



Women and Parkinson's Disease: Addressing Differences and Unmet Needs

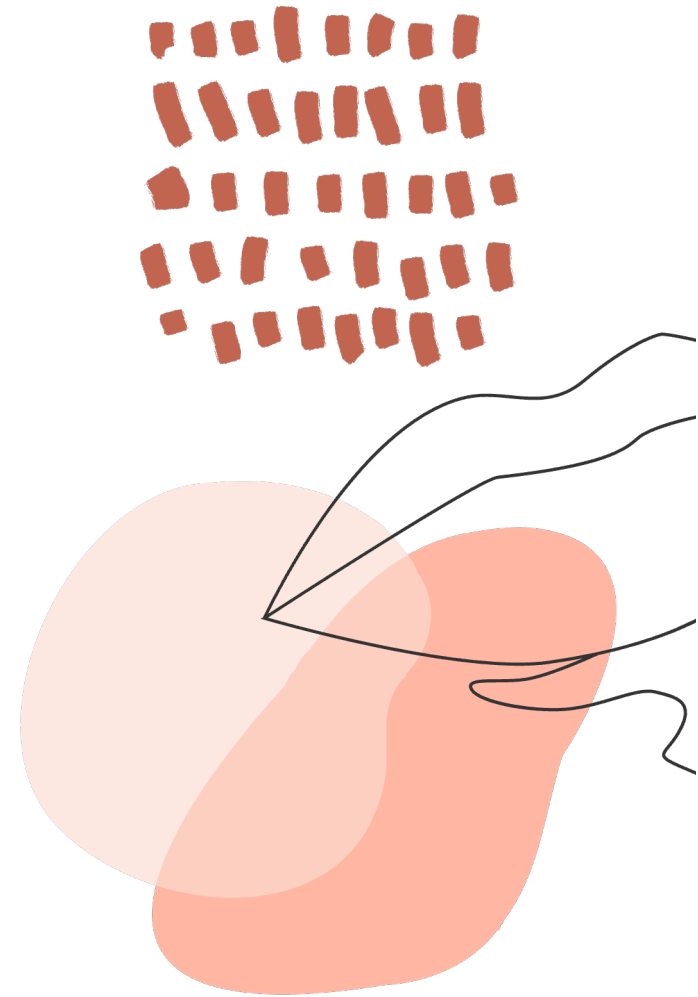
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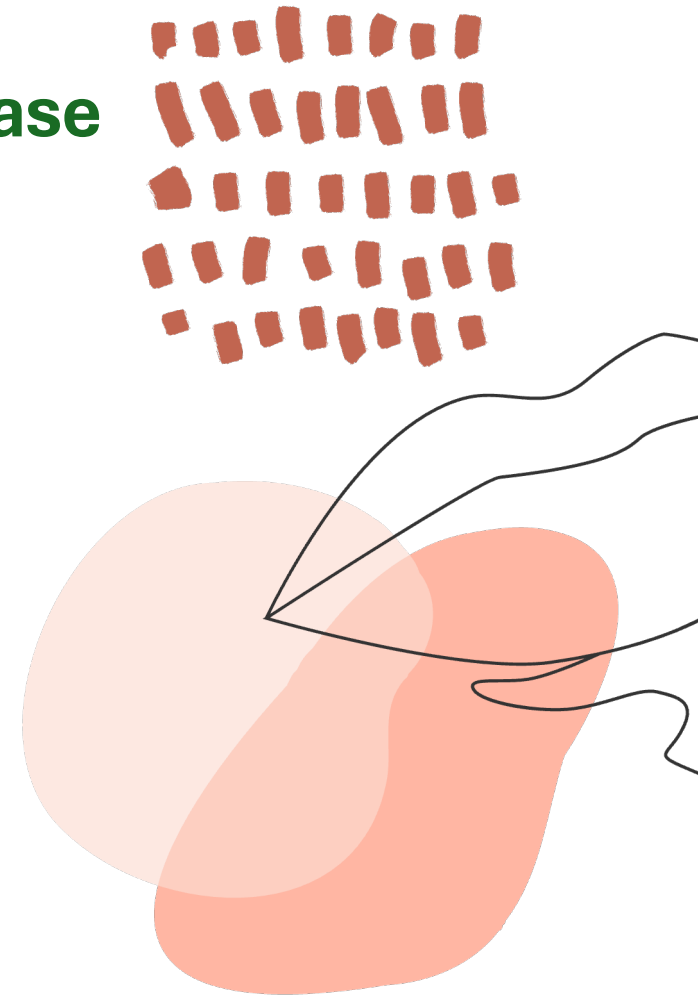
Introduction

- **Clinical Differences**
- **Risk Factors in Women**
- **Therapy Differences**
- **Biological Mechanisms Underlying Differences**
- **Unmet Needs of Women**
- **Current Scope of Research in Women**



