

## GAPS &amp; CONTROVERSIES

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

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**ABSTRACT:** Personalized medicine considering sex, gender, and cultural context has become the vanguard of delivery of care. However, women's issues in Parkinson disease (PD), especially from a psychosocial standpoint, have been an overlooked field. The key research areas include women-inclusive drug and device studies and genetic and hormonal considerations. Moreover, women with PD need to be educated and empowered on how to communicate their symptoms and needs, get engaged in research, get organized as a community, and support one another. Women with PD need tools to help track and convey their unique motor and nonmotor symptoms and psychological and social support needs. The management of PD needs to be customized to include the unique stages of women's lives, including menstrual cycles, pregnancy, perimenopause, menopause, and postmenopause. Specific guidelines for the use of hormonal treatments and customized dopamine replacement dosing need to be developed. Women

need guidance on culturally sensitive wellness and self-care strategies that are customized for them. Basic core competencies in knowledge for all clinicians treating women with PD need to be established, including how to accurately diagnose, proactively identify, and treat the symptoms of PD in women and to ensure timely referral for specialty care, advanced therapies, and research studies. Caregivers and families need guidance on holistically supporting women with PD. The voices of women living with PD must be amplified to catalyze real change in this neglected field. This paper provides an overview of the current knowledge, gaps, and possible strategies to deal with the unmet needs of women living with PD with a focus on the clinical and psychosocial aspects. © 2022 International Parkinson and Movement Disorder Society

**Key Words:** estrogen; women; Parkinson's disease; sex differences

Sex and gender issues in medicine are an important topic that touches essentially all medical specialties.<sup>1</sup> Cardiologists, oncologists, and other specialists are already very familiar with sex and gender differences and their impact on patient care and research outcomes.<sup>2,3</sup> In neurology, there has been increasing awareness of the effect of sex and gender differences on

prevention, diagnosis, and management mainly in the fields of stroke, epilepsy, dementia, and migraine.<sup>4-6</sup> In Parkinson's disease (PD), though the impact of sex and gender has been previously described<sup>7</sup> and it has been largely reported that PD is more common in men than in women, a recent review emphasized the need for further study of this complex topic.<sup>8</sup> In PD, there is

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growing literature pointing out possibly relevant differences in nonmotor and motor symptoms in both the prodromal and clinical phases.<sup>9</sup> Nevertheless, this evidence has not yet garnered enough attention and consideration to result in the customization of clinical practice and to inspire new avenues of preclinical and clinical research. Furthermore, most research has focused on biological differences between women and men, neglecting to place these in the psychosocial context that impacts clinical care and quality of life of women with PD and other movement disorders.

This paper provides a brief summary of the current data; identifies gaps that have yet to be targeted; and proposes possible strategies for management, advocacy, and research in women living with PD. True personalized medicine looks to put the person living with PD at the heart of management or research. With that in mind the voices of women with PD have been raised through the coauthorship of this paper by three women living with PD.

## What We Know

Much of what is known in this field has conflicting results and has controversies in management and major gaps in knowledge. Therefore, we briefly discuss the current state of the literature in each section along with the corresponding gaps and controversies.

## Gaps and Controversies

### Epidemiology

Many epidemiologic studies have found that both prevalence and incidence of PD are lower in women compared to men.<sup>8,10-12</sup> In the 2016 Global Burden of Disease Study, age-standardized prevalence of PD was 1.4 times higher in men than in women.<sup>13</sup> However, the ratio is lower in Asia (0.95–1.2),<sup>14,15</sup> possibly due to differences in methodology and environmental and/or genetic factors. Interestingly, over the years the incidence of PD in women has remained stable, whereas it has increased in men.<sup>16</sup> These findings support an important role of sex-specific genetic and epigenetic factors in PD pathophysiology that merit further study.<sup>17-19</sup>

### Risk Factors

Sex and gender interactions may have differential effects on several PD risk factors, though there are conflicting studies. For example, caffeine consumption is related to a lower risk of PD among men but not women.<sup>20</sup> However, among postmenopausal women, those on hormone replacement therapy (HRT) who consumed caffeine actually had an increased risk of PD.<sup>20</sup> In a recent population-based cohort study, PD risk was lower in current male smokers compared to current female smokers with the same level of

exposure.<sup>21</sup> In contrast, the PD risk-lowering effect of alcohol consumption was more pronounced in women than in men.<sup>21</sup> Pesticide exposure has also been related to the development of PD, though prior studies have found this association only in men and not women.<sup>22,23</sup> Therefore, more research needs to be done to resolve these conflicting results.

### Sex Hormones

Sex differences in PD epidemiology suggest a neuroprotective role of estrogen. In preclinical studies, estrogen has been shown to have antiapoptotic and antioxidant effects,<sup>24</sup> in addition to inhibiting  $\alpha$ -synuclein fibril stabilization and aggregation.<sup>25</sup> Several studies have demonstrated that higher total lifetime estrogen exposure may be associated with a decreased risk of PD in women,<sup>26-29</sup> although some other studies have been inconclusive.<sup>24,30-34</sup>

The timing of estrogen exposure and association with sexual hormones may be critical factors<sup>35</sup>; it has been shown that postmenopausal estrogen-only treatment among women with hysterectomy may increase the risk of PD compared to no increased risk when women experience natural menopause and receive usual treatment with a combination of estrogen and progesterone.<sup>36</sup> A recent retrospective analysis showed that greater duration of HRT was associated with reduced risk of neurodegenerative disease, including PD.<sup>37</sup> In contrast, however, another study of women experiencing natural menopause showed that the use of HRT for more than 5 years was associated with an increased PD risk of 17% compared to postmenopausal women who never used HRT.<sup>28</sup>

Current literature reveals conflicting data on the impact of HRT on PD risk, with one possible explanation in the complex interaction between timing and duration of hormone exposure and the interaction with other genetic and environmental risk factors.<sup>35</sup> Elucidation of the actual effects of reproductive factors, HRT, and oral contraceptive pill (OCP) use on the risk of PD may help identify mechanisms and pathways responsible for these effects and determine strategies for prevention of PD in the future. Currently, the effects of HRT on PD risk remain inconclusive and need further study. The interplay between these factors is complex, though targeting sex differences in the pathophysiology of PD may open new avenues of investigation and development of sex-specific treatments.

