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Estrogens and Parkinson Disease

Neuroprotective, Symptomatic, Neither, or Both?

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Parkinson disease is a neurodegenerative disorder caused by substantia nigra dopamine cell death and is characterized by bradykinesia, rigidity, rest tremor, and postural instability. Epidemiologic and clinical studies have suggested that gender and estrogen play a role in modulating Parkinson disease. The etiology of the estrogenic effect is unclear—it may be neuroprotective, symptomatic, or both. Retrospective studies suggest a possible neuroprotective role. Interventional studies have suggested a positive modulatory role or no role at all. While it is difficult to establish whether there is a true neuroprotective benefit of estrogen in the setting of even mild symptomatic benefit, laboratory data suggest such a neuroprotective role. Estrogen may act as an antiapoptotic agent, an antioxidant, or a neurotrophic modulating agent, promoting crosstalk with neurotrophic factors. The selective estrogen receptor modulators (SERMs) may also confer neuroprotection. However, prior to establishing the role of estrogen in Parkinson disease, additional study, including of the SERMs, is warranted.

Key Words: Parkinson disease; estrogen; selective estrogen receptor modulators; levo-dopa; nigrostriatal system.

Introduction

Parkinson disease is a progressive neurodegenerative disorder, afflicting more than 1 million individuals in the United States alone *(1)*. It causes stiffness, slowness, tremor, unsteady gait, and falls. While initial response to medication for Parkinson disease is usually excellent, within about 5 yr of starting levo-dopa (L-dopa), most patients develop a fluctuating and inadequate response to the medication, either "wearing off"; a reemergence of parkinsonian symptoms prior to the next dose of medication; or dyskinesias, involuntary choreiform movements. In contrast to Alzheimer disease, epidemiologic data have demonstrated that the incidence of Parkinson disease is greater in men than women *(2,3)*, suggesting that female gender may be protective for the development of Parkinson disease. Further, some clinical features of Parkinson disease are different between the sexes: for example, women develop more dyskinesias and require less L-dopa than men, even when adjusted for body weight *(4,5)*.

Therapies aimed at modulating the course of Parkinson disease focus on neuroprotection to retard the degenerative course or symptomatic treatment to improve the disabling symptoms. Therefore, interventions that delay the onset of Parkinson disease, retard its progression, or diminish its symptoms could significantly improve the quality of life. Estrogen has been shown to decrease nigrostriatal cell death as well as modulate the course of Parkinson disease *(6–9)*. Because female gender may confer protection from the development of Parkinson disease and has been associated with a different clinical course, better understanding of the gender differences and the role estrogen plays in mediating these differences holds promise for expanded understanding and treatment. This review addresses gender differences in the epidemiology and clinical course of Parkinson disease, briefly addresses mechanisms by which estrogen may mediate some of these differences, and then assesses the clinical data supporting and refuting a neuroprotective and symptomatic role for estrogen.

Gender Differences in Epidemiology

Parkinson disease is pathologically characterized by degeneration of the substantia nigra with loss of melanized pigmented dopaminergic neurons, with Lewy body inclusions in the remaining neurons *(10,11)*. Parkinson disease is under the umbrella of parkinsonian disorders (parkinsonism), which include conditions with additional clinical and neuropathologic features, such as multiple-system atrophy and progressive supranuclear palsy.

PD is a common disorder that, although affecting men at a greater rate than women, is extremely prevalent among women. Prevalence estimates of parkinsonism (for both sexes) vary, ranging between 80.6 *(12)* and 187 *(13)* per 100,000 persons/yr, and parkinsonism may afflict as many as 1:100 individuals over the age of 60 *(14)*. Most studies demonstrate gender differences in the incidence of Parkinson disease. The adjusted relative risk of Parkinson disease in men compared with women was 2.13 (confidence interval: 1.11–4.11) in

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a cohort of 4341 Italian individuals ages 65–84 who were followed through screening or examination for an average of 3 yr to assess the incidence of Parkinson disease *(2)*. Because the incidence of Parkinson disease increases with age, and women constitute a greater proportion of the aged population, Parkinson disease is highly prevalent among women. Some incidence studies suggest that the gender differences decrease with age *(15)*, whereas others show increases with aging *(16)*.