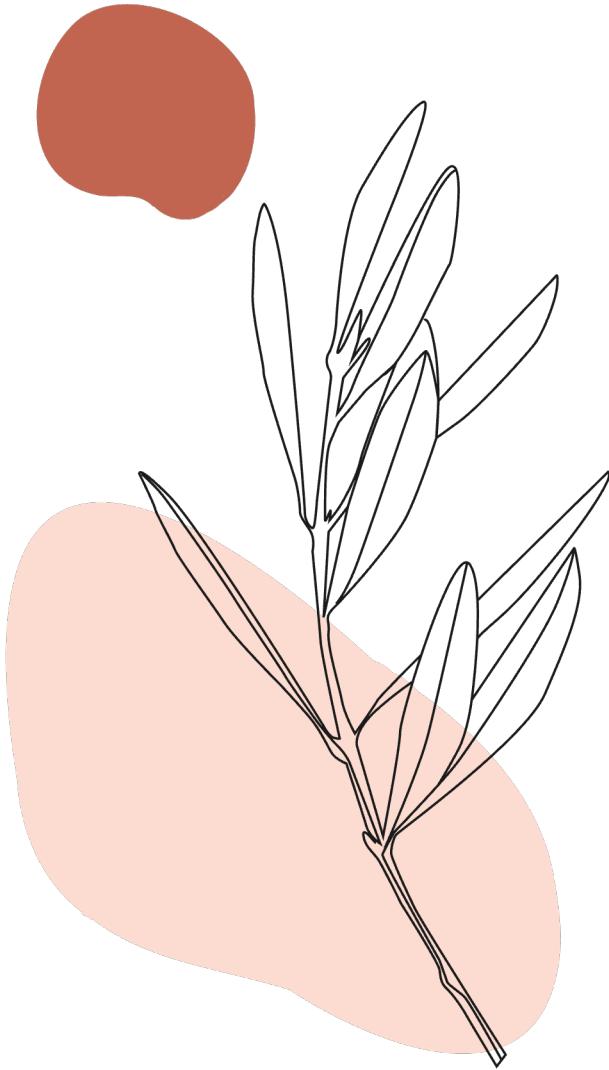
Gender Differences in Parkinson's Disease

- PD affects men twice more often than women
- Women show distinctive symptoms and differences in response to therapies compared to men
- **Women are less likely to have specialist (neurologist) care.**
- Women and men show distinctive prodromal markers of PD



Risk Factors

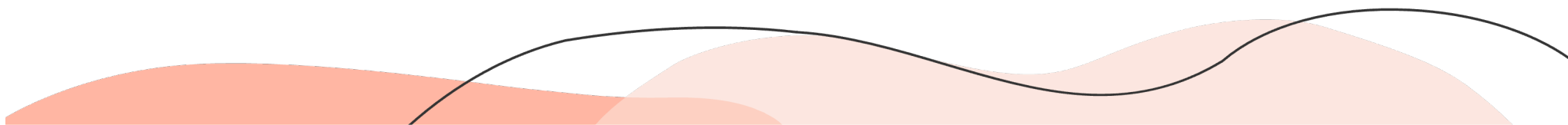
- **Genetic risk factors**
 - LRRK2 mutation seems to have equal effect in women and men
- **Anemia**
- **Women have some protective factors compared to men**
 - Lower rates of head trauma
 - Less pesticide exposure – occupational exposures
 - Estrogen – protective?



Differences in Symptoms Experienced

- **Motor Symptoms**

- Symptoms can emerge later in women
- Reduced rigidity/stiffness
- Tremor is more common presenting symptom
- Higher propensity for gait instability
- Higher risk for developing levodopa-related motor complications like dyskinesias



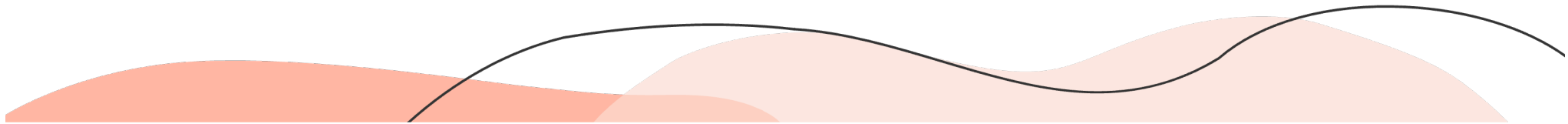
Differences in Symptoms Experienced

- **Non-Motor symptoms that are more common in women**

- Fatigue
- Depression
- Restless legs
- **Pain**
- Weight changes
- Excessive sweating
- Constipation

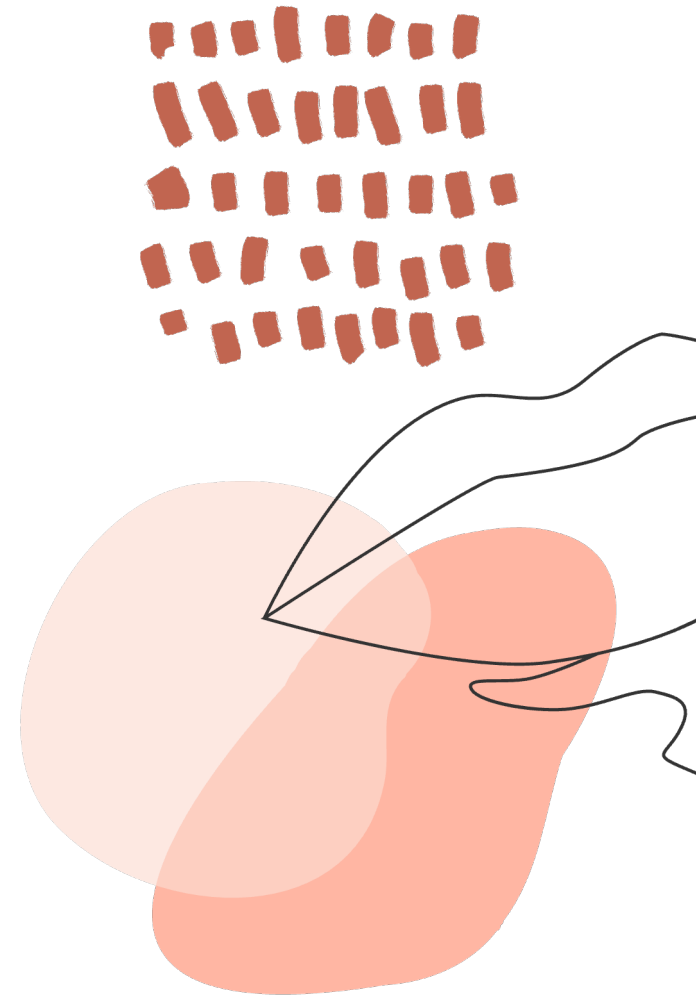
Less common in women:

- Cognitive impairment
- Autonomic dysfunction
- REM behavior disorder



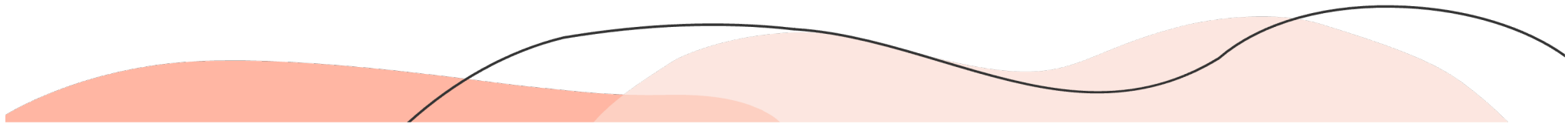
Unique Challenges Faced by Women with Parkinson's Disease

- **Estrogen and Menopause: its effect on PD symptoms.**
 - Hormone replacement therapy (HRT) and its impact on treatment.
- **Progression of the disease and treatment in women**
 - Gender-specific responses to medications (side effects, efficacy)
 - Deep Brain Stimulation (DBS) in women



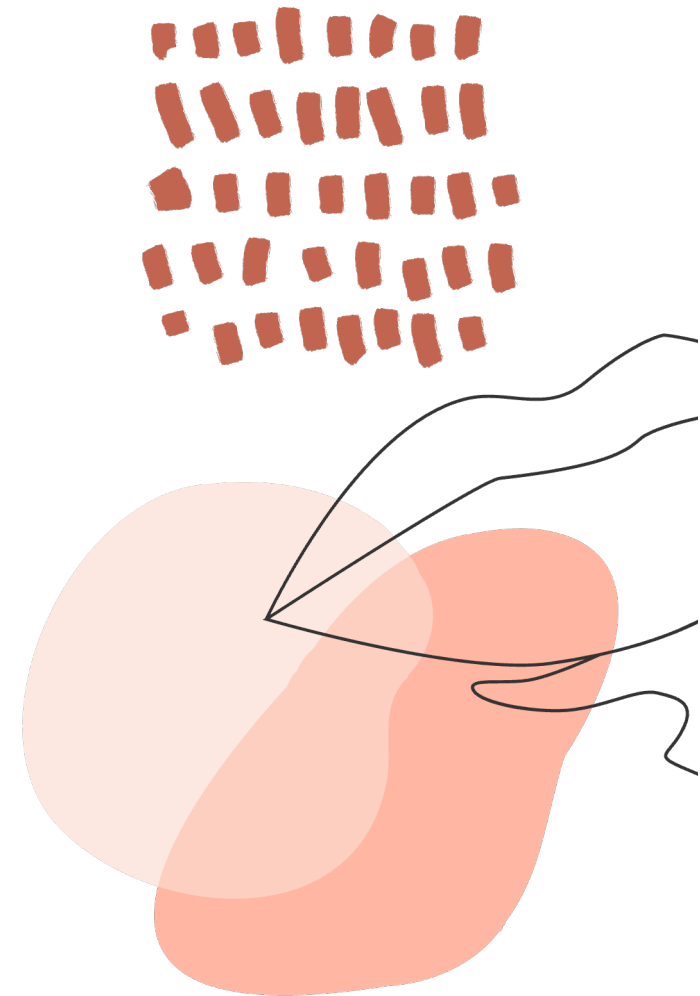
Considerations in Treatment of PD in women

- **# 1 Levodopa – gold standard treatment of PD**
 - Studies have showed greater bioavailability of levodopa in women
 - Women perhaps require lower doses
 - Women are more likely to develop drug-related dyskinesias than men
- **Deep Brain stimulation**
 - Quality of life measures improved more in women than in men
 - Particularly in mobility, stigma and cognition
 - Women are less likely to get this treatment – they make up less than 25% of the population referred for DBS
 - This also comes back to the fact women receive less subspeciality care



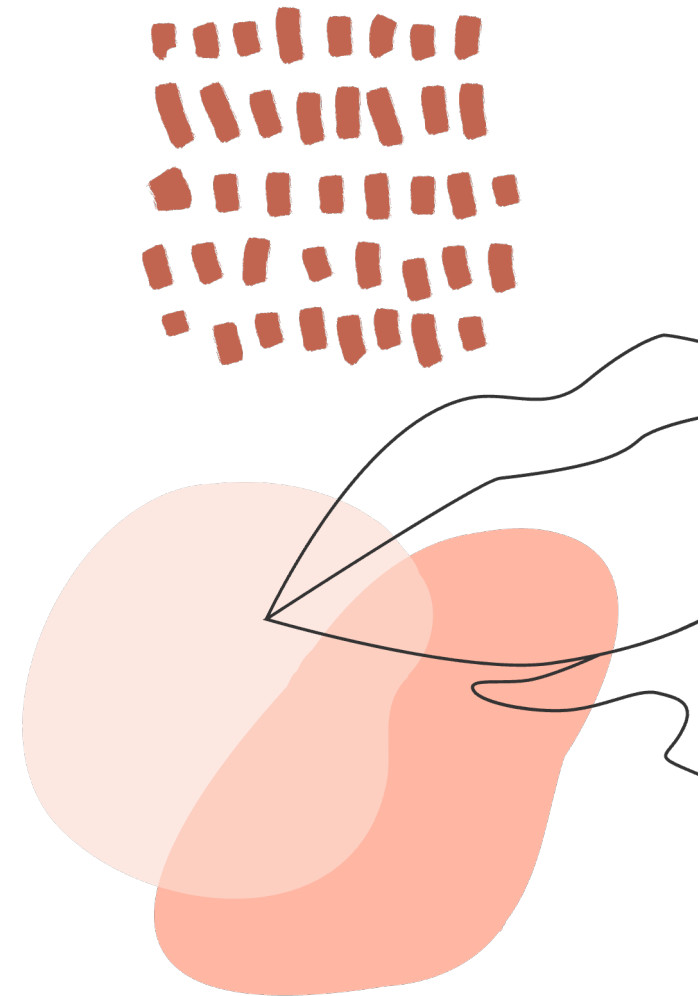
Psychosocial and Quality of Life Considerations

