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REVIEW

Sex Differences in Parkinson's Disease: A Narrative Review

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ABSTRACT

Sex differences in epidemiology, clinical features, and therapeutical responses are emerging in several movement disorders, even though they are still not widely recognized. Parkinson's disease (PD) is not an exception: men and women suffering from PD have different levels of disability. Research has been performed using multiple databases and scientific journals; this review summarizes the available evidence on sex differences in PD regarding epidemiology, risk factors, genetics, clinical phenotype, social impact, and therapeutic management. The role of hormones in determining such differences is also briefly discussed. The results confirm the existence of differences between men and women in PD; women have a higher risk of developing disabling motor complications and non-motor fluctuations compared to men, while men have a higher risk of developing cognitive impairment, postural instability, and gait disorders. Improving our knowledge in these differences may result in the implementation of strategies for disease-tailored treatment and management.

Keywords: Parkinson's disease; Sex differences; Motor symptoms; Non-motor symptoms; Estrogen

Key Summary Points

Why carry out this study?

Sex differences in Parkinson's disease (PD) have been reported in various aspects, such as epidemiology, risk factors, clinical symptoms, treatments, and drug reactions. Biological and environmental factors may underlie these differences, and estrogen may have neuroprotective properties.

The aim of this publication is to perform a narrative review of recently published information on sex-related differences in patients with PD; increased recognition of their impact is a determining factor in the management of this neurodegenerative disease.

What was learned from this study?

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The results confirm the existence of differences between men and women in PD; women have a higher risk of developing disabling motor complications and non-motor fluctuations, while men have a higher risk of developing cognitive impairment, postural instability, and gait disorders. Moreover, women with PD experience disparities in care.

Further studies are needed in this area to improve our understanding of sex differences in PD.

INTRODUCTION

Parkinson's disease (PD) is the second most frequent neurodegenerative disease after Alzheimer's [1], affecting approximately 1% of people over the age of 60 [2]. PD is more common in older people; however, in recent year there has been an increase in juvenile onset [3]. Globally, approximately 10 million people live with PD, with a higher incidence in Caucasians than in Asians and Africans [4, 5]. Due to the increase in life expectancy, a 50% increase in the number of individuals affected by PD is expected by 2030 [4]. PD is characterized by typical motor manifestations such as tremor, slowness of movement, muscular stiffness, and postural instability. In addition to these, there may be non-motor symptoms such as constipation, pain, mood or cognitive deterioration, swallowing problems, and urinary and sleep disorders [6]. The cause of PD remains unknown but seems to result from a complicated interplay of genetic and environmental factors leading to the degeneration of dopaminergic nigrostriatal neurons and consequent dopamine deficiency [7–9]. Moreover, neurological disorders may be influenced by sex differences in brain organization, structure, and function [10]. Genetic and hormonal factors determined by sex characteristics are important in the development and functioning of brain structures from conception [11]. In addition to these intrinsic biological factors, other external socioeconomic and environmental factors including lifestyle can contribute to sex differences in the risk of developing the disease, influencing its course and prognosis [12]. The aim of this publication is to perform a narrative review of recently published information on sex-related differences in patients with PD, to increase the recognition of their impact as a determining factor in the management of this neurodegenerative disease. From a practical point of view, precise identification of the sex differences is important for tailoring treatment, predicting outcomes, and meeting other individual and social needs in women and men with PD: these data may serve as a starting point for further research on the influence of sex and gender in PD. As this is a narrative review, a systematic literature review was not conducted. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Epidemiology, Risk Factors, and Mortality