Clinical Differences in Parkinson disease by Gender

There are symptomatic clinical differences between men and women with Parkinson disease. Women with Parkinson disease have increased dyskinesias at equivalent dosages of L-dopa *(4,5)*. Furthermore, men have been shown to have significantly worse motoric function than women after 5 yr of disease, despite taking more L-dopa *(5)*. This suggests either that Parkinson disease is more malignant and rapidly progressive in men, or that men do not have as optimal a response to L-dopa. Women are usually prescribed lower doses of L-dopa than men *(5)*. Men with Parkinson disease also seek medical advice earlier than women. There are several possible explanations. First and most likely, men may reach a symptomatic threshold earlier, supporting the notion that Parkinson disease is more progressive in men. Second, women may be at a lower risk of Parkinson disease during perimenopausal years, when they had been recently exposed to higher endogenous estrogen levels than age-matched men, and may have a milder course, therefore presenting later. Finally, there may be issues of gender bias in seeking and receiving medical attention, which are independent of biologic factors.

Laboratory Data Suggest a Modulatory Role for Estrogen in the Nigrostriatal System

While clinical gender differences may be attributed to nonhormonal influences, there is a wealth of basic scientific data that gives mechanisms by which estrogen may mediate gender-specific differences. Animal and cell culture studies suggest that estrogen may mediate both nigrostriatal viability and neurotransmission. Improved cell survival in vitro and in animal models holds promise that estrogen may be neuroprotective, and increased dopaminergic neurotransmission may translate into improved symptomatology.

A Basis for Estrogen Effects in Nigrostriatal System: Receptor-Dependent and -Independent Mechanisms

Estrogen may be mediating its effects through classic (genomic) or nonclassic mechanisms. Estrogen's action is currently known to occur through two different intracellular estrogen receptors (ERs): ERα and the more recently discovered ERβ. It may also work through additional putative membrane receptors *(17)*. While ERs were previously thought not to exist in the nigrostriatal system, both ERα and ERβ have been demonstrated in the nigrostriatal system during development *(18)*, and, more important, expression of ERβ has been demonstrated in the substantia nigra and the ventral tegmental area (VTA) *(19,20)*. In particular, around midbrain dopamine-containing cell groups, ERβ immunoreactivity was found in subsets of dopaminergic and nondopaminergic neurons in the dorsal VTA and the substantia nigra pars lateralis *(20)*. There is a difference between ERβ immunoreactivity in male and female rat brains, suggesting that estrogen may exert its function in different brain regions in a gender-specific manner *(19)*. Effects of estrogens may be stereospecific and may vary depending on the subtype of ER as well. Stimulation of ERα has been associated with cell survival, whereas ERβ induces apoptosis *(21)*. Alternatively, estrogen may be working through nonclassic mechanisms independent of nuclear receptors *(22)*.

Table 1
Possible Mechanisms of Estrogen in Parkinson Disease

Symptomatic	Neuroprotective
Dopaminergic	Antiapoptotic
Promoting DA synthesis and release	Antioxidant
Increasing DA receptor affinity	Neurotrophic
Altering DA uptake	modulating agent
Decreasing DA degradation (e.g., COMT inhibition)	
Nondopaminergic	
Opioid	
Glutamatergic	
GABAergic	

Modulatory Effects of Estrogen

Estrogen's effects on the nigrostriatal system can be classified on the level of chemical and neuroanatomic changes, and/or neuronal survival (see Table 1).

Modification of Dopaminergic Transmission

Estrogen modulates dopaminergic neurotransmission via pre-, post-, and perisynaptic mechanisms *(23–25)*. Presynaptically, estrogen may modulate dopamine (DA) synthesis and release *(23,24,26)*. Estrogen-treated ovariectomized (OVX) female mice had increased neuronal DA synthesis and release *(27)*. 17β-Estradiol increases striatal tyrosine hydroxylase activity in OVX rats *(26)* and could therefore stimulate DA synthesis. Dopaminergic synaptic contacts change during the estrous cycle, implicating a role for estrogen *(28)*. Estrogen also changes DA receptor density and affinity. In OVX female rats and male rats treated with estrogen, DA receptor density is increased *(29–31)* and the D2 receptor shifted from high affinity to low affinity *(32)*. Estrogens may alter the intracellular milieu by increasing transcription of microtubular proteins and synaptic vesicles *(33)*. Postsynaptically, estrogen decreases catechol-*o*-methyl-