- Coping with the social stigma and emotional toll of PD.
- Perceptions of womanhood can change
- Women with PD can feel unattractive and may express a feeling a loss of femininity resulting in a destructive self-image.
- It can affect interpersonal relationships with family, friends and spouses



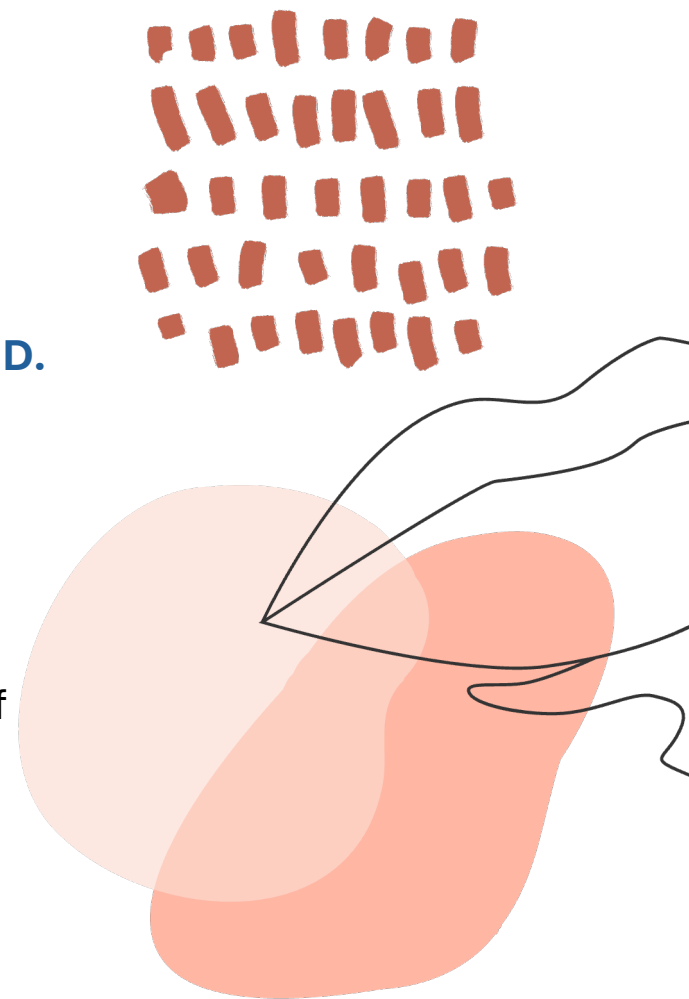
Psychosocial and Quality of Life Considerations

- **Caregiving and Family Roles**
 - The unique burden of caregiving often assumed by women.
 - Challenges for women balancing personal care and family responsibilities.
 - Women with PD are twice as likely to have a paid caregiver



We need more:

- **Social support systems and resources for women with PD.**
- **Research**
 - High quality, prospective, longitudinal studies analyzing gender differences.
 - Can translate into more tailor-made management of PD for women



Why are there Sex Differences in PD?

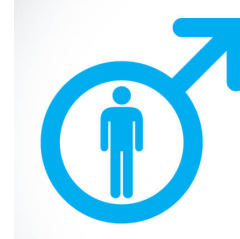
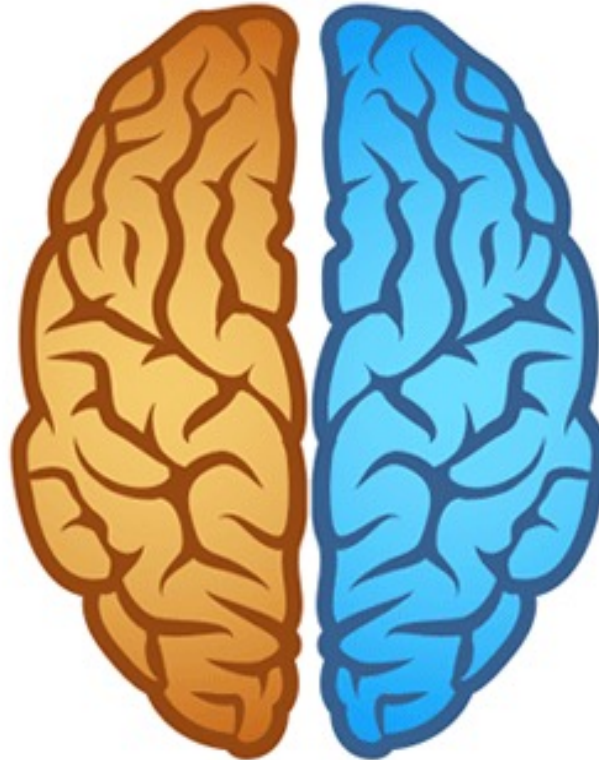


