

Gender Differences in the Natural History and Management of Parkinson's Disease

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Parkinson's disease (PD) is a progressive neurodegenerative disorder that has been estimated to affect up to 1% of Americans over the age of 65.¹ While there is currently an insufficient amount of information on gender disparities in PD, available data suggest that there are differences in the epidemiology, symptoms, medication effects and surgical outcomes for women and men with the disease.²

Changes in the levels of estrogen during the female lifecycle may contribute to gender disparities in PD patients. The role of estrogen in neuroprotection has been studied in animal models, and some research suggests that dopaminergic neurons (which are depleted in PD) are preserved under estrogen's influence.

This article reviews the current knowledge about gender differences in PD and discusses recent research as well as future areas for research.

Idiopathic Parkinson's Disease

Idiopathic PD is a disorder characterized by loss of dopaminergic neurons in the substantia nigra of the midbrain, resulting in the classic

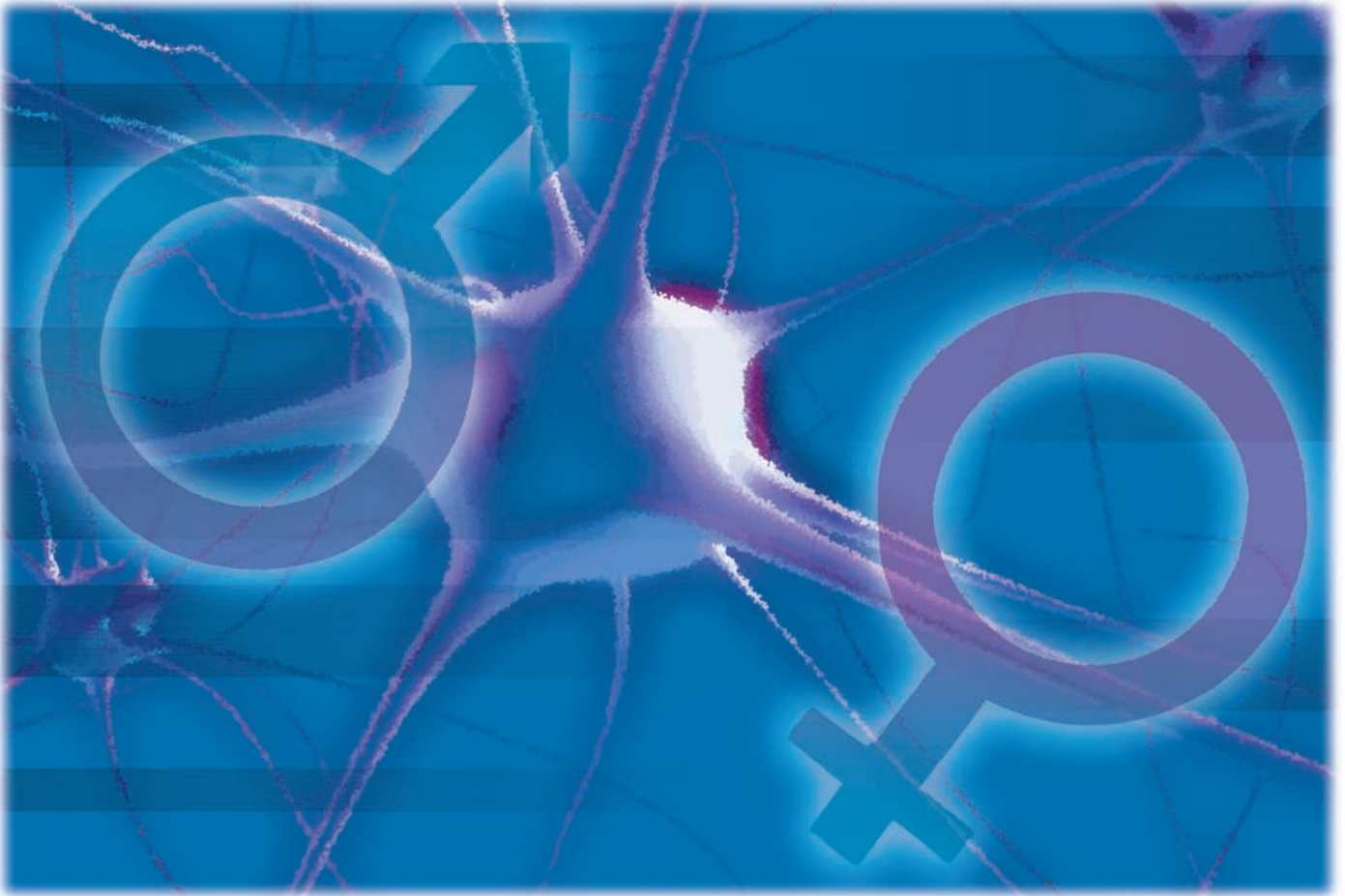
syndrome of PD: tremor, bradykinesia, rigidity and postural instability (Table 1, page 16). The etiology of this debilitating disorder is unclear, although both genetic and envi-

ronmental factors are thought to play a role. Diagnosis of idiopathic PD is based on clinical criteria. Although lab tests and neuroimaging are not diagnostic, imaging is often performed to rule out alternative etiologies.