### Awareness, Delayed Diagnosis or Misdiagnosis, and Communication

PD is often thought of as a disease affecting a specific demographic, that is, older white men. This stereotype is reflected in the long-standing illustration of the stooped elderly man that dominates medical media. This perception has been further documented by a

survey of public knowledge where the most frequently mentioned group nominated as more likely to suffer from PD were elderly men.<sup>38</sup> Although recently there have been efforts to modify this attitude,<sup>11</sup> more needs to be done.

For women, there is a delay in getting both an accurate diagnosis of PD and a referral to a movement disorder specialist.<sup>39,40</sup> Clinical differences in presentation are not entirely responsible for delays in diagnosis of PD in this population. Some factors lie with women themselves, such as a decreased tendency to disclose or emphasize bothersome symptoms during medical assessments. Perceptions by physicians that PD is more common in men may also contribute to delays.<sup>39</sup> These inequities are further magnified in marginalized communities within countries where traditionally underserved minorities are more likely to have missed or delayed diagnosis.<sup>41</sup>

Very little is known about the experience of the sexual and gender minority groups such as women in the lesbian, gay, bisexual, transsexual, and queer (LGBTQ) intersectional overlap arenas. Prevalence remains unknown, and this may be different in these communities due to variations in potential risk factors for disease such as smoking and use of gender-affirming hormones.<sup>42</sup> Older members of the LGBTQ community were surveyed about the relationship they have with their doctor, and 33% reported stigma around their sexual orientation, which led to general mistrust of the medical system.<sup>43</sup> Discrimination and stigma as barriers to accessing care in traditional healthcare models may hinder knowledge, diagnosis, involvement with multidisciplinary approaches to treatment, and participation in all aspects of medical management.<sup>42</sup>

Delays in diagnosis may lead to more dissatisfaction with care in women with PD versus men with PD. Women with PD can feel like they are not being heard or that what matters to them most is not considered.<sup>44,45</sup> Negative-care experiences can impact symptom reporting.<sup>44</sup> Women may not consistently share their concerns or symptoms with their providers, particularly around mental health and other sensitive topics (eg, pelvic floor problems), and are therefore not treated for these issues.<sup>44</sup> Research showed that women with PD have worse pelvic floor health issues than control women and are less likely to report their symptoms. Women with PD get accustomed to living with associated discomfort. They may downplay their symptoms and may not realize the association of these symptoms with their PD and therefore do not receive treatment.<sup>46</sup>

The cultural behaviors associated with sex and gender in relation to how people living with PD feel about their lived experience of their symptoms are rarely researched or discussed. A study of older people with PD found that women prioritize symptoms that affect their ability to organize and strengthen social

relationships. Women were more likely to become distressed when unable to fulfill their domestic responsibilities.<sup>47</sup> In addition, research on gender identity has shown that the quality of life of androgynous men and women (ie, with coexistent strong feminine and masculine characteristics) was significantly better for coping with PD.<sup>38</sup> This is a very important field of research that should be explored further.

## Motor and Nonmotor Symptoms

There is accumulating evidence demonstrating that women with PD may have a unique constellation of both motor and nonmotor symptoms as compared to men. Women present with a more tremor-dominant PD and may have slower progression that may superficially imply that their disease is milder.<sup>48</sup> There is conflicting data regarding the impact of sex on progression of disability in PD.<sup>49,50</sup> However, considering a host of psychosocial and nonmotor issues and greater propensity to dyskinesias, there is certainly a tremendous symptom burden facing women with PD.<sup>8,9</sup> In the nonmotor domain, women report more genitourinary dysfunction and less gastrointestinal dysfunction, less cognitive decline and less hallucinations compared to men.<sup>51,52</sup> In fact, very recent research has shown that prodromal constipation in women may result in lower cognitive performances and more severe apathy in early-stage PD.<sup>53</sup> Women report less sexual dysfunction than men, but this may be due to underreporting by women who may be less likely to talk about these sensitive issues or not being asked by their mainly male providers.<sup>54</sup> On the contrary, women have more mood disturbances such as anxiety and depression, sleep disorders, fatigue, and apathy.<sup>55</sup> Restless legs, pain, and facial masking are also more common and severe in women.<sup>56,57</sup> All these differences result in a worsening of quality of life and increased stigma in women compared to men with PD.<sup>57,58</sup> Furthermore, women with PD differ in their presentation of depression from men with more symptoms of feelings of worthlessness, irritability, agitation, self-punishment, loss of pleasure, and self-dislike.<sup>59</sup> Women with PD often present with more emotional impairment compared to men as measured by PDQ-39 (Parkinson's Disease Questionnaire).

A prospective study showed women to have higher propensity to develop nonmotor fluctuations within 4 years of diagnosis compared to men.<sup>60</sup> As mentioned earlier, women also have increased risk of developing dyskinesias compared to men, likely due to differences in levodopa metabolism and lower body weight.<sup>61-63</sup> Studies have shown that there is greater bioavailability of L-dopa in women<sup>64</sup> and that the genetic determinants of dyskinesias may differ among men and women<sup>65</sup> (see Fig. 1).



**FIG. 1.** Common symptoms and psychosocial issues that may be observed in women living with Parkinson's disease.

## Management and Treatment

Studies focusing on disparities in access to advanced therapies such as deep brain stimulation (DBS) are lacking. Women with PD are less likely to get this expensive treatment and in fact make up less than 25% of the population referred for DBS.<sup>66</sup> One of the most common reasons women do not get DBS was patient preference (28%).<sup>10,66</sup> Although women less commonly undergo DBS, they can experience greater health-related quality-of-life improvement after DBS, particularly in domains of mobility, stigma, and cognition, which makes it important to provide this treatment to women.<sup>67</sup> Considering the more recent trend to provide DBS earlier in the disease,<sup>68</sup> this topic should be further studied. Moreover, considering the different profiles and burden of motor and nonmotor symptoms in women, PD treatment should be customized accordingly. It should not be a one-size-fits-all approach; for example, there are many management issues such as impulse control disorders and dopamine dysregulation syndrome that are reported more commonly in men, whereas women who may weigh less than men may need to be prescribed less dopamine. Thus, bespoke care is important for both men and women living with PD depending on their own unique attributes and cultural contexts.