Dopaminergic neurons less vulnerable to neurodegeneration

Increased markers of mitochondrial dysfunction and protein clearance

Increased growth hormone levels, lower luteinizing hormone levels

Estrogen and progesterone may be neuroprotective, but subject to changes based on life stage of women



Dopaminergic neurons more vulnerable to neurodegeneration

Increased markers of inflammation and oxidative stress

Elements on Y chromosome may make men more susceptible to PD and link to progression

Testosterone may worsen neurodegeneration

An examination of male-female differences in progression and mortality of Parkinson's disease

S.G. Diamond, BA; C.H. Markham, MD; M.M. Hoehn, MD; F.H. McDowell, MD; and M.D. Muentner, MD

1990: Initial Studies

Parkinson's disease in women: A call for improved clinical studies and for comparative effectiveness research

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^c Center for the Study of Aging and Human Development

^d Movement Disorders Center, Departments of Neurology and Neurosurgery, McKnight Brain Institute, Gainesville, FL, USA

2010: Call for More Research

Unmet Needs of Women Living with Parkinson's Disease: Gaps and Controversies

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⁵Be NutritionWise, Dublin, Ireland

⁶Grenoble Alpes University, Faculty of Medicine, Division of Neurology, CHUGA, Grenoble Institute of Neurosciences, Grenoble, France

2022: Continued Need for More Research

Gap: Redefining the Image of Parkinson's Disease

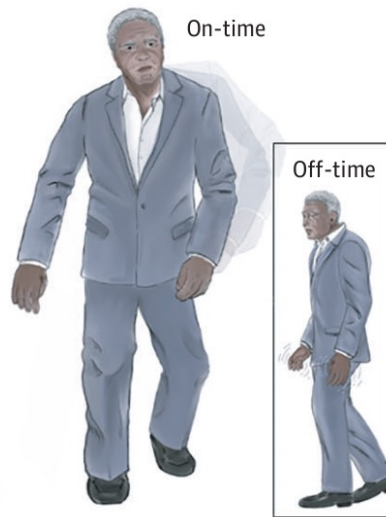
A 1886 Illustration of Parkinson disease



B Mild motor-predominant Parkinson disease



C Intermediate Parkinson disease



D Diffuse malignant Parkinson disease



Gap: How are Risk Factors Different in Women



Caffeine



Smoking



Pesticide
Exposure



Occupational
background



Genetics



Bone density



Lifetime hormone
exposure

In men, caffeine and smoking have been linked to reduced risk of PD, and pesticide exposure has been linked to increased risk of PD.

Risk relationship is not that clear in women.

Women's Health Initiative Observational Study that enrolled and followed 91,627 postmenopausal women, 50 to 79 years, found ~3000 developed PD.

Evidence of excess risk for occupations in health technology, social work, teaching/counseling, and building and ground cleaning and maintenance

α -Synuclein
LRRK2
PINK-1

Dopamine receptor and transporter
Dopamine metabolism
Neuronal signaling and maturation

Few studies showing differences in how these genes are expressed and how mutations affect disease differently in women vs men

Lower bone density and osteoporosis have been shown associated with increased risk of PD in postmenopausal women

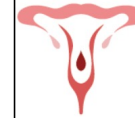
Gap: How do Different Life Stages of Women Affect Their PD Journey

Average age at menopause transition (perimenopause): 45-55 y/o

Pre-symptom phase ~10-12 years before PD diagnosis

Average age of PD onset: 60-65 y/o

Subramanian et al., 2022



Menses

- Pre-menstrual worsening of symptoms
- Role of hormonal regulation, contraception
- Young-onset PD – impact on relationships, career, family planning



Pregnancy

- Pre-conception counselling
- Maternal safety and wellbeing
- Teratogenicity of medications
- Guidance around childbirth
- Breastfeeding safety



Perimenopause

- Worsening of symptoms
- Natural menopause vs surgical menopause (hysterectomy with or without oophorectomy)
- Timing and type of HRT (estrogen only vs combined estrogen-progesterone)



Postmenopause

- Role of hormone replacement therapy
- Breast cancer
- Osteopenia/osteoporosis
- Pelvic floor dysfunction
- Transition in social roles (grandparent, retirement, bereavement)

Role of Estrogen in PD

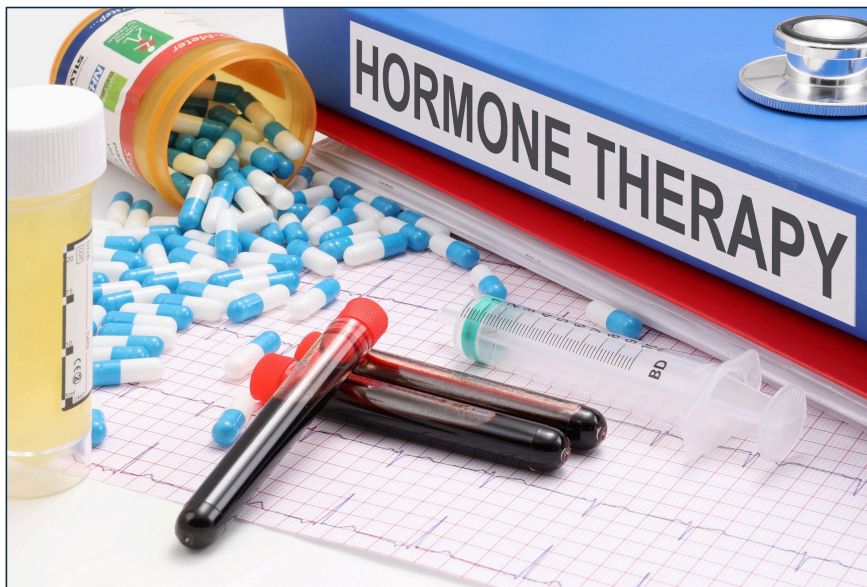


Photo license: [CC BY-SA](#)

Increased risk of PD in men – does estrogen make women less vulnerable?

