



Review

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

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ABSTRACT

The incidence and prevalence of Parkinson's disease (PD) is expected to rise precipitously over the next several decades, as will the associated healthcare related costs. The epidemiology and disease manifestations of PD may differ when comparing women to men. Women are for example less likely to acquire PD, and in several studies have demonstrated a delayed onset of motor symptoms. Women, however, are more likely to experience PD-related complications that may lead to disability (e.g. depression and medication-associated dyskinesia). Further, there are purported differences in the treatment and treatment outcomes in PD men compared to women. Whether estrogen, other hormonal activity, or whether multiple factors underpin these findings remains unknown. Also unknown is whether estrogen itself may represent a therapeutic option for symptomatic PD treatment. This review summarizes what is known about gender differences in epidemiology, clinical features, treatment outcomes (medical and surgical/deep brain stimulation), and social impact among all available PD studies. We offer expert opinion regarding the shortcomings of the current evidence, and we propose a detailed list of studies that will help to clarify important gender related PD questions. Our hope is that this review will spark comparative effectiveness research into improving care and outcomes in women with PD.

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1. Introduction

Parkinson's disease (PD) is a progressive neurological condition that occurs due to the loss of dopamine producing brain and degeneration of both motor and non-motor basal ganglia circuitry. Typical manifestations include resting tremor (which is absent in approximately 20%), bradykinesia, rigidity and gait impairment. PD is associated with disability, morbidity, institutionalization, high health care utilization, costs, and even mortality [1–6]. Although there is no cure for PD, there are medical, behavioral, and surgical treatment modalities, most notably dopamine replacement/agonist therapy and deep brain stimulation, which both have been shown to improve symptoms.

The incidence and prevalence of PD is high and is rising as the population ages [7,8]. In a diverse sample of New York City residents, the prevalence of PD measured over a 4-year period was 107 per 100,000 persons, and over a 3-year period the average incidence rate was 13 per 100,000 person-years [9]. According to Dorsey et al. [10], the population of PD patients over age 50 in the United States is expected to double to 600,000 by 2030. However, the largest growth is expected to occur in Asian countries, with a population of 5 million PD patients expected in China by 2030. Factors to explain this growth include improved medical care and care access (especially in developing countries) and resultant increased life-expectancy. With improvements in health care also comes increased length of disease duration. Therefore expanding countries are met with the dual threat of increase in incidence and prevalence and subsequent strain on their burgeoning yet unstable health care infrastructures. Awareness of this impending disease burden is critical to shaping treatment strategies and social policies [10].

The epidemiology and disease manifestations of PD appear to differ slightly in men and women. Gender differences in PD are important to consider, given their potential impact on treatment strategies, outcomes, and social planning. This review will examine data on gender differences in incidence, prevalence, and disease characteristics, as well as treatment outcomes and social impact.

The underpinnings of the gender differences in PD are unknown. Some experts have pointed to hormonal levels [11–15] and others to the deposition of Lewy Bodies in the hypothalamus (part of the degenerative process) [16]. In this review we will highlight what is known about differences between men and women in PD and offer an expert opinion as to what studies need to be done to clarify important remaining questions.

2. Epidemiology

2.1. Gender differences in incidence, prevalence and age of onset of PD

There is a greater incidence of PD in men than in women [17], persisting across age groups [17,18]. In a community-based prospective study performed in Norway the incidence of PD was 1.5 times higher in men compared to women across all age groups

[19]. This finding has been replicated in two meta-analyses, which reported similar age-adjusted male:female incidence rate ratios of 1.49 (95% confidence interval (CI) 1.24–1.95, $p=0.031$) [20] and 1.46 (95% CI 1.24–1.72, $p<0.001$) [21].