### Hormonal Life Stages: Premenstrual, Pregnancy, and Premenopausal

Care for women with PD must include acknowledgment of their unique hormonal life stages (see Fig. 2) and how these can impact their disease. Women often report worsening of motor symptoms in the premenstrual phase.<sup>69-73</sup> In fact, an advocate-driven survey of 200 women with PD corroborated this phenomenon (<https://www.pdangers.com/blog/women-and-pd>). The decrease in premenstrual estrogen is likely responsible for this effect, with conflicting reports of the benefit from taking extra L-dopa during this time frame. This area is largely unexplored and should be better studied.

Although PD, in general, is diagnosed at an older age, approximately 5% of women are diagnosed before age 40.<sup>74</sup> This group of young-onset PD (YOPD) patients includes women considering a pregnancy after diagnosis and who may be having ongoing menses and associated hormonal fluctuations that may need to be managed by contraception or hormonal regulation. With increasing maternal age and increasing incidence of PD, especially YOPD worldwide, pregnancy in women with PD will be more common in the future. PD symptoms have been reported to worsen during pregnancy and the postpartum,<sup>75-77</sup> but the pathophysiology is not well understood. L-Dopa monotherapy is the most reported treatment during pregnancy and does not seem to confer an increased risk of birth defects or

adverse outcomes.<sup>75</sup> Amantadine is a known teratogen and should not be used in pregnancy.<sup>75</sup> However, there are no evidence-based guidelines on the management of PD during pregnancy, and literature on maternal safety, especially around C-sections, obstetrical anesthesia, postpartum depression, and fetal outcomes, is scarce.

Women with PD may also report premenopausal worsening of symptoms, postulated to be due to a decrease in estrogen.<sup>73</sup> Once women have been diagnosed with PD, the question arises whether HRT could be beneficial in treating fluctuations in PD symptoms during perimenopause and postmenopause. There has been confusion about whether and when to start HRT.<sup>78-80</sup> Neurologists and gynecologists should collaborate in research as well as clinical care for women with PD during all these hormonal transitions. For example, to be able to properly advise and guide women who are considering a pregnancy in the future, an international prospective registry is needed (see Fig. 2).

### Psychosocial and Mental Health Issues

Women, particularly in midlife, may encounter significant caregiving responsibilities within the family along with occupational and other competing demands.<sup>81</sup> In a small Brazilian study, women with PD, despite their possible changes in performance ability, often continued doing their usual activities, including care of family and home. Men, on the contrary, seemed to be more limited in their abilities to handle the limitations that their disease places on them as well as to handle a lack of support.<sup>82</sup> This observation needs to be corroborated in other cultural contexts. “Although I realize that getting this disease is not my fault, it did compromise my roles as a mother of a young child, the daughter of an elderly parent, a wife, and a business partner.” This quote was from a participant in a qualitative study of the impact of PD on couple relationship<sup>83</sup> and reflects the various roles and responsibilities that women play within their family units and their communities. It also shows that this level of responsibility is not restructured by the diagnosis of a chronic illness like PD. It is worth noting that the women who perceive themselves as caregivers are more likely to be in poor health, have difficulty in accessing needed medical care, and experience greater degrees of depression.<sup>65,81</sup> All these aspects should have careful consideration in the multidisciplinary management of PD.

### Relationship Issues

Women with PD have significantly less social support, more psychological distress, and worse self-reported (but not physician-reported) disability and health-related quality of life at initial PD care visits compared to men.<sup>65</sup> This may result in an increased incidence of depression or may manifest in negative self-image or other unhelpful views. In fact, when





## 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)

**FIG. 2.** . The life stages of women living with PD and issues experienced in each stage: Common issues faced by women living with PD in each life stage are highlighted along with important comorbidities that should be considered in treatment during these stages. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

women are diagnosed with PD, their perceptions of their own womanhood can change.<sup>84</sup> How they view their own bodies and their perception of what others think of them can be very negative. This includes the impact of their physical symptomatology and the limitations that those symptoms place on their ability to take care of themselves. Women with PD can feel unattractive and may express a feeling a loss of femininity resulting in a destructive self-image.

PD can affect interpersonal relationships with family and friends. Many of these issues with self-perceived burden of disease, disability, and quality of life are not well captured on currently available PD rating scales. Spousal relationships change, and whereas some become closer, many are negatively affected by physical changes, increased dependence, and the adverse effects on sexual intimacy. This, in many cases, can serve as an

added stressor, sometimes leading to a complete breakdown of the marital relationship.<sup>84</sup>

Given the millions of women affected worldwide with PD, and the known differences in this disease's manifestations and effects between genders, remarkably very little has been done to understand those differences or tailor management to consider the unique needs of women. It has been reported that women with PD have less psychosocial support and caregiving resources.<sup>52,65</sup> Surprisingly, these issues have not been fully explored to date (see Table 1 for summary of needs).

### Caregiving

Across all health conditions, including PD, women are more likely to be caregivers than men, tend to provide more hours of care and more hands-on care, and