Compared to women without PD, women with PD have higher testosterone levels and lower estrogen levels

Higher occurrence of PD in post-menopausal women compared to pre-menopausal women

Greater duration of fertile life associated with delayed onset of PD in some but not all studies

In animal studies, estrogen has been shown to have protective benefits – decreases inflammation and preserves dopamine-producing brain cells

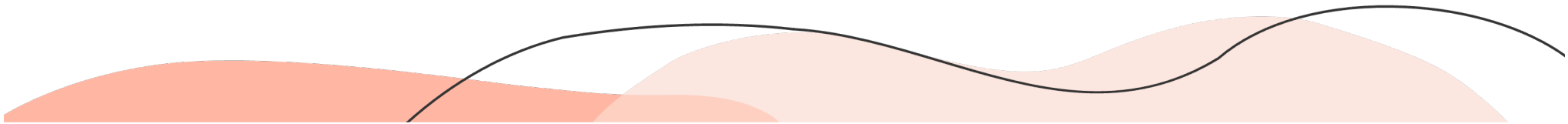


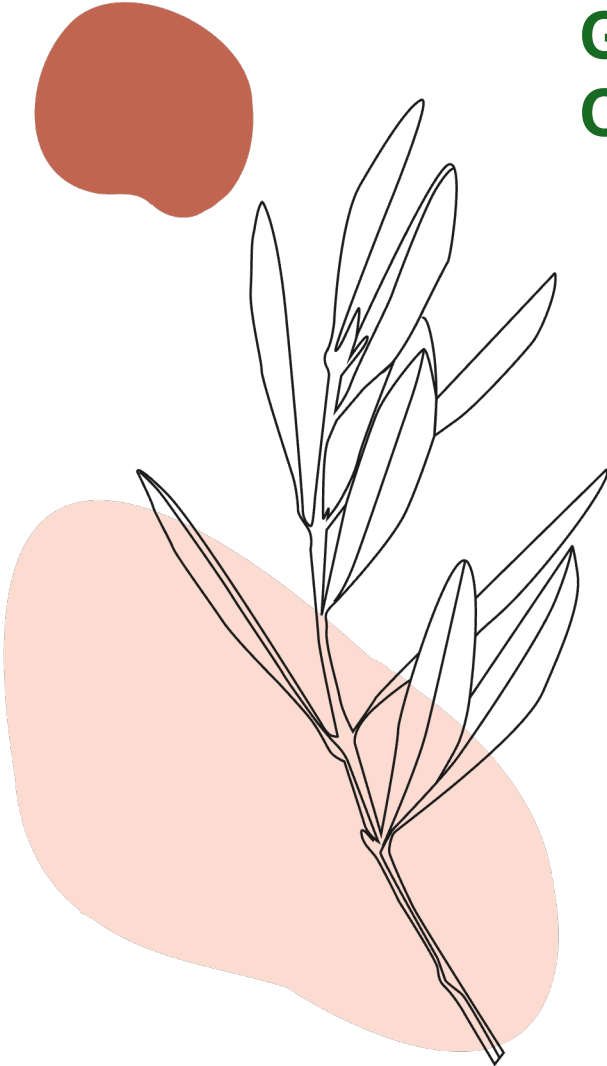
Hormone Replacement Therapy?

- **Conflicting data:** Some studies show that hormone replacement therapy reduces risk of PD, while others show no effect or increased risk of PD
- **Many variables in hormone replacement therapy:**
 - Estrogen vs estrogen/progesterone combination
 - Type of estrogen (esterified vs conjugated)
 - Way of administration (oral, patch, injection, cream)
 - Type of menopause (surgical vs natural)
- **Window of opportunity:** Use of hormone replacement in midlife/early menopause more protective compared to use in late life?

Gap: Understanding Factors that Affect Quality of Life in Women

- Women with PD have **significantly less social support, more psychological distress, and worse self-reported disability and quality of life** at initial PD care visits compared to men
- Women tend to have **more caregiving responsibilities** within family along with occupational and other **competing demands**
- With the diagnosis of PD, women's **perceptions** of their own womanhood and of what others think of them can become very **negative**.
- Women may **prioritize symptoms that affect their ability to organize and strengthen social relationships** and become distressed when unable to fulfill domestic responsibilities





Gap: Delays in Diagnosis, Misdiagnosis, Care Experience...