Sex differences in both prevalence and incidence of PD are widely reported [13]. The prevalence of PD is 1.5 times higher in men than in women, and the incidence, adjusted for age, is on average twice as high in men as in women (19/100,000 for men and 9.9/100,000 for women) [14, 15]. Higher incidence ratios are reported in western countries and South America, in comparison to Asian populations [16]. The onset of symptoms in women is delayed on average 2.2 years compared to men [17]. Men with PD were found to have a slightly higher mortality risk than women; male sex is therefore an important risk factor for the development of PD [18]. Although young people can be affected as well, the risk of PD increases with age, and this male risk preponderance may be more pronounced in older age [19]. Other risk factors may also differ between the two sexes. Some studies have shown an increased risk of PD in men due to head trauma, immunological diseases, or exposure to pesticides, solvents, and metals [20, 21]. Caffeine consumption seems to lower PD risk more in men than in women, probably because of an interaction between caffeine and

hormones [22]. Urate (uric acid) is a potent antioxidant, and oxidative stress is thought to play a role in the pathogenesis of PD. Rodent models of PD have provided consistent evidence that urate can protect against dopaminergic neuron degeneration [23]. High urate levels have been associated with lower PD risk and with a better PD prognosis, but the association is consistent among men and weaker among women, suggesting a sex-specific relationship between urate levels and nigrostriatal dopamine depletion in men [24]. The reduced risk of PD among women is not completely understood. Differences in underlying biology, environmental exposures, and behaviors may be important, suggesting a multifactorial origin [25].

Neurochemical Differences

Sex differences begin during embryonic brain development [26] and continue throughout its growth, affecting brain morphology and neuronal connectivity [11]. It was reported that at disease onset, women showed higher striatal dopamine binding levels and a higher baseline number of dopamine neurons than men [27]. This is relevant to PD, in which the loss of dopamine neurons gradually leads to clinical symptoms [28]. Thus, with a higher reserve of dopamine neurons, women are likely to develop clinical symptoms later in life compared to men [28]. The basal ganglia in humans present a sex-related dimorphism, particularly in the dopaminergic system: its malfunction is important not only in the development of PD but also in chorea and in Tourette syndrome [29]. This could be linked to the estrogenic status in women in the preclinical phase of the disease [29]. Furthermore, a significant reduction in the content of gangliosides, phospholipids, and water was highlighted in the substantia nigra (SN) of men but not of women. These neurochemical changes provide evidence of a selective neuronal loss in the SN of men with PD that is correlated with disease duration and severity [30].

Genetics

Gene expression patterns in dopaminergic neurons differ between men and women, and the effect of PD in this gene expression is strongly influenced by sex. The genes overexpressed in females are mainly involved in signal transduction, neuronal maturation, and oxidative stress protection, while the genes overexpressed in males (*SNCA* and *PINK1*) are implicated in the pathogenesis of PD [31]. These sex differences may create a more disadvantageous condition for neurodegeneration in men [31]. Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are a common cause of genetic PD. Some studies have found a higher prevalence of *LRRK2* mutations among women than among men [32]. Abnormalities in the LRRK2 protein may cause neurodegeneration through its kinase activity, with downstream effects on alpha-synuclein and neuroinflammation [32]. A well-validated genetic risk factor for PD is a mutation in the gene encoding the lysosomal enzyme glucocerebrosidase (β-D-glucosyl-*N*-acylsphingosine glucohydrolase; GBA) that degrades the glycosphingolipid glucocerebroside: GBA deficiency has deleterious effects on nigrostriatal function [33, 34]. A recent systematic review and meta-analysis clarified that there is a gender difference between female and male patients with PD, with a higher prevalence of this mutation in women with PD [35], especially for the most severe variants [36]. PD is a synucleinopathy, a neurodegenerative disease characterized by the abnormal accumulation of alpha-synuclein (α-syn) [37]. Experimental studies have demonstrated elevated nigral α-syn accumulation after pharmacological inhibition with the GBA inhibitor conduritol B epoxide (CBE) [38]. Much attention has been focused on the X and Y sex chromosomes which may influence the sex differences, in particular on the SRY region of the Y chromosome that encodes transcription factors responsible for gonadal differentiation and consequently of the production of sex hormones [39]. Moreover, X-chromosome galactosidase alpha (GLA) mutations increase the risk of PD only in women [40]. In conclusion, it is hypothesized that the alterations in chromosomal, hormonal,

and other factors still unknown would lead to a dimorphism of the basal ganglia, resulting in distinct pathogenetic mechanisms for the two sexes highlighted at a clinical level [41].