**TABLE 1** Overview of gaps in management, advocacy, and research for women with PD

<b>Management</b>
- Improve access to subspecialty care and advanced therapies (ie, DBS) for women with PD
- Recognize specific motor and nonmotor symptoms to help with optimizing management and personalizing treatment
- Customize treatment for women's body weight and unique drug metabolism
- Develop a tool to communicate with providers, improve symptom tracking tool (diary including menstrual cycles)
- Develop tools to facilitate discussion of hormonal factors to help empower women to bring these topics up with their providers
- Develop strategies to ameliorate the cyclical exacerbation, for example, taking extra PD medication and wellness strategies like yoga, mindfulness, and extra sleep
- Customize counseling to help women weigh risk/benefit of HRT in PD with comorbidities, for example, osteoporosis and breast, ovarian, and uterine cancers
- Refer women to allied health professionals for specific comorbid issues (eg, pelvic floor dysfunction, osteopenia, weight loss)
- Create international prospective registries to advise women with PD who are considering a pregnancy in the future
- Foster collaboration between neurologists and gynecologists
<b>Psychosocial</b>
- Guide self-care/stress reduction strategies for women with PD
- Guide lifestyle choices in diet, exercise, mind-body approaches, and social connection strategies that may particularly benefit women
- Counsel on wellness to meet women where they are from diagnosis in a culturally competent way
- Create culturally sensitive resources for communities, including LGBTQ and women of color, with PD— guide planning for the future, especially for single women
- Educate male caregivers with curated resources and support
- Explore other models of support: mentorship from other women, women-only support groups
- Facilitate the ability to build a trusting patient/HCP relationship based on understanding and empathy
<b>Advocacy</b>
- Increase awareness in the community to improve the recognition of PD in women and the intersection of other underrepresented groups (ethnic, LGBTQ)
- Educate HCPs on the importance of referral to a movement disorders specialist for women
- Educate providers on the making of an early diagnosis, customized assessment of burdensome symptoms, addressing women's PD needs
- Increase awareness of hormonal stages in the lives of women with PD
- Enhance global perspectives of women's issues across the world
- Connect more women with PD to each other
<b>Increasing engagement of women in research</b>
- Understand why women are not engaging in research and develop strategies to improve engagement
- Increase HCP awareness to provide information on clinical trials suitable for women
- Move research into community settings or online to make access easier
- Make research recruitment information socially and culturally relevant for women (provide translator services and incentives)
- Recruit more women in clinical drug trials to improve counseling on the effects and side effects of treatments
- Develop strategies to enforce stakeholder buy-in to engage women in research (ie, FDA, granting agencies)
<b>Research on</b>
- Improving animal models of PD that account for sex hormone interactions
- Interaction between sex/gender and PD risk (epidemiology, environmental exposure, genetic and epigenetic factors)

(Continues)

**TABLE 1** *Continued*

- Reproductive factors (eg, natural vs. surgical menopause) on PD risk in women
- Protective effects of estrogen and effects of timing of exposure
- Reduction of monthly hormonal fluctuations using, for example, a continuous OCP
- Randomized controlled trial to study timing of HRT use, duration, influence of the type of HRT used

Abbreviations: PD, Parkinson's disease; DBS, deep brain stimulation; HRT, hormone replacement therapy; LGBTQ, lesbian, gay, bisexual, trans-sexual, and queer; HCP, healthcare providers; OCP, oral contraceptive pill; FDA, U.S. Food and Drug Administration.

are more involved in day-to-day tasks compared to men.<sup>85</sup> Demands of caregiving tend to affect self-identity and perception in wives compared to husbands, who seem to be less impacted in these domains by their responsibilities.<sup>86</sup> Because married women with disability receive fewer hours of informal caregiving compared to married men with the same level of limitations, women who are ill are more likely to need nonspousal help to fill in the gaps in their needs. Consequently, women with PD are twice as likely to have a paid caregiver.<sup>85</sup> Furthermore, because of the increased life expectancy of women, there may be many more years where alternative caregiving may need to be arranged because women with PD may outlive their spouse.<sup>87</sup> In a longitudinal, prospective observational study of PD, the odds of caregiver accompaniment at baseline visit were lower for women compared to men, and women had a faster rate to using a paid caregiver than men.<sup>87</sup> A nationwide study examining long-term care in PD found that women with PD are more likely to reside in a nursing home than men with PD.<sup>88</sup> These factors should be considered when planning care and management of PD in women.

### Wellness Strategies

There is an overall lack of robust research into lifestyle interventions for PD management and even less so regarding gender. Women with PD have higher levels of osteoporosis<sup>89</sup> with lower bone mineral density and higher fracture risk versus matched controls,<sup>90</sup> and greater weight loss earlier in the disease course.<sup>91</sup> Women with PD should be screened for osteopenia/osteoporosis on diagnosis with PD and referred to a dietitian and a physiotherapist as part of a multidisciplinary team so that appropriate interventions can be undertaken to prevent malnutrition and bone deterioration. Women with PD also have a higher incidence of pelvic floor disorders versus matched controls,<sup>46</sup> supporting the screening for pelvic floor disorders and referral to physiotherapy for education regarding pelvic floor preservation.

Research indicates that there are different motivators for men and women to engage in physical activity. Women tend to be more motivated by enjoyment of the activity and social support,<sup>92</sup> whereas being male and

married can indicate longer time spent performing exercise.<sup>93</sup> Women with PD might not have enough time to devote to exercise and self-care due to the higher burden of work/family care. Considering the impact of exercise, physical and stress-relieving activities in PD, there is a lack of gender-focused outcomes.<sup>94</sup> Multidisciplinary care should be tailored according to not only sex-related symptoms and comorbidities but also sex- and gender-specific psychosocial issues.

### Engagement of Women in Research

Women with PD are underrepresented in clinical trials.<sup>95</sup> As PD is the fastest-growing and second-largest neurological condition worldwide, it warrants equality in the study of gender differences.<sup>96</sup> High-quality, prospective, longitudinal studies analyzing gender differences may identify reliable gender-sensitive biomarkers and social markers that could translate into a more tailored clinical approach for the diagnosis and management of women with PD.<sup>97,98</sup>

There are very few reasons for women with PD not participating in clinical trials. The longer time to diagnosis and the lower access to neurologist care for women with PD may result in reduced referral to research studies.<sup>40,99</sup> The Fox Trial Finder research into patient recruitment indicates that women prefer online engagement versus face-to-face visits. This disparity may be caused by the fact that women are often working and/or the main caregivers in their families, including of their older parents, and hence lack the time to attend face-to-face trial visits.<sup>44,100</sup> There is a concern that a subset of older people and those of lower socioeconomic groups who do not have access to technology, may be left out.<sup>101</sup>

Research consortia should foster inclusivity of underrepresented groups such as women with PD of different ethnicities.<sup>39,99</sup> The Michael J. Fox Foundation Fostering Inclusivity in Research Engagement for Underrepresented Population in Parkinson's Disease is an example of one such initiative.