Likewise, age-adjusted PD prevalence rates are higher in men than in women, even across different ethnic groups [9]. Some studies suggest that the prevalence of PD in men is almost two times higher than in women [6,7,22]. Further, age at onset tends to be later in women compared to men, though more data are needed in this area. One study reported an average age of onset of 53.4 years in women compared to 51.3 years in men [23]. In a separate community-based prospective study, age of onset of PD was found to be 68.6 in women compared to 66.3 years in men ($p=0.062$) [19]. Differences in reported ages of onset between the two studies may be due to clinic- versus community-based sampling. The gender-based difference in prevalence was not observed in some studies conducted in Asian populations [24], but methodological issues limit the interpretation of that finding.

2.2. Potential role of estrogen in epidemiological differences

The higher prevalence and incidence of PD in men compared to women and the potential delay in symptom onset among women has prompted researchers to ask whether estrogen has a role in PD. Laboratory *in vitro* data, case-controlled and prospective cohort studies, in addition to larger epidemiological surveys have all hinted at the possibility of a neuroprotective disease modifying effect of estrogen against PD. However, this notion is highly controversial and hotly debated among experts (author observations).

Factors leading to dopaminergic and non-dopaminergic neuronal degeneration in PD are thought to be multi-factorial, arising from mechanisms such as oxidative stress, inflammation, mitochondrial dysfunction, proteosomal malfunction, etc. [25,26]. Estrogens, on the other hand, are believed to influence dopamine synthesis, metabolism, and transport, and can also modulate dopamine receptor function [27]. Astrocyte and microglial injury due to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) have been shown to vary according to estrogen status, thus it has been hypothesized that the potential antioxidant property of estrogen may have a direct effect on dopaminergic neuronal survival and recovery in early PD [28].

Recent clinical and epidemiological studies have explored the association between estrogen activity and development of PD. Retrospective data have suggested that early menopause, shorter length of time from the onset of menarche to menopause, and a summation of total pregnancies exceeding 30 months, may be risk factors for PD. These findings support the notion that endogenous estrogen may play a protective role against PD development, however this remains speculative [11,12]. This theory was further supported by a small case-control study which found that the odds of developing PD were higher for women who had undergone a hysterectomy (with or without oophorectomy) [13]. The authors of that study proposed that early hysterectomy may have been a marker for ovarian dysfunction that contributed to uterine symptoms,

and eventually prompted hysterectomy. In a larger prospective epidemiologic study, participants with either unilateral or bilateral oophorectomies prior to menopause were at increased risk of “parkinsonism” and the risk was higher in those who were younger at the time of their surgery [14].

Evidence related to the association between exogenous estrogen use and the development of PD is even more uncertain. In a retrospective case-controlled study, postmenopausal use of estrogen replacement therapy was associated with lower odds of developing PD [29]. However, a separate retrospective study found that among women with surgical menopause, use of exogenous estrogen replacement was associated with substantially higher rates of PD (adjusted odds ratio (OR) 2.6, 95% CI: 1.1–6.1), whereas among women with natural menopause, there was no significant risk associated with exogenous estrogen use [12]. This apparent conflict is troublesome, but may be partially explained by differences in surgical vs. natural menopause, as there are likely unmeasured confounders in women with surgical menopause. The role of endogenous and exogenous estrogen in PD progression and management deserves major research focus as it may reveal important implications for disease outcomes.

2.3. Other potential contributors to gender-based differences in PD epidemiology

Wooten et al. [20] reviewed other potential explanations for the higher incidence and prevalence of PD among men, including increased exposure to toxins and head trauma [30]. Genetic risk factors such as X-linkage of disease [31] have also been proposed. Others have suggested that selective mortality and delay in diagnosis secondary to limited access to care may explain lower reported prevalence rates among women as well as among African-Americans [9]. Higher baseline dopamine levels have also been noted in women when compared to men, and this may be a key factor in influencing the delay of disease onset among women [23].