Hormones

Sex hormones are among the main factors in structural differences and functions of the brain [42], as well as critical factors for sex differences in the susceptibility to disease [19]. The most important hormone is estrogen, more precisely 17β-estradiol, which is recognized for its neuroprotective activity that may benefit women, even in the case of PD [19]. The development of symptomatic PD may be delayed by higher physiological striatal dopamine levels, possibly due to the longer estrogen exposure during a female's lifetime [17]. Estrogen might also prevent Lewy body deposition through specific α-synuclein anti-aggregation and fibril destabilization properties [28, 43]. Estrogen is an important regulator of dopaminergic cell plasticity and function, stimulates the extension and branching of the neurites [41], and reduces the autophagy and severity of neuronal injury in mice [44, 45]. Many genetic studies have shown a close relationship between autophagy and PD pathophysiology [46, 47]. Estrogen can rescue dopaminergic neurons by restoring impaired autophagy in patients with PD and reduce the rate of apoptosis [48, 49]. Emerging evidence indicates that mitochondrial dysfunction is also closely associated with the pathogenesis of sporadic and familial PD [50]. Mitochondria, as a source of energy, are critical for sustaining proper brain and nerve cell activity [51]. Impairment of mitochondrial function can result in cell damage and death, which can lead to neurodegenerative disorders [50]. Estrogen increases antioxidant responses and potentiates respiratory chain activity in the female brain by inducing the expression of mitochondrial proteins and enzymes [42]. Neural stem cells (NSCs) have shown a protective effect that might be related to their ability to modulate estrogen balance, increasing mitochondrial biogenesis and limiting oxidative stress and mitochondrial autophagy [52].

The neuroprotective action of estrogens can also arise from the activation of anti-inflammatory pathways [41]. Neuroinflammatory processes are considered critical in the onset and development of neurodegenerative diseases. Estrogen has been found to modulate the response of microglia and astrocytes against oxidative and inflammatory injury in rodent models of PD, resulting in dopamine neuron protection [53]. Animal models with estrogen deprivation show dopaminergic neuron loss and altered dopaminergic metabolism and transporter uptake, which can be partially reversed by the administration of exogenous estrogen [28]. The MitoPark mouse model, which was created by inducing mitochondrial dysfunction and effectively expresses progressive movement disorders as seen in PD, displays more severe phenotypes in males than in females, and females that underwent ovariectomy exhibited a course similar to that of males [54]. Another important female gonadal hormone is progesterone, which has demonstrated neuroprotective activity in animal models of PD [55]. In mice injected with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), progesterone prevented striatal depletion of dopamine and its metabolites and prevented dopamine transporter (DAT) downregulation in the striatum and substantia nigra [56]. Progesterone elicited neuroprotective and neuromodulatory effects on striatal dopaminergic, glutamatergic, and GABAergic neurotransmission systems in rats with unilateral injection of 6-hydroxydopamine (6-OHDA) [57]. In the brains of women, the highest levels of progesterone metabolites dihydroprogesterone and allopregnanolone were found in the substantia nigra, while male patients had reduced levels of these hormones in plasma and cerebrospinal fluid [58, 59].

A recent study of human postmortem brain tissue found that allopregnanolone was increased in the substantia nigra in the early stage of PD as compared to controls, while it was reduced in the advanced stage of PD. The authors suggest that a potentially protective upregulation of allopregnanolone occurs in the early stages of PD, followed by downregulation of progesterone metabolites at later stages that may exacerbate PD [60]. On the other hand,