Low socioeconomic status may lead to an inability to take time from work or lack of schedule flexibility to attend clinical trial appointments. It has been postulated that women may be risk averse with regard to surgical intervention such as DBS. However, more



research is needed to further corroborate this and to elucidate whether women may be more risk averse to experimental pharmacological and surgical trials as well.<sup>102</sup>

More than 10 years ago, a call was launched for improved clinical studies and comparative effectiveness research to include women with PD.<sup>103</sup> Only recently have funding organizations such as the European Commission, the Canadian Institutes of Health Research, and the U.S. National Institutes of Health made efforts to influence researchers to integrate sex and gender focus into the entire study pipeline from hypothesis to publication.<sup>80</sup> Sadly, little to no progress has been made to fulfill these recommendations.<sup>8</sup> Because “a better understanding of PD for some means a better understanding of PD for all,”<sup>99</sup> a customized precision-based approach to clinical trials will allow the betterment of care for all people living with PD worldwide (see Table 1 for a summary on the most relevant needs for women with PD).

## Conclusions

Though there have been several recent publications on the topic of sex and gender differences in PD, there has been a lack of coordinated effort to provide practical guidance on the management of issues that tremendously impact the quality of life of women living with PD and to foster focused research in this area. The movement toward personalized medicine in PD is a “call to arms” to create a framework to address these gaps and to establish global collaboration to address key research questions, including drug and device studies inclusive of women and genetic and hormonal considerations. This is a call for both women with PD and physicians. Women with PD need to be educated and empowered on how to communicate their symptoms and needs, get engaged in research, get organized as a community, and support one another. Women need tools to help track and convey their unique motor and nonmotor symptoms and psychological and social support needs. We propose a symptom diary that includes hormonal cycle tracking and a PD symptom reporting guide. The management of PD needs to be customized to include the unique stages of women’s lives, including menstrual cycles, pregnancy, perimenopause, menopause, and post menopause, and the unique comorbid issues that women encounter. Specific guidelines for the use of OCP, HRT, and customized dopamine replacement dosing need to be developed. Women need guidance on culturally sensitive wellness and self-care strategies that are customized for them. Basic core competencies in knowledge for all clinicians treating women with PD need to be established, including how to accurately diagnose; proactively identify and treat the

unique symptoms of PD in women; and ensure timely referral for specialty care, multidisciplinary management, advanced therapies, and research studies. Caregivers and families need guidance on holistically supporting women with PD.

The current momentum in addressing disparities in healthcare must include women’s issues in PD. The voices of women living with PD must be amplified to catalyze real change in this neglected field and represent the true heterogeneity of this progressive disease. ■

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## References

1. Gender and Health [Internet]. World Health Organization. 2021 [cited 2021 Dec 7]. Available from: [https://www.who.int/health-topics/gender#tab=tab\\_1](https://www.who.int/health-topics/gender#tab=tab_1)
2. de Bellis A, de Angelis G, Fabris E, Cannata A, Merlo M, Sinagra G. Gender-related differences in heart failure: beyond the “one-size-fits-all” paradigm. *Heart Fail Rev* 2020;25:245–255.
3. Zheng D, Trynda J, Williams C, Vold JA, Nguyen JH, Harnois DM, et al. Sexual dimorphism in the incidence of human cancers. *BMC Cancer* 2019;19(1):684.
4. Cordonnier C, Sprigg N, Sandset EC, Pavlovic A, Sunnerhagen KS, Caso V, et al. Stroke in women—from evidence to inequalities. *Nat Rev Neurol* 2017;13:521–532.
5. Ferretti MT, Martinkova J, Biskup E, Benke T, Gialdini G, Nedelska Z, et al. Sex and gender differences in Alzheimer’s disease: current challenges and implications for clinical practice: position paper of the dementia and cognitive disorders panel of the European academy of neurology. *Eur J Neurol* 2020;27(6):928–943.
6. Vervik KG, MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. *Lancet Neurol* 2017;16:76.
7. Shulman LM. Gender differences in Parkinson’s disease. *Gend Med* 2007;4(1):8–18.
8. Meoni S, Macerollo A, Moro E. Sex differences in movement disorders. *Nat Rev Neurol Nat Res* 2020;16:84–96.
9. Iwaki H, Blauwendraat C, Leonard HL, Makarious MB, Kim JJ, Liu G, et al. Differences in the presentation and progression of Parkinson’s disease by sex. *Mov Disord* 2021;36(1):106–117.
10. Willis AW, Schootman M, Kung N, Wang X-Y, Perlmutter JS, Racette BA. Disparities in deep brain stimulation surgery among insured elders with Parkinson disease. *Neurology* 2014;82(2):163–171.
11. Armstrong MJ, Okun MS. Time for a new image of Parkinson disease. *JAMA* 2020;77(11):1345–1346.
12. Hirsch L, Jette N, Frolkis A, Steeves T, Pringsheim T. The incidence of Parkinson’s disease: a systematic review and meta-analysis. *Neuroepidemiology* 2016;46:292–300.
13. Feigin VL, Nichols E, Alam T, Bannick MS, Beghi E, Blake N, et al. Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the global burden of disease study 2016. *Lancet Neurol* 2019;18(5):459–480.
14. Abbas MM, Xu Z, Tan LCS. Epidemiology of Parkinson’s disease—east versus west. *Mov Disord Clin Pract* 2018;5(1):14–28.