3. Consequences of Parkinson's disease in women

3.1. Possible gender-based difference in motor symptoms

Some studies have suggested that women with PD tend to have a delay in the onset of certain motor symptoms, compared to men with PD [19]. At presentation, women are more likely than men to exhibit the tremor-dominant PD phenotype, which seems to be associated with a slower deterioration in Unified Parkinson's Disease Rating Scale (UPDRS) scores [23]. One study observed that among patients with PD for greater than 5 years, overall UPDRS motor scores were better in women compared to men [32]. Many motor symptoms other than tremor (such as difficulty writing, fumbling/clumsiness, and gait instability) were found to occur less frequently in female PD cohorts, although symptoms were assessed by self-report [33]. Other authors found that dyskinesias were reported more frequently by women than by men [32]. These findings however have not been rigorously confirmed.

The effect that estrogen may have on differences in motor symptoms remains unclear. In a small questionnaire study, motor UPDRS scores and subjective visual analogue motor scores were not associated with estrogen and progesterone levels during menstruation [34]. Larger prospective studies have suggested that the delay in onset of motor symptoms may be related to higher levels of dopaminergic activity at disease onset in females [23,35]. However, there are no known gender differences in rate of physiological deterioration of dopaminergic brain activity, or overall clinical motor score deterioration once PD symptoms develop [23], although this has not yet been carefully and rigorously measured.

Further investigation is needed to determine whether the potential neuroprotective/disease modifying effects of estrogen may become less effective with the loss of dopaminergic neurons during disease progression. Further, more research is needed to confirm whether higher levels of dopaminergic activity exist in women and whether that may account for a delay in the clinical onset of symptoms.

3.2. Possible gender-based difference in neuropsychiatric symptoms

The neuropsychiatric manifestations of PD may also differ in men and women. Cognitive impairment, as measured by the Mini-Mental Status Examination score, has been reported more commonly in men with PD [32], although it has also been more studied in men. In one univariate analysis, male sex was associated with impairment in several cognitive domains of the Montreal Cognitive Assessment tool, including memory, visuospatial and executive function, attention, and language function. However, the gender effect was attenuated in a multivariate analysis, which controlled for age, education and disease severity [36]. If the finding of worse cognitive impairment in men with PD is confirmed, it will differ from the gender-based disparity in cognitive impairment observed in many unselected populations of older adults. Although findings are not universal, women are typically more likely to experience cognitive decline [37], and are at higher risk for developing dementia when compared to matched male groups [38]. The reasons for the opposite tendency observed in PD populations are unknown, although there is speculation that this reflects slower progression of disease among women.

3.3. Gender differences in physical disability in PD

Women with PD generally report greater disability and worse quality of life when compared to men with PD [22]. However, one small study found no gender differences in PD patients' reporting of fatigue or physical activity level at baseline [39]. Objective measures of disability are lacking in PD literature but one study reported that women had worse UPDRS postural instability scores as compared to men [40], although this finding requires verification. Older women's functional disadvantage, compared to their male peers, has been well-documented in general populations of older adults, and does not seem to be specific to PD [41–43].

3.4. Gender differences in behavior and affect in PD

In one study of persons with Parkinson's disease who live in nursing homes, the prevalence of behavioral problems was found to be similar between men and women [44]. There were gender differences, however, among specific types of behavior disturbances. Women tended to be less likely to have wandering, verbal and physical abusiveness, but were more likely to have depressive symptoms [44]. Depression is a commonly reported treatment side-effect in women with PD, and it has been associated with distress [33]. Occurrence of hallucinations has not been found to differ significantly by sex [44,45], although this outcome can be difficult to determine in older adults with cognitive impairment. According to two studies that relied on questionnaire data and one study that used clinical criteria, rapid eye movement behavior disorder (RBD) appears to present more commonly in men [46–48]. There may be additional gender-based differences in the treatment of affective and behavioral disorders in PD. In a sample of nursing home patients with PD, men were more likely to receive antipsychotics, whereas women were more likely to receive antidepressants, although this finding may not be generalizable to community-dwelling PD patients [44].