the role of androgens in the nigrostriatal dopaminergic system in PD is still unclear [61]. To date, the effects of testosterone supplements on dopaminergic function have been the subject of debate, since both neuroprotective and toxic effects of testosterone are reported [62]. The higher androgen level relative to estrogen in women in the postmenopausal state and its role in the increased incidence of PD after menopause remain to be investigated. Nevertheless, in gonadectomized female rats, dihydrotestosterone treatment was found to have no effect on 6-OHDA toxicity, whereas estradiol showed a protective effect, suggesting that increasing androgen levels in females have no damaging effect on the dopaminergic system [63]. Female patients who had increased exposure to estrogen were found to have a significantly reduced risk of developing PD over the course of their lives [28]. Greater fertile life duration and number of pregnancies may be associated with delayed age of PD onset [64]. On the other hand, women who have undergone ovariectomy or are taking oral contraceptives have a higher risk of PD, and symptoms may worsen during or prior to menstruation due to the decrease in estrogen levels [19]. Nevertheless, postmenopausal estrogen use is associated with a decreased risk of developing PD, and estrogen may also decrease levodopa-induced dyskinesia in women [65, 66]. Finally, estrogen may also influence levodopa treatment in PD: female patients with low lifetime estrogen exposure had lower dopamine transport availability and required greater changes in monthly levodopa equivalent dose [67].

Motor Symptoms

Sex differences in motor symptoms are present from the onset of the disease [68, 69]. At disease onset, women have a more benign phenotype [70] and a prevalence of tremor compared to men (67% vs. 48%) [71]. However, greater postural instability has been observed in women, and the female sex is among the predictors of the risk of falls, while greater rigidity, more frequent abnormal postures such as camptocormia, and higher risk of gait freezing were detected in men [72]. Women have a higher ratio of dopamine receptor 1 (D1) to dopamine receptor 2 (D2) in the striatum compared to men. Considering that in the basal ganglia, motor functions are facilitated through the D1 direct pathway and inhibited through the D2 indirect pathway, this sex difference in the expression ratio of the dopamine receptors may contribute to the later appearance of motor symptoms in women [73]. A 5-year longitudinal analysis of 423 patients with PD from the Parkinson's Progression Markers Initiative database reported that men had a significantly higher score than women in part III (motor symptoms) of the Movement Disorder Society Unified Parkinson's Disease Rating Scale, during the ON status (when the patient is supposed to be optimally treated). They also required a higher dosage of dopaminergic drugs. These results suggest that the progression of the disease is faster in men than in women [74]. Men present writing difficulties, speech problems, and sialorrhea more frequently than women [72].

In contrast to this more benign phenotype of PD parkinsonian motor symptoms, women have a higher risk of complications due to pharmacological treatment with levodopa [71]. Women develop motor fluctuations and dyskinesia more frequently than men [75]. In particular, the risk of "wearing off" is approximately 80% higher in women than in men, with a significant economic burden [76]. A "sex effect" has been clearly demonstrated for the onset and severity of levodopa-induced dyskinesia. Female sex is the most important independent risk factor, irrespective of body weight, in the development of levodopa-induced dyskinesia. The risk for dyskinesias is three times higher in women, with an average of 4 years of time to dyskinesia development in women, and 6 years in men [77]. A "brittle response" to levodopa has recently been described in women to define the presence of highly disabling dyskinesias after taking small doses of levodopa (e.g., 100 mg or less per dose). Dyskinesia is strongly correlated with levodopa bioavailability, and women achieve significantly higher maximum plasma concentrations of levodopa than men [78]. A wearing-off effect is also associated with levodopa plasma levels, and their stabilization may contribute to reducing this complication [79]. Several factors may

play a role in this sex discrepancy, including differences in absorption, lower body weight and lower body mass index, alteration of the central networks, and genetic polymorphism [80].