15. Maeda T, Shimo Y, Chiu S-W, Yamaguchi T, Kashiwara K, Tsuboi Y, et al. Clinical manifestations of nonmotor symptoms in 1021 Japanese Parkinson's disease patients from 35 medical centers. *Parkinsonism Relat Disord* 2017;38:54–60.
16. Savica R, Grossardt BR, Bower JH, Eric Ahlskog J, Rocca WA. Time trends in the incidence of parkinson disease. *JAMA Neurol* 2016;73(8):981–989.
17. Simunovic F, Yi M, Wang Y, Stephens R, Sonntag KC. Evidence for gender-specific transcriptional profiles of nigral dopamine neurons in Parkinson disease. *PLoS One* 2010;5(1):e8056. <https://doi.org/10.1371/journal.pone.0008856>
18. Lee J, Pinares-Garcia P, Loke H, Ham S, Vilain E, Harley VR. Sex-specific neuroprotection by inhibition of the Y-chromosome gene, SRY, in experimental Parkinson's disease. *Proc Natl Acad Sci U S A* 2019;116(33):16577–16582.
19. Gillies GE, Pienaar IS, Vohra S, Qamhawi Z. Sex differences in Parkinson's disease. *Front Neuroendocrinol* 2014;35:370–384.
20. Ascherio A, Chen H, Schwarzschild MA, Zhang SM, Colditz GA, Speizer FE. Caffeine, postmenopausal estrogen, and risk of Parkinson's disease. *Neurology* 2003;60(5):790–795.
21. Kim R, Yoo D, Jung YJ, Han K, Lee JY. Sex differences in smoking, alcohol consumption, and risk of Parkinson's disease: a nationwide cohort study. *Parkinsonism Relat Disord* 2020;71:60–65.
22. Frigerio R, Sanft KR, Grossardt BR, Peterson BJ, Elbaz A, Bower JH, et al. Chemical exposures and Parkinson's disease: a population-based case-control study. *Mov Disord* 2006;21(10):1688–1692.
23. Savica R, Grossardt BR, Bower JH, Ahlskog JE, Rocca WA. Risk factors for Parkinson's disease may differ in men and women: an exploratory study. *Horm Behav* 2013;63:308–314.
24. Bourque M, Dluzen DE, di Paolo T. Neuroprotective actions of sex steroids in Parkinson's disease. *Front Neuroendocrinol* 2009;30(2):142–157.
25. Hirohata M, Ono K, Morinaga A, Ikeda T, Yamada M. Anti-aggregation and fibril-destabilizing effects of sex hormones on  $\alpha$ -synuclein fibrils in vitro. *Exp Neurol* 2009;217(2):434–439.
26. Gatto NM, Deapen D, Stoyanoff S, Pinder R, Narayan S, Bordelon Y, et al. Lifetime exposure to estrogens and Parkinson's disease in California teachers. *Parkinsonism Relat Disord* 2014;20(11):1149–1156.
27. Canonico M, Pesce G, Bonaventure A, le Noan-Lainé M, Benatru I, Ranoux D, et al. Increased risk of Parkinson's disease in women after bilateral oophorectomy. *Mov Disord* 2021;36(7):1696–1700.
28. Yoo JE, Shin DW, Jang W, Han K, Kim D, Won HS, et al. Female reproductive factors and the risk of Parkinson's disease: a nationwide cohort study. *Eur J Epidemiol* 2020;35(9):871–878.
29. Kusters CDJ, Paul KC, Duarte Folle A, Keener AM, Bronstein JM, Bertram L, et al. Increased menopausal age reduces the risk of Parkinson's disease: a Mendelian randomization approach. *Mov Disord* 2021;36(10):2264–2272.
30. Rugbjerg K, Christensen J, Tjønnelund A, Olsen JH. Exposure to estrogen and women's risk for Parkinson's disease: a prospective cohort study in Denmark. *Parkinsonism Relat Disord* 2013;19(4):457–460.
31. Lv M, Zhang Y, Chen G, Li G, Rui Y, Qin L, et al. Reproductive factors and risk of Parkinson's disease in women: a meta-analysis of observational studies. *Behav Brain Res* 2017;335:103–110.
32. Casas S, Giuliani F, Cremaschi F, Yunes R, Cabrera R. Neuromodulatory effect of progesterone on the dopaminergic, glutamatergic, and GABAergic activities in a male rat model of Parkinson's disease. *Neurol Res* 2013 Sep;35(7):719–725.
33. Jarras H, Bourque M, Poirier AA, Morissette M, Coulombe K, di Paolo T, et al. Neuroprotection and immunomodulation of progesterone in the gut of a mouse model of Parkinson's disease. *J Neuroendocrinol* 2020;32(1):e12782.
34. Litim N, Morissette M, di Paolo T. Effects of progesterone administered after MPTP on dopaminergic neurons of male mice. *Neuropharmacology* 2017;117:209–218.
35. Marras C, Saunders-Pullman R. The complexities of hormonal influences and risk of Parkinson's disease. *Mov Disord* 2014;29:845–848.
36. Popat RA, van den Eeden SK, Tanner CM, McGuire V, Bernstein AL, Bloch DA, et al. Effect of reproductive factors and postmenopausal hormone use on the risk of Parkinson disease. *Neurology* 2005;65(3):383–390.
37. Kim YJ, Soto M, Branigan GL, Rodgers K, Brinton RD. Association between menopausal hormone therapy and risk of neurodegenerative diseases: implications for precision hormone therapy. *Alzheimers Dement (N Y)* 2021;7(1):e12174.
38. Moore O, Kreitler S, Ehrenfeld M, Giladi N. Quality of life and gender identity in Parkinson's disease. *J Neural Transm* 2005;112(11):1511–1522.
39. Saunders-Pullman R, Wang C, Stanley K, Bressman SB. Diagnosis and referral delay in women with Parkinson's disease. *Gend Med* 2011;8(3):209–217.
40. Willis AW, Schootman M, Evanoff BA, Perlmuter JS, Racette BA. Neurologist care in Parkinson disease: a utilization, outcomes, and survival study. *Neurology* 2011;77(9):851–857.
41. Pan S, Stutzbach J, Reichwein S, Lee BK, Dahodwala N. Knowledge and attitudes about Parkinson's disease among a diverse group of older adults. *J Cross Cult Gerontol* 2014;29(3):339–352.
42. Lin C-YR, Rosendale N, Deeb W. Expanding sexual and gender minority research in movement disorders: more than awareness and acceptance. *Parkinsonism Relat Disord* 2021;87:162–165.
43. Ye M, Kahana B, Kahana E, Xu S. Trust in the Doctor-Patient Relationship Enhances Well-Being and Life Satisfaction Among Older LGBTQ People. 2018. Available from: [https://academic.oup.com/innovateage/article/2/suppl\\_1/123/5170333](https://academic.oup.com/innovateage/article/2/suppl_1/123/5170333)
44. Parkinson's Foundation. Women and Parkinson's: closing the gender gap in research and care A patient-centered agenda for change [Internet]. 2019 [cited 2021 Dec 7]. Available from: <https://www.parkinson.org/pd-library/books/women-and-pd-agenda>
45. Tolson D, Fleming V, Schartau E. Coping with menstruation: understanding the needs of women with Parkinson's disease. *J Adv Nurs* 2002;40(5):513–521.
46. Gupta A, LaFaver K, Duque KR, Lingaiah A, Meriwether KV, Gaskins J, et al. Pelvic floor health in women with Parkinson's disease. *J Parkinsons Dis* 2021;11(2):857–864.
47. Solimeo S. Sex and gender in older adults' experience of Parkinson's disease. *J Gerontol B Psychol Sci Soc Sci* 2008;63(1):S42–S48.
48. Haaxma CA, Bloem BR, Borm GF, Oyen WJG, Leenders KL, Eshuis S, et al. Gender differences in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2007;78(8):819–824.
49. Post B, Merkus MP, de Haan RJ, Speelman JD. Prognostic factors for the progression of Parkinson's disease: a systematic review. *Mov Disord* 2007;22:1839–1851.
50. Marras C, Rochon P, Lang AE. Predicting motor decline and disability in Parkinson disease a systematic review. *Arch Neurol* 2002;59(11):1724–1728.
51. Nicoletti A, Vasta R, Mostile G, Nicoletti G, Arabia G, Iliceto G, et al. Gender effect on non-motor symptoms in Parkinson's disease: are men more at risk? *Parkinsonism Relat Disord* 2017;35:69–74.
52. Cerri S, Mus L, Blandini F. Parkinson's disease in women and men: what's the difference? *J Parkinsons Dis* 2019;9(3):501–515.
53. Picillo M, Palladino R, Erro R, Alfano R, Colosimo C, Marconi R, et al. The PRIAMO study: age- and sex-related relationship between prodromal constipation and disease phenotype in early Parkinson's disease. *J Neurol* 2021;268(2):448–454.
54. Raciti L, de Cola MC, Ortelli P, Corallo F, lo Buono V, Morini E, et al. Sexual dysfunction in Parkinson disease: a multicenter Italian cross-sectional study on a still overlooked problem. *J Sex Med* 2020;17(10):1914–1925.
55. Hu T, Ou R, Liu H, Hou Y, Wei Q, Song W, et al. Gender and onset age related-differences of non-motor symptoms and quality of life in drug-naïve Parkinson's disease. *Clin Neurol Neurosurg* 2018 Dec;175:124–129.