Women with delay in getting diagnosis and referral to movement disorders specialist

Women in underserved minorities are more likely to have missed or delayed diagnosis

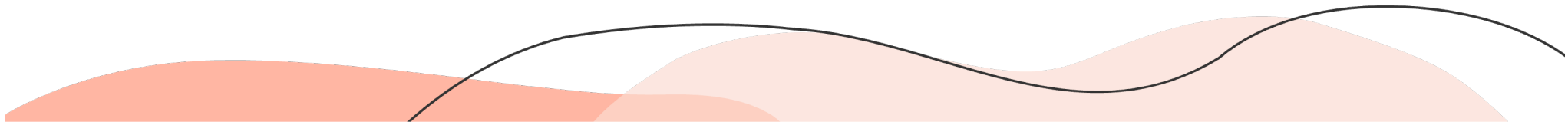
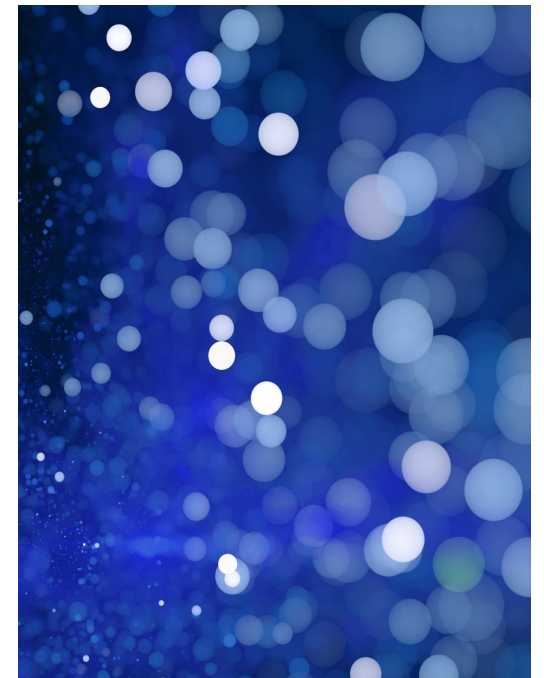
Less known about experiences of women in sexual and gender minority groups

Women with PD can feel like they are not being heard

Women may not consistently share their concerns or symptoms with their providers, particularly around mental health and other sensitive topics (i.e., pelvic floor problems)

Looking Ahead...Care and Management

Improve	Improve access to care and advanced therapies (i.e. DBS)
Customize	Customize treatment based on their personal symptoms, body weight, and unique metabolism
Ask about	Ask about sensitive topics (i.e. pelvic floor issues, mood, bone health) and refer women to specialists
Provide	Provide guidance on self-care, stress-reduction and social connection strategies that may be particularly beneficial to women
Educate	Educate male caregivers so they can understand the disease better and have resources to provide support
Develop	Develop more models of support for women in the community



Looking Ahead...Women Health Factors

- Increase awareness of hormonal stages in women living with PD
- Better collaboration between neurologists and gynecologists
- Discuss risk/benefit of hormone replacement therapies with women based on their unique history
- Develop tools that empower women to bring up women's health issues with providers
- Develop strategies to help PD symptom exacerbations with menstrual cycles, menopause, pregnancy



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Raising Awareness for Women with PD

Parkinson's Foundation

❖ Women and PD Teams to Advance Learning and Knowledge (Women and PD Talk) Project

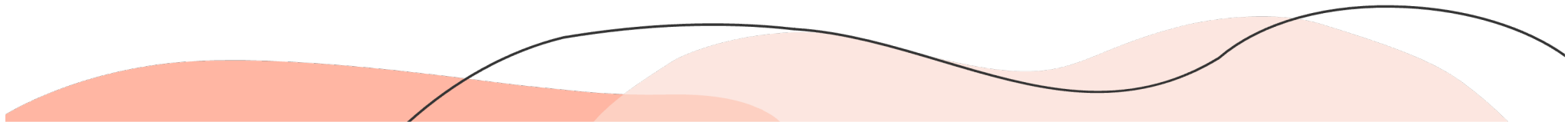
- Over 2 years, 10 regional forums, as well as a national forum, were held across U.S. to understand the experiences of women with PD.
- Led to **the first national research and care agenda specific to women with PD** to address priorities identified by women and disparities experienced by women
“Women and Parkinson’s: Closing the Gender Gap in Research and Care”

Women's Parkinson's Project

❖ Founded by women living with PD, *goal to elevate the voices of women with PD*

PD Avengers

❖ Women and Parkinson's Working Group, *increasing awareness, engagement and hope for women with PD*



Research: Tracking Experiences of Women with PD

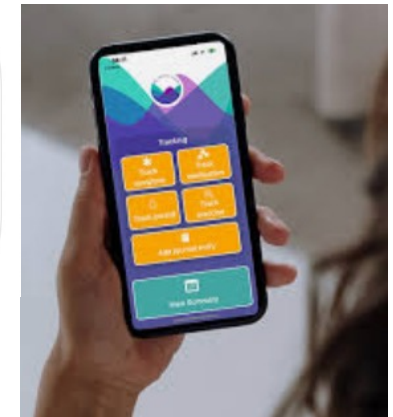
PD Generation

Women-specific questionnaire to address women's experiences and their PD clinical history

Fox Insight – Online Clinical Study

“Experiences of Women Living with PD: Female Health and Home Life”

“Experiences of Women Living with PD - Pre, Peri, and Post Menopause”



Digital app that allows tracking of PD symptom fluctuations across the menstrual cycle

Self-Image in Women with Parkinson's Disease

Soania Mathur^{a,*}, Kristi LaMonica^{a,b}, Helen Matthews^{a,c} and Kat Hill^a

^aPD Avengers (Global Alliance to End Parkinson's Disease), Vancouver, BC, Canada