Non-Motor Symptoms

Although PD is classically considered a movement disorder, non-motor symptoms (NMS) are also relevant [81], with some already present during the prodromal phase of the disease and others more frequent during the advanced phase [82, 83], and are generally poorly understood and consequently poorly treated [84]. NMS involve various clinical aspects, including cognitive and sexual dysfunction, psychiatric and behavioral problems, cardiovascular symptoms, sleep, and gastrointestinal and genitourinary disorders [85]. Although many NMS are very common even in healthy elderly subjects, several studies have demonstrated a significantly higher prevalence in patients with PD [86]. In recent years, several studies have suggested the existence of sex-related differences in NMS [87]. Anxiety, sadness, depression, fatigue, dysphagia, constipation, and pain are more common in women, while men suffer more from sialorrhea, urinary dysfunction, hypotension, sleep behavior disorders, and daytime sleepiness [88–90]. The PRIAMO study found a significant correlation between psychiatric symptoms in women, and in particular anxiety, and the prevalence of more severe cardiovascular symptoms. This observation suggests that anxiety and cardiovascular autonomic symptoms may overlap, with a possible mutual worsening of the two disorders [91]. Impulse control disorders, a common complication of dopamine agonist medication, may also differ between sexes, with men more likely to develop compulsive sexual behavior and women more likely to develop pathological shopping and "binge eating" [92]. NMS can fluctuate either along with or irrespective of motor ON/OFF phenomena. With the progression of disease, women present a worsening of non-motor symptoms and non-motor fluctuations (NMF) compared to men; therefore, female sex represents a risk factor for the development of NMF [93, 94]. Mood-related NMF (i.e., anxiety, mood changes) are more prevalent in women, but despite this difference, they do not receive different treatments than men, suggesting that NMF remain mostly undertreated in women [95, 96]. Mild cognitive impairment is present in 30–40% of patients from the early stages of the disease and can evolve in the advances stages towards dementia, with a significant impact on patients' and caregivers' quality of life [97]. Women progress towards cognitive impairment more slowly than men, and male sex is considered an important predictor of cognitive impairment in PD [98, 99]. Moreover, there is a sex-specific pattern for these cognitive changes, with deficits in verbal fluency and facial emotion recognition more prevalent in men, while a reduction in visuospatial cognition occurs more frequently in women [98, 99].

Pregnancy

Pregnancy in PD is rare [100], as the most common age of onset is beyond the childbearing years and the proportion of patients younger than 50 years is only 5% of the overall cases [101]. The incidence of pregnancy in PD is unknown and is limited to the cases reported in the literature [102]. Generally, there is a worsening of both motor and non-motor symptoms during pregnancy, although it rarely significantly affects activities of daily living [103]. Reduction or withdrawal of dopaminergic treatment may have a role in the worsening of parkinsonian symptoms [102]. There are no specific guidelines for the use of antiparkinsonian treatments during pregnancy. Levodopa has the best safety data and has not been associated with birth complications or specific teratogenicity; therefore, it is considered the first-line treatment in pregnant women with PD [104]. Amantadine is the only drug that has resulted in heart malformations in babies with first trimester exposure, and thus should be avoided. The information for other pharmacological and surgical treatments is less clear [105]. Data on breastfeeding are very limited, and breastfeeding is typically not suggested while on antiparkinsonian medications [105]. Deep brain stimulation could be a safe option in the management of young

women with PD who wish to become pregnant, in light of its efficacy with regard to psychomotor status and medication sparing [106]. An optimized care plan should include close cooperation between neurology and obstetric teams during pregnancy and delivery [104].

Disease Care and Quality of Life

Evidence suggests that women with PD experience a longer time from onset of symptoms to diagnosis [107] and to the first visit with a movement disorder specialist [108]. Women also receive less frequent neurologist care [109]. Specialist care is associated with a reduced risk of hip fracture, hospitalizations for PD-related illness, and skilled nursing facility admission [110]. Mortality and healthcare costs are lower for patients seen by a specialist, who are also more likely to use occupational, physical, and speech therapy. Consequently, women are at greater risk for negative health outcomes [111, 112]. Women with PD are more likely to be widowed or alone and more frequently use a paid caregiver, while men with PD are more likely to have a spouse as their primary caregiver [113]. A retrospective study involving 85 patients with PD showed that male patients tended to have an informal caregiver (family members, partners), while women were less frequently cared for by their partners [114]. Caring for a person with PD becomes increasingly challenging with the progression of the pathology, which may increase comorbidities, anxiety, and depression and may also be a barrier to caring for their own health needs. Women caregivers frequently suffer from mood disorders and are unable to adequately manage their own chronic condition, becoming more vulnerable [114]. Female patients generally have a poorer quality of life than men, especially in terms of emotional well-being, social support, and psychological distress [115]. Screening and management of psychological distress and anxiety, particularly for women, should therefore be implemented as part of the clinical care of PD [115]. In conclusion, while the risk of developing PD is reduced in women, those diagnosed with the disease can encounter greater hurdles in obtaining an accurate diagnosis, may be less likely to see medical specialists, experience worse quality of life, and receive less social and familial care than men with PD. Addressing these disparities and other sex-specific needs among the population of PD women can improve their quality of life [116].