56. Martinez-Martin P, Falup Pecurariu C, Odin P, Hilten JJ, Antonini A, Rojo-Abuin JM, et al. Gender-related differences in the burden of non-motor symptoms in Parkinson's disease. *J Neurol* 2012;259(8):1639–1647.
57. Prenger MTM, Madray R, van Hedger K, Anello M, Macdonald PA. Social symptoms of Parkinson's disease. *Parkinson's Dis*. 2020;2020: 8846544. <https://doi.org/10.1155/2020/8846544>
58. Crispino P, Gino M, Barbagelata E, Ciarambino T, Politi C, Ambrosino I, et al. Gender differences and quality of life in Parkinson's disease. *Int J Environ Res Public Health* 2020;18(1):198.
59. Perrin AJ, Nosova E, Co K, Book A, Iu O, Silva V, et al. Gender differences in Parkinson's disease depression. *Parkinsonism Relat Disord*. 2017;36:93–97.
60. Picillo M, Palladino R, Moccia M, Erro R, Amboni M, Vitale C, et al. Gender and non motor fluctuations in Parkinson's disease: a prospective study. *Parkinsonism Relat Disord* 2016;27:89–92.
61. Sharma JC, Bachmann CG, Linazasoro G. Classifying risk factors for dyskinesia in Parkinson's disease. *Parkinsonism Relat Disord* 2010;16(8):490–497.
62. Hassin-Baer S, Molchadski I, Cohen OS, Nitzan Z, Efrati L, Tunkel O, et al. Gender effect on time to levodopa-induced dyskinesias. *J Neurol* 2011;258(11):2048–2053.
63. Arabia G, Zappia M, Bosco D, Crescibene L, Bagalà A, Bastone L, et al. Body weight, levodopa pharmacokinetics and dyskinesia in Parkinson's disease. *Neurol Sci*. 2002;23:s53–s54.
64. Kumagai T, Nagayama H, Ota T, Nishiyama Y, Mishina M, Ueda M. Sex differences in the pharmacokinetics of levodopa in elderly patients with Parkinson disease. *Clin Neuropharmacol* 2014;37(6):173–179.
65. Abraham DS, Gruber-Baldini AL, Magder LS, McArdle PF, Tom SE, Barr E, et al. Sex differences in Parkinson's disease presentation and progression. *Parkinsonism Relat Disord*. 2019;69: 48–54.
66. Shpiner DS, di Luca DG, Cajigas I, Diaz JS, Margolesky J, Moore H, et al. Gender disparities in deep brain stimulation for Parkinson's disease. *Neuromodulation* 2019;22(4):484–448.
67. Hariz G-M, Limousin P, Zrinzo L, Tripoliti E, Aviles-Olmos I, Jahanshahi M, et al. Gender differences in quality of life following subthalamic stimulation for Parkinson's disease. *Acta Neurol Scand* 2013;128(4):281–285.
68. Weiss D, Volkmann J, Fasano A, Kühn A, Krack P, Deuschl G. Changing gears – DBS for dopaminergic desensitization in Parkinson's disease? *Ann Neurol* 2021;90(5):699–710.
69. Jurado-Coronel JC, Cabezas R, Ávila Rodríguez MF, Echeverría V, García-Segura LM, Barreto GE. Sex differences in Parkinson's disease: features on clinical symptoms, treatment outcome, sexual hormones and genetics. *Front Neuroendocrinol* 2018;50:18–30.
70. Horstink MWIM, Strijks E, Dluzen DE. Estrogen and Parkinson's disease. *Adv Neurol* 2003;91:107–114.
71. Quinn NP, Marsden CD. Menstrual-related fluctuations in Parkinson's disease. *Mov Disord* 1986;1(1):85–87.
72. Sandyk R. Estrogens and the pathophysiology of Parkinson's disease. *Int J Neurosci* 1989;45(1–2):119–122.
73. Castrioto A, Hulliger S, Poon Y-Y, Lang AE, Moro E. A survey on the impact of the menstrual cycle on movement disorders severity. *Can J Neurol Sci* 2010;37(4):1349.
74. Mehanna R, Jankovic J. Young-onset Parkinson's disease: its unique features and their impact on quality of life. *Parkinsonism Relat Disord* 2019;65:39–48.
75. Seier M, Hiller A. Parkinson's disease and pregnancy: an updated review. *Parkinsonism Relat Disord* 2017;40:11–17.
76. Maltête D, Grangeon L, le Goff F, Ozel G, Fetter D, Ahtoy P, et al. Four cases of Parkinson disease diagnosed during the postpartum period. *Obstet Gynecol* 2017;130(1):1349.
77. Olivola S, Xodo S, Olivola E, Cecchini F, Pietro LA, Driul L. Parkinson's disease in pregnancy: a case report and review of the literature. *Front Neurol* 2020;10:1349.
78. Saunders-Pullman R, Gordon-Elliott J, Parides M, Fahn S, Saunders HR, Bressman S. The effect of estrogen replacement on early Parkinson's disease. *Neurology* 1999;52(7):1417–1422.
79. Song Y, Li S, Li X, Chen X, Wei Z, Liu Q, et al. The effect of estrogen replacement therapy on Alzheimer's disease and Parkinson's disease in postmenopausal women: a meta-analysis. *Front Neurosci* 2020;14(157).
80. Tsang K-L, Ho S-L, Lo S-K. Estrogen improves motor disability in parkinsonian postmenopausal women with motor fluctuations. *Neurology* 2000;54(12):2292–2298.