3.5. Gender differences in comorbidities that may impact care in PD patients

The management of women with PD requires attention to several common comorbidities. Compared to women without PD, women with PD have a twofold increased risk of hip fracture and also have an estimated 7.3% lower bone mineral density (BMD) score [49]. In the same prospective cohort study of 8105 community-dwelling women, ages 65 and older, increases in fracture risk among those with PD ($n = 73$) seemed to be specific to hip fractures [49]. Community-dwelling women with PD were more likely to present with a history of depression when compared to men (similar to what was found in nursing homes) [40]. Medical treatment for PD symptoms may exacerbate certain comorbidities, and there are gender-based differences in side-effect profiles. In one study of treatment-related side-effects in PD, women were more likely than men to develop worsening edema but less likely to report somnolence [45]. In PD, as in the general population of older adults, higher levels of disability and comorbidity among women may not translate into higher mortality. Overall 3-year mortality among nursing home patients with PD has been estimated at 50%, and male gender, rather than female gender, was associated with increased mortality risk [50]. This is also consistent with the general population of PD patients, in which mortality is higher in men compared to women [51].

4. Treatment and management of Parkinson's disease in women

Medical treatment of PD includes levodopa, dopamine agonists, anticholinergics, monoamine oxidase inhibitors, amantadine and several other pharmacologic agents on the market and under study. The treatment impact of sex hormone has been studied in men with PD, who tend to have lower levels of testosterone [52]. However, large treatment trials of testosterone replacement did not improve motor outcomes [53]. Surgical treatments, such as deep brain stimulation and lesion therapy can be effective in the treatment of selected PD symptoms in a subset of patients. There are purported differences in the treatment receipt and outcomes in men and women. Whether estrogen or other hormonal activity can explain these differences remains unclear, as does whether estrogen itself may represent a therapeutic option in the treatment of PD.

4.1. Gender differences in medical treatment outcomes

Although men may exhibit more severe motor dysfunction, women are known to develop more levodopa-induced dyskinesias [32,54,55]. Women with PD, however, have a greater response to levodopa compared to men, and this difference may be explained by the increased bioavailability of levodopa in women [34].

4.2. Gender differences in surgical treatment receipt and outcomes

A systematic review of the literature between 1985 and 1999 on pallidotomy, thalamotomy and deep brain stimulation procedures revealed that women with PD were less likely than men to undergo PD-related surgical intervention (35% females and 65% males) [56]. In a small prospective study of 38 PD patients who underwent surgical treatment, time between disease onset and surgical therapy appeared to be longer in women compared to men (mean time 15 years vs. 10 years, $p < 0.01$) [57]. Whether this was due to delayed onset of symptoms and differing disease course among women, access to care, or disparities in candidate selection for surgery was unclear. Although women with PD generally have worse disability

status compared to men [40,57], in a small study of PD patients who received bilateral subthalamic deep brain stimulation, the ability to perform activities of daily living seemed to improve more in women compared to men [55]. This finding was replicated in a study that investigated gender differences in clinical status before and after several forms of surgery used to address PD symptoms, including deep brain stimulation directed toward the thalamus, pallidum or subthalamic nucleus, as well as pallidotomy and thaladotomy lesions [57]. Following surgical intervention, women also had greater improvement in emotions and in their social life [57]. In light of the delayed time to surgery for women, yet a greater improvement in clinical status post-surgery, Hariz et al. suggested that women should be considered as candidates more often and earlier in the disease course [57]. However, these data are derived from small samples in relatively uncontrolled analyses and more research is needed to better understand disparities.

