to know if it's right for you?

**Same indications as DBS but do not want to/cannot pursue invasive surgery**

- Excellent response to PD medications
- Intolerable PD medication side effects (nausea, vomiting, dyskinesias)
- High dose burden (too many pills!)
- Unbearable motor fluctuations (medication runs out too fast)

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### How to know if it's not for you?

- Procedural high risk (evaluated by surgeon or anesthesia)
- Structural brain lesions where intended targets are (tumors, strokes, malformations)
- Unable to have an MRI

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### Comparing procedures

Deep Brain Stimulation	Focused Ultrasound
Invasive procedure	Non-invasive procedure
Hardware implanted	No hardware implanted
Overnight stay	Can leave in the same day
Reversible process	Irreversible Process
Can be adjusted over time	Cannot be readjusted
Longer-term benefits	Unilateral procedure for most cases*
	Undetermined long-term benefits

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