^bRussell Sage College, Troy, NY, USA

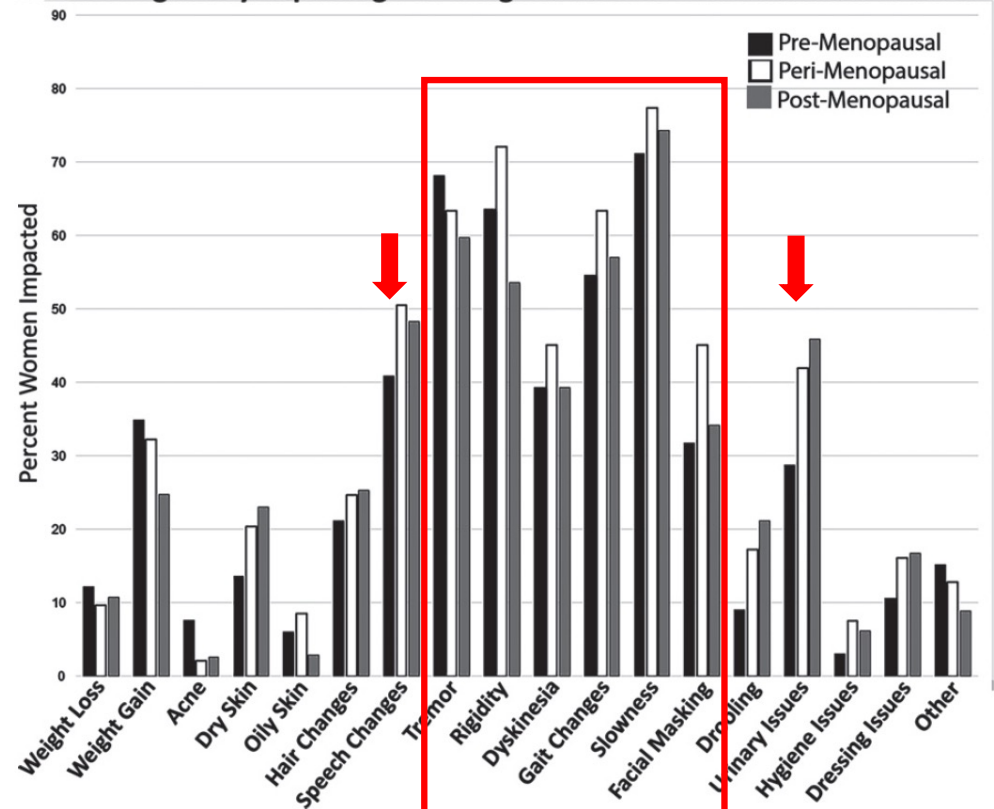
^cCure Parkinson's, London, UK

2,627 women participated in the Experience of Women with PD survey by PD Avengers, deployed through Fox Insight

61% of women reported their PD negatively impacts their self image

After motor symptoms, women next report that speech changes and urinary issues negatively impact their self-image

Factors Negatively Impacting Self-Image in Women With Parkinson's Disease



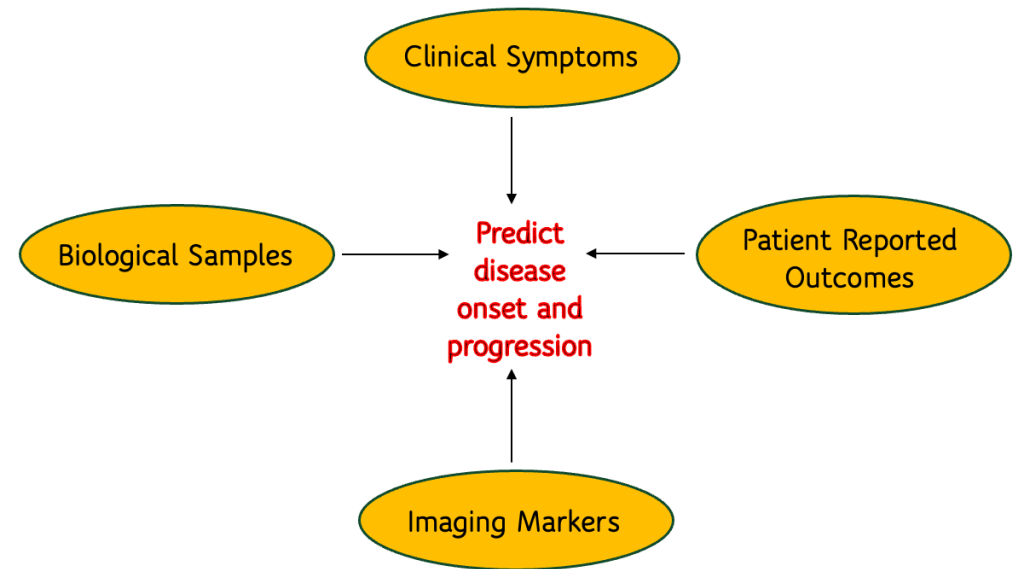
Research: Biomarkers in PD



Parkinson's Progression Markers Initiative

Insights that could lead to critical advancements, from earlier identification of people who may be at risk for developing PD to innovative new treatments that could improve quality of life and slow disease progression.

Analyses that will compare differences between men and women.



>2000 Participants enrolled and being followed

Men: 54.5% of total study participants

Women: 45.5% of study participants

Priorities for Future Research

Inclusiveness:

- Women need to be included in PD research!
- Including women across diversities, demographics, stage and onset of PD

Areas of Research:

- Needs to be designed around the unique needs of women
- Must include topics examining the effect of biological sex and sex hormones, on PD risk, progression and response to treatments
- Should dissect differences between PD, aging, and menopause
- Needs to include not just effects on biomarkers in women but also quality of life in women



Studies Recruiting Participants at UCSF

PD GENERation: Mapping the Future of Parkinson's Disease



Parkinson's
Progression
Markers
Initiative

TOPAZ

Trial of Parkinson's and Zoledronic Acid
Fracture Prevention Study



Study in Parkinson's Disease of Exercise
Phase 3 Clinical Trial

**Psilocybin Therapy for Depression
in Parkinson's Disease**



EXCEL-PD

Exercise for Cognitive Excellence in
Parkinson's Disease

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Questions & Answers