4.3. Possible role of estrogen in the treatment of PD

Both animal and clinical studies have suggested a possible neuroprotective or disease modifying effect of estrogen on dopaminergic neuronal systems. However, whether exogenous estrogen can modulate the progressive deterioration of dopamine in PD is less certain. This exciting research arena may yield more tailored therapy for women and novel treatment options for men. The findings to date are intriguing, though certainly not conclusive. In a retrospective study of 138 patients with PD who were levodopa naive, the use of estrogen was associated with an improvement in UPDRS scores [58]. The Parkinson's Disease on Estrogen Therapy Replacement in Menopause Years (POETRY) trial, a multi-center randomized double-blinded controlled trial, proposed to study the safety, tolerance and effect of estrogen replacement therapy (ERT) on control of symptoms of PD [22]. Twenty-three patients were recruited, however, recruitment was limited by the release of the Women's Health Initiative study results which demonstrated potential risks associated with ERT. Findings in the limited group of patients enrolled in POETRY suggested that ERT was safe and well-tolerated. Among women with PD who received ERT, the investigators noted objective improvement in motor function as measured by the UPDRS scale. However, levodopa-induced dyskinesias were a common side-effect of medical therapy in women with PD, and ERT did not seem to improve dyskinesia [22]. In another randomized double-blind prospective study, women with PD and known motor fluctuations who received low dose estrogen had greater improvement in motor fluctuations ("on" and "off" times) as well as in UPDRS motor scores [59]. In a prospective, double-blind, placebo-controlled study, estrogen use was associated with a lower than expected amount of intravenous levodopa dosing required to achieve best anti-Parkinson's effects [60].

Estrogen use may also moderate the development of cognitive decline in women with PD, although once again, many questions remain. In an observational study of 24,402 nursing home patients with PD, women who were estrogen users were more likely to be cognitively intact as measured by the Mini-Mental Status Exam (MMSE) and Test for Severe Impairment (45% of estrogen users compared to 33% of non-estrogen users, $p < 0.001$) [44]. The effect persisted after controlling for age, although other likely confounders exist that could not be adjusted for in this analysis. Estrogen replacement in older adult women may improve verbal memory [61], but has not been shown to improve working memory [62], which is often impaired in persons with PD progression [63].

Shulman [15] proposes that across the literature there are inconsistencies in the type of estrogen replacement, duration of estrogen therapy, and temporal relationship of estrogen use in relation to other medical and surgical treatment modalities. She points out that there is little literature on how estrogen may affect specific

Table 1
A call for improved clinical studies and comparative effectiveness research.

Area of uncertainty	Problems w/current studies	Future studies needed
Role of estrogen in epidemiological gender differences in Parkinson's disease (PD)	-Small samples -Retrospective studies -Incomplete control for confounders -Outcomes that are not PD specific -Measures and outcomes assessed by self-report/recall	-Large-scale prospective studies evaluating endogenous and exogenous estrogen in PD occurrence and progression
Role of brain pathology in epidemiological gender differences in PD	-Have not utilized available real-time functional imaging -Limited data on gender differences in relevant pathology (hypothalamus, dopamine activity)	-Use of functional imaging to detect gender differences in pathology of PD -Prospective studies to evaluate gender differences in dopaminergic activity in PD development and progression
Gender differences in PD presentation and symptoms	-Small studies -Retrospective data collection -Few symptoms and signs assessed	-Large prospective studies assessing symptoms and signs associated with PD -Prospective studies that consider patient-reported outcomes as well as objective measures of function -Prospective inclusion of newly diagnosed PD patients
Gender differences in effectiveness of PD treatment	-Lacking many relevant outcomes -Limited data on gender differences in outcomes of medication treatment -Differences in surgical treatment outcomes reported small studies, with limited control of confounders	-Randomized controlled trials, powered to detect differences in medical and surgical treatment effectiveness in women vs. men -Randomized controlled trial of estrogen therapy for management of PD symptoms in women with PD, with attention to adverse outcomes -Studies of medical decision-making processes in PD that may explain gender-based referral biases for surgery or choice of medical agents
Gender differences in social impact of PD	-Few, small studies assessing psychosocial parameters and societal burden of PD -Reliance on retrospective data	-Prospective studies with detailed evaluation of potential predictors of poor quality of life and reduced social involvement -Randomized, controlled trials to assess the effectiveness of multi-component interventions designed to impact patient-reported outcomes and reduce social burden of PD, with attention to differences in gender-specific roles

symptoms associated with PD, or what the potential adverse effects might be in a PD population. Therefore, further large-scale studies are needed to replicate results and to elucidate the role of estrogen in the treatment of PD symptoms in women.