Treatment

Although the international scientific societies have recommended considering different variables in the pharmacological approach for patients with PD (e.g., age, motor symptom severity, motor fluctuations), no sex-specific guidelines or recommendations are available to date [117]. Men and women are treated with similar dopaminergic medications and therapeutic regimens [118]; however, several studies find that women are prescribed a lower levodopa equivalent daily dose, probably because they are more likely to experience levodopa-related dyskinesia and motor fluctuations [119]. Levodopa dosage per kilogram of body weight is a significant and independent risk factor for the development of dyskinesias in PD [120–122]. Notably, this factor appears to contribute to a higher incidence of dyskinesias in women with PD [120, 121]. While few studies have attempted to define specific levodopa dose thresholds for clinical practice, available evidence suggests that a daily levodopa dose exceeding 5.6–5.8 mg/kg/day strongly predicts the likelihood of dyskinesia developing over the course of the disease (odds ratio: 3.61) [120–122]. Therefore, it is crucial that this threshold is assessed before initiating levodopa treatment in both women and men, along with regularly monitoring of body weight changes throughout the progression of PD. No other data are available regarding sex differences of antiparkinsonian drugs, except for safinamide, where two international multicenter studies demonstrated the same treatment efficacy in both sexes despite women showing more motor complications and non-motor fluctuations than men at baseline [123, 124]. Male patients receive more prescriptions for antipsychotic drugs, although psychiatric symptoms are more common in women, probably because men are more prone to becoming

Table 1 Main sex differences in Parkinson's disease

Differences in risk factors	Smoking, caffeine, and uric acid: women < men Alcohol: men > women
Differences in motor symptoms	Postural instability and gait disorder: women < men
Differences in non-motor symptoms	Depression, anxiety, pain: women > men Cognitive impairment: men > women
Differences in motor complications (wearing-off; dyskinesia)	women > men
Accessibility to deep brain stimulation	women < men
Accessibility to medical/social support (specialists, nurses, caregivers)	women < men

aggressive than women [125]. Deep brain stimulation (DBS) is an effective treatment in PD, particularly for patients with poor symptom control and motor complications, which are more common in women [126]. Despite this, women are less likely to receive DBS and also access surgical procedures later than men [127]. Men and women have similar improvements in motor symptoms after DBS; however, after DBS women have greater improvement in quality of life and dyskinesia, while in men there is an improvement in camptocormia [128]. Evidence suggests that many behavioral interventions and modifications (e.g., exercise, certain diets, voice and speech therapy) may improve PD motor and non-motor symptoms [129]. Physical therapy, in particular, may be more beneficial for women in improving bone mineral density, given their higher prevalence of osteoporosis [130, 131].

CONCLUSIONS

Sex differences in PD risk, symptoms, treatment, and care are pronounced; however, many knowledge gaps remain, including the role of estrogen. This article offers a narrative review of recent information, presenting these differences from various perspectives (Table 1).

Several studies show that women have an initial more benign phenotype, however, as the disease progresses, they develop highly disabling complications compared to men. In addition to this variability, there are other sex differences that cannot be simply attributed to biological factors, such as decline in health-related quality of life, accessibility to advanced therapeutics, and disparities in care and support environment. Women are also underrepresented in clinical studies, and trial results are generally described in the overall population, without exploring potential differences between men and women. Therefore, a consideration of sex differences may facilitate the development of strategies for the management of patients with PD, and help them to maintain their life activities with appropriate medical treatment.

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Declarations

Conflict of Interest. Carlo Cattaneo is an employee of Zambon SpA. Javier Pagonabarraga has received compensation for speaker-related activities from Zambon SpA. All authors declare no other competing interests or financial disclosures for this review.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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