Therapy for PD focuses on control of both motor (tremor, bradykinesia) and non-motor (depression, autonomic dysfunction) symptoms, and on preventing disability (Table 2, page 16). Although the progression of PD cannot be halted or delayed by any available therapies, multiple drugs are now available to treat PD, including levodopa, dopamine agonists and drugs that inhibit enzymes involved in dopamine metabolism, such as monoamine oxidase (MAO) inhibitors and catechol-O-methyltransferase (COMT) inhibitors.

Epidemiology

PD is more common in men than in women. Studies report the ratio of males to females with PD to be between 1.5 and 3.7.³⁻⁵ A disproportionate male incidence is also seen



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in other types of parkinsonism (vascular and post-encephalitic), but equal numbers of men and women experience drug-induced parkinsonism.⁴ Women have a longer life expectancy than men, which may result in a longer lifespan with PD symptoms.⁶ Thus, greater longevity in women results in a rising percentage of females affected with PD, despite the lower incidence in this group. There is conflicting evidence regarding a possible difference in mortality between men and women with PD.⁷⁻⁹

One of the largest PD trials, the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism

(DATATOP) study, enrolled PD patients in an approximate 2:1 ratio of men to women,¹⁰ which is reflective of many clinical PD trials. Both the underlying disparity of prevalence and a disparity in motivation to participate in clinical trials likely explain these inequitable gender ratios.¹⁰

Female Lifecycle Changes and PD

The female lifecycle is characterized by hormonal fluctuations coinciding with menstruation, pregnancy and menopause. Medical and surgical interventions that affect or involve hormonal changes include administration of oral contraceptives and hormone therapy (HT), as well as hysterectomy and oophorectomy. The effect of fluctuations of endogenous and exogenous hormonal levels on brain function—and PD specifically—has begun to be studied. A recent case-control study found that the risk of PD was greater in women with reduced years of fertility (less than 36 years), greater duration of

cumulative pregnancies (more than 30 months) or an earlier onset of menopause.¹¹

Fewer years of fertility resulting in reduced levels of endogenous estrogen over a woman's lifespan may be a risk factor for PD.^{11,12} One retrospective study compared women with and without PD, and found that women with PD were more likely to have undergone surgical hysterectomy than were women without PD.¹³ Women with PD also tended to have earlier menopause and used estrogen therapy (ET) less frequently than women without PD. In an additional study, bilateral oophorectomy was found to increase the risk of PD (hazard ratio [HR] 2.0, $P = .047$), but not unilateral oophorectomy (HR, 0.9).¹⁴ The sample sizes in these studies are small and the latter study did not report on the use of HT following surgical menopause. Taken together, these studies suggest that less exposure to endogenous and

Table 1. Symptoms of Parkinson's Disease*

Classic Symptoms

- Tremor
- Rigidity
- Bradykinesia
- Postural instability

Other Symptoms that may Accompany Parkinson's Disease

- Depression
- Anxiety
- Apathy
- Difficulty swallowing
- Speech changes
- Urinary problems or constipation
- Seborrhea
- Sleep problems
- Cognitive dysfunction
- Orthostatic hypotension
- Muscle cramps and dystonia
- Pain
- Fatigue and loss of energy
- Sexual dysfunction

*Adapted from National Institute of Neurological Disorders and Stroke, *Parkinson's Disease: Hope Through Research*

Table 2. Standard Approaches to Management of Mildly Impaired Parkinson's Patients*

- *Levodopa*: reduces symptoms of Parkinson's disease during both early and advanced stages of disease
- *Dopamine agonists* (eg, *bromocriptine*, *pergolide*, *apomorphine*, *pramipexole*, *ropinirole*): given alone or in conjunction with levodopa to mimic role of dopamine in the brain
- *Monoamine oxidase (MAO) B inhibitors* (eg, *selegiline*, *rasagiline*): inhibit monoamine oxidase B enzyme, which breaks down dopamine in the brain
- *Catechol-O-methyltransferase (COMT) inhibitors* (*entacapone*, *tolcapone*): prolong the effects of levodopa by preventing breakdown of dopamine.
- *Amantadine*: can help reduce symptoms of Parkinson's disease and reduces levodopa-induced dyskinesia.
- *Anticholinergics* (*trihexyphenidyl*, *benztropine*): decreases activity of acetylcholine to help reduce tremors and muscle rigidity

*Adapted from National Institute of Neurological Disorders and Stroke, *Parkinson's Disease: Hope Through Research*

exogenous estrogens may be associated with an increased risk of PD.