5. Social impact

Women are likely to experience many complications of PD which have significant impact on their quality of life and their capacity to contribute to and engage in the community. With the aging of the population, society is expected to experience commensurate caregiver and economic burdens associated with PD.

5.1. Social impact of common complications in women with PD

A Norwegian study of older women found that their most important determinants of quality of life were: sensory abilities, relationships with others, ability to learn, ability to remember important information and make decisions, feeling hopeful, and the ability to participate in the community [64]. These findings underscore the importance that older women place on societal contact and social contributions. Unfortunately, many of the PD-related complications that disproportionately affect women threaten their ability to fulfill these cherished societal roles. Motor fluctuations, including levodopa-induced dyskinesias, are common among women with PD, and are associated with poor quality of life [65,66]. Functional disability seems to occur more frequently in women with PD compared to men, and functional disability itself, as measured by the Schwab and English disability scale is also associated with worse quality of life. Depression is also common in women with PD and has been linked to poor quality of life among patients with PD [67]. Both medical and surgical treatments among women with PD are known to improve both physical and emotional status.

Since these factors have a significant impact on women's ability to remain active members of society, advancement in gender-specific medical and surgical therapy is important. Special attention to the predictors that may relate to impaired quality of life and social involvement is warranted in an effort to help reduce the overall social burden of this disease.

5.2. Gender-specific considerations related to caregiving in PD

Caregiver stress is impacted by the level of the patient's cognitive impairment, behavioral disturbances, and functional disability [68], all of which can prove severe in late-stage PD and can also potentially vary by gender. Women with PD are thought to have less cognitive impairment and fewer abusive behavior disturbances, but they have higher functional disability when compared to men. For both men and women with PD, the presence of a caregiver may assist in preventing hospitalizations and delaying nursing home admissions [68]. However, because of the female survival advantage, disabled women are more likely than disabled men to lack a spousal caregiver.

6. Conclusion

Although epidemiological studies suggest that the incidence and prevalence of PD in women is lower than in men, and that the age of onset is delayed, with the aging population, the number of afflicted women remains very high and is increasing. Moreover, women seem to be at increased risk of experiencing some of the clinical manifestations and complications of PD. Whether estrogen plays a significant role in epidemiologic gender differences, disease characteristics, and management of PD in women is still under investigation and warrants further study. In both genders, the impact of PD is significant for patients, caregivers, and for soci-

ety. In light of the small number of high-quality, appropriately powered studies that have focused on women with PD or gender differences in the disease, we believe this review should serve as a call for improved clinical research and comparative effectiveness research. We have suggested several studies that will be required to advance the field (Table 1).

Contributors

J.M. Pavon: Performed literature review, interpreted findings, drafted manuscript, involved in manuscript review and revision; H.E. Whitson: Provided project oversight, performed literature review, interpreted findings, involved in manuscript review and revision; M.S. Okun: Provided expert opinion, involved in manuscript review and revisions.

Conflict of interest

J.M. Pavon and H.E. Whitson: No competing interests; M.S. Okun: Dr. Okun has in the past received honoraria for educational talks for Medtronic. Dr. Okun serves as a consultant and is the National Medical Director for the National Parkinson's Foundation (NPF). Dr. Okun receives research support from NIH, NPF, Parkinson Alliance, and Michael J. Fox Foundation.

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