81. Donelan K, Falik M, DesRoches CM. Caregiving: challenges and implications for women's health. *Womens Health Issues* 2001;11(3):185–200.
82. Navarro-Peternella FM, Marcon SS. Quality of life of a person with Parkinson's disease and the relationship between the time of evolution and the severity of the disease. *Rev Lat Am Enfermagem* 2012;20(2):384–391.
83. Hodgson JH, Garcia K, Tyndall L. Parkinson's disease and the couple relationship: a qualitative analysis. *Fam Syst Health* 2004;22(1):101–118.
84. Fleming V, Tolson D, Schartau E. Changing perceptions of womanhood: living with Parkinson's disease. *Int J Nurs Stud* 2004; 41(5):515–524.
85. Prizer LP, Kluger BM, Sillau S, Katz M, Galifianakis NB, Miyasaki JM. The presence of a caregiver is associated with patient outcomes in patients with Parkinson's disease and atypical parkinsonisms. *Parkinsonism Relat Disord* 2020;78:61–65.
86. Chappell NL, Dujela C, Smith A. Caregiver well-being: intersections of relationship and gender. *Res Aging* 2015;37(6):623–645.
87. Dahodwala N, Shah K, He Y, Wu SS, Schmidt P, Cubillos F, et al. Sex disparities in access to caregiving in Parkinson disease. *Neurology* 2018;90(1):e48–e54.
88. Safarpour D, Thibault DP, DeSanto CL, Boyd CM, Dorsey ER, Racette BA, et al. Nursing home and end-of-life care in Parkinson disease. *Neurology* 2015;85(5):413–419.
89. Ozturk EA, Gundogdu I, Tonuk B, Kocer BG, Tombak Y, Comoglu S, et al. Bone mass and vitamin D levels in Parkinson's disease: is there any difference between genders? *J Phys Ther Sci* 2016;28(8):2204–2209.
90. Bystrytska M, Povoroznyuk V, Grygorieva N, Karaban I, Karasevich N. Bone mineral density and risk of osteoporotic fractures in women with Parkinson's disease. *J Osteoporos* 2020;2020: 5027973.
91. Wills AMA, Pérez A, Wang J, Su X, Morgan J, Rajan SS, et al. Association between change in body mass index, unified Parkinson's disease rating scale scores, and survival among persons with Parkinson disease secondary analysis of longitudinal data from NINDS. *JAMA Neurol* 2016;73(3):321–328.
92. Urell C, Zetterberg L, Hellström K, Anens E. Factors explaining physical activity level in Parkinson's disease: a gender focus. *Physiother Theory Pract* 2021;37(4):507–516.
93. Zaman A, Ellingson L, Sunken A, Gibson E, Stegemöller EL. Determinants of exercise behaviour in persons with Parkinson's disease. *Disabil Rehabil* 2021;43(5):696–702.
94. Göttgens I, van Halteren AD, de Vries NM, Meinders MJ, Ben-Shlomo Y, Bloem BR, et al. The impact of sex and gender on the multidisciplinary Management of Care for persons with Parkinson's disease. *Front Neurol* 2020;11:576121.
95. Tosserams A, Araújo R, Pringsheim T, Post B, Darweesh SKL, Int'Hout J, et al. Underrepresentation of women in Parkinson's disease trials. *Mov Disord* 2018;33(11):1825–1826.
96. Dorsey ER, Sherer T, Okun MS, Bloem BR. The emerging evidence of the Parkinson pandemic. *J Parkinsons Dis* 2018;8:S3–S8.
97. Georgiev D, Hamberg K, Hariz M, Forsgren L, Hariz GM. Gender differences in Parkinson's disease: a clinical perspective. *Acta Neurol Scand*. 2017;136:570–584.
98. Lee SK. Sex as an important biological variable in biomedical research. *BMB Rep* 2018;51:167–173.

99. Gilbert RM, Standaert DG. Bridging the gaps: more inclusive research needed to fully understand Parkinson's disease. *Mov Disord*. 2020;35:231–234.
100. Chahine LM, Chin I, Caspell-Garcia C, Standaert DG, Brown E, Smolensky L, et al. Comparison of an online-only Parkinson's disease research cohort to cohorts assessed in person. *J Parkinsons Dis* 2020;10(2):677–691.
101. Vaswani PA, Tropea TF, Dahodwala N. Overcoming barriers to Parkinson disease trial participation: increasing diversity and novel designs for recruitment and retention. *Neurotherapeutics* 2020; 17(4):1724–1735.
102. Dalrymple WA, Pusso A, Sperling SA, Flanigan JL, Huss DS, Harrison MB, et al. Comparison of Parkinson's disease patients' characteristics by indication for deep brain stimulation: men are more likely to have dbs for tremor. *Tremor Other Hyperkinet Mov (N Y)* 2019;9:1–5.
103. Pavon JM, Whitson HE, Okun MS. Parkinson's disease in women: a call for improved clinical studies and for comparative effectiveness research. *Maturitas* 2010;65:352–358.

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