There are limited reports of pregnancy in women with PD; however, one case report suggests that pregnancy caused progression of the symptoms of PD.¹⁵ It is unclear whether the progression of PD was due to the effects of pregnancy over a 9-month period, or the natural course of this neurodegenerative illness.¹⁵

Additionally, estrogen has been suggested to have an influence on PD symptoms. Some studies have suggested that ET can provide a significant reduction in PD symptoms without altering drug-related dyskinesias.^{16,17}

Other Factors: Caffeine and PD

Epidemiologic studies have shown gender-specific associations between the risk of PD and caffeine consumption.¹⁸⁻²⁰ There appears to be an inverse relationship between caffeine intake and PD risk; however, this relationship has been found only in men and not in women. Furthermore, data specifically examining the use of ET found that women who drank more coffee and were taking ET actually had a higher risk of developing PD.^{19,20} This finding was replicated in an animal model of PD, which found that ET prevented the protective effect caffeine demonstrated on dopaminergic cell loss.²¹ This appears contradictory to the previous findings in the literature (of less estrogen exposure increasing the risk of PD in women); however, there may be an interaction between caffeine and estrogen that explains these findings.

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Gender Disparities in PD Symptoms

Gender comparisons of PD symptoms in sample populations of clinical trials have shown similar rates of tremor, rigidity, bradykinesia and handwriting difficulty in women and men.^{10,22} It is difficult to draw conclusions from these studies since the generalizability of populations in clinical trials is limited by predetermined inclusion criteria. Likewise, subjects recruited from subspecialty clinics are likely to be selected subgroups. In one study, women were more likely to report pain as a major component of their symptoms—describing discomfort of the neck and lower back—and were also more likely to describe depression as “continually distressing” than their male counterparts.²² Dizziness, slowing of hand movements and loss of facial expression were more frequently troubling to women surveyed during visits to a PD center.²³ In a novel study performed at a Canadian PD center,²⁴ on initial presentation women had greater PD severity with more postural in-

stability than men. This may indicate that women present for medical diagnosis and treatment later than men, or that PD progression is more rapid in females.

Several studies have suggested that estrogen may also have an influence on PD symptoms in women. One observational study found that elderly women with PD who were taking ET for primary or secondary osteoporosis prevention had more depressive symptoms and were more likely to be on an antidepressant than were non-users of ET;²⁵ however, women taking ET were less likely to have severe cognitive impairment than women with PD who were not taking ET. Data on concurrent use of dopaminergic agents were not provided. Interestingly, several randomized controlled trials of non-PD patients suggest that ET may result in fewer depressive symptoms and/or improved scores on psychological and social well-being questionnaires.^{26,27}

Several other studies have suggested that HT may be protective for the development of dementia in the PD setting.^{28,29} A single study suggested that ET may have a beneficial effect on balance, which can be a major disability in PD;³⁰ however, this finding has not been adequately tested and has been refuted by others.³¹ Some studies have found that ET may be beneficial for symptom severity in early PD prior to initiation of levodopa therapy, and may even be helpful in reducing levodopa dosage.^{32,20} Reducing fracture risk and maintaining bone strength with nonpharmacologic methods or pharmacologic therapies includ-

ing ET are important goals in PD management.

Although the cited studies suggest a symptomatic effect of estrogen on PD, the relative effects of estrogen and progesterone on neuronal function and survival remain unclear.

Estrogen and Neuroprotection

While evidence from the last 15 years generally supports the hypothesis that estrogen stimulates the dopamine pathways and has neuroprotective effects, studies of animal models from the 1970s and 1980s suggest that estrogen has antidopaminergic effects models.³³⁻³⁷ Estrogen modulates dopaminergic neurotransmission, and may act as an anti-apoptotic agent or antioxidant.³⁸ Animal studies have demonstrated that estrogen modulates dopamine by altering expression and function of the dopamine receptor, and by stimulating dopamine release and reuptake.^{39,40} Estrogen has also been found to regulate dopaminergic neuronal plasticity and stimulate neurite extension and branching.⁴¹ Some studies have suggested that estrogen may be protective to dopaminergic neurons prior to toxic insults.^{36,42-44} Estrogen may also modulate MAO and COMT activity (enzymes involved in dopamine metabolism) through various mechanisms.^{36,45} Altered neurotransmission following gonadal hormone withdrawal may contribute to degenerative disorders (such as PD) occurring at menopause in predisposed women.

Other mechanisms for estrogen's putative neuroprotective effects have been suggested. Estrogen's molecu-

Levodopa administration has also been found to significantly improve motor function in women—more so than in men.

lar ring structure may act as a free radical scavenger.⁴⁶⁻⁴⁸ It also may activate the mitogen-activated protein kinase pathway, which modulates Bcl-x(L) expression to reduce neuronal injury after exposure to toxins.^{49,50} There are many other mechanisms by which estrogen may play a role in the incidence, severity and management of PD in women.^{2,51} These varied roles may contribute to the observed gender differences; however, more research is needed to translate estrogen's effects on the nigrostriatal dopaminergic system into guidelines for clinical management.

Gender Differences in PD Therapy

Gender differences are generally not acknowledged in published clinical guidelines of PD management.⁵² However, evidence of gender disparities in medication response, pharmacokinetics and adverse effects suggests the need for more attention to gender differences in clinical management. In general practice, levodopa is the most potent agent used to treat PD; it remains the mainstay of therapy,

although newer medications—such as dopamine agonists and drugs that inhibit enzymes involved in dopamine metabolism (inhibitors of MAO and COMT)—are also frequently used. Greater symptomatic relief can often be achieved with combinations of these medications. Agents aimed at protecting dopamine neurons continue to be actively studied but, thus far, compounds including coenzyme Q10, creatine, minocycline, vitamin E, selegiline and rasagiline have no solid evidence to support their use for delaying PD progression.⁵³ The major conundrum in the management of PD is the development of adverse effects with chronic levodopa therapy. Although levodopa and other antiparkinsonian medications remain effective throughout the duration of the disease, chronic therapy results in fluctuations of response and involuntary movements (dyskinesia) in most patients, and drug-induced psychosis in a subset of patients.

Standard dosing of PD medications results in women receiving higher dosages of levodopa in milligrams per kilogram of weight. This may explain why several studies show that women are more likely to have drug-related dyskinesias.⁵⁴⁻⁵⁷ Levodopa administration has also been found to significantly improve motor function in women—more so than in men.⁵⁸ Although drug-related dyskinesias are a major problem in PD management, no studies of levodopa dose adjustment by weight have been conducted.

Pramipexole (PPX) is a dopamine agonist often used with levodopa to increase the dopaminergic effect.

Studies suggest that women have a greater levodopa bioavailability than men and that pharmacokinetic properties differ between the sexes.^{59,60} These studies support a gender difference in the clearance of dopaminergic agents, which may play a role in gender-specific dosing of PD medications.

COMT, an enzyme involved in levodopa and dopamine metabolism, has been found to have lower activity in women compared with men, and is downregulated by 17-beta estradiol.^{61,62} This gender difference in COMT inhibition has been found to be negated by use of an estrogen-receptor antagonist.⁶³ The COMT inhibitors (like tolcapone and entacapone), which are used to increase the amount of levodopa available for transport to the brain, have also been reported to have different tolerability profiles based on gender, which may result from disparities in optimal levodopa dosage.^{64,65} In addition, hormonal factors may play a role, since catecholestrogen (an estrogen metabolite) competitively inhibits COMT enzyme activity. The lower levels of COMT in women may contribute to the beneficial effects of ET in postmenopausal women with PD.^{20,32}

Surgical therapies for PD, such as deep brain stimulation, thalamotomy and pallidotomy, are being used more frequently for symptomatic control in selected patients. One analysis of patients who had undergone one of these surgical procedures for PD found that both sexes improved, but women experienced greater benefit in their activities of daily living, emotional health and social functioning.⁶⁶

The possibility of gender disparities in access to surgery and clinical trials should be considered by referring physicians.

Unfortunately, one third of 145 clinical trials of surgery in PD did not report the gender of their study subjects. Among the articles that did report gender, the sex distribution of patients who underwent surgery was 35% female and 65% male.⁶⁷ The possibility of gender disparities in access to surgery and clinical trials should be considered by referring physicians.

Conclusions

The average age at onset of PD is about 60 years, with many patients diagnosed in the fifth and sixth decades of life. The actual timing of the onset of the disease process (pre-clinical) is unknown, but it is generally believed that neuronal injury begins 5–10 years prior to the initial symptoms. Therefore, the onset of PD bridges the premenopausal and menopausal years, and all facets of the physiologic changes of the years of fertility, perimenopause and menopause experienced by women with PD. This differentiates PD from Alzheimer's disease, the most common neurodegenerative disorder. Our understanding

of gender differences in the natural history and management of PD is just beginning. Greater recognition and knowledge of these gender differences will foster improved diagnosis and management of this disease. ■

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This article includes discussion of off-label use of medications.

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