transferase (COMT) gene transcription, as measured by 50% decreased COMT mRNA transcription *(34)* and reduction in COMT activity *(35)*. The COMT inhibitor entacapone is a symptomatic pharmaceutical treatment for Parkinson disease because it can increase "on" time (relief of parkinsonism) by 5% *(4)*. Hence, if estrogen decreases the COMT system, it may have pharmacologic potential for increasing DA availability and be antiparkinsonian. Estrogen also alters monoamine oxidase activity *(36)*, and similar pharmacologic correlates with the mildly antiparkinsonian medication selegiline can be inferred.

Neuroprotective Effects of Estrogen

Estrogen has been demonstrated to influence neural development through effects on differentiation and neural plasticity *(6,17)*, although the timing may markedly change the effect because estrogens may promote cell death during development and cell survival in aging *(37)*. Estrogen may act as an antioxidant or as a neurotrophic modulating agent, promoting cross talk with neurotrophic factors, or as an antiapoptotic agent. These effects may be through regulation of nuclear receptors, through modulation of the membrane receptors, or it may be receptor independent. Assessing neurotoxicity with glutamate, Sawada et al. *(38)* showed that neuroprotection of rat ventral mesencephalic cultures occurring with β-estradiol pretreatment was present when either the biologically active β- or α-estradiol was used, and whether or not ERs were blocked. This also supports a role for estrogen in reducing oxidative stress, since preincubation with β-estradiol suppressed intracellular oxygen radicals induced by hydrogen peroxide *(38)*. Callier et al. *(39)* demonstrated that both 17α-estradiol and 17β-estradiol protect dopaminergic neuronal cultures from toxicity induced by L-methyl-4-phenylpyridinium or 6-hydroxy dopamine, suggesting nongenomic effects, possibly also through antioxidant properties. Further, pretreatment with estrogen decreases 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced apoptosis *(40)*. Cyr et al. *(41)* and Garcia-Segura et al. *(6)* review extensively these and other studies implicating neuroprotective effects.

Multiple roles for estrogen in the nigrostriatal system have therefore been shown in animal models: estrogen may modulate neuronal development and plasticity, modify neural transmission, and decrease nigral cell death.

Clinical Data on Role of Estrogen in Parkinson Disease

A Neuroprotective Role for Estrogen?

Clinical data regarding the role of estrogen are conflicting. Most clinical data support a role of estrogen in improving parkinsonism, whereas some data refute a positive estrogenic effect. The development of Parkinson disease is believed to be multifactorial, with a genetic component prominent in early onset Parkinson disease, and environmental factors are believed to exert a greater effect in later onset Parkinson disease *(42)*. Smoking and caffeine consumption have both been demonstrated to decrease the risk of Parkinson disease; however, the protective effect of caffeine was only noted in men *(43)*. If estrogen's effect is antiapoptotic, then exogenous estrogen exposure might be associated with a lower prevalence of Parkinson disease or may delay its onset. Two studies did not demonstrate a role of prior estrogen exposure in affecting the risk of developing Parkinson disease *(44,45)*, although in one study ascertainment of hormone use was done retrospectively, and the other study was small. Despite the retrospective nature, Marder et al. *(44)* were able to demonstrate an association between decreased dementia with Parkinson disease and exogenous hormone replacement.

Others have argued that exogenous estrogen is not the determining factor, but that duration from menopause is more predictive, and that this accounts for the narrowing of the male/female difference in incidence with increasing age *(15)*. Because parkinsonism may start perimenopausally, and cell loss may be in the premenopausal years, exogenous postmenopausal estrogen may not be the only estrogenic factor. Rather, a matrix of endogenous and exogenous estrogen exposure, which factors in age at menarche, pregnancy and lactation, oral contraceptive use, age at surgical or natural menopause, as well as postmenopausal endogenous hormone levels, may be more revealing.

Endogenous estrogen levels may be of great importance, because men may have greater estradiol (via aromatization of testosterone) in later life than women. Therefore, the absence of a protective effect of exogenous estrogens suggests that the gender difference in Parkinson disease may be estrogen independent, or may reflect a complex matrix of estrogen exposures that is not revealed in the limited studies to date. In a population-based case-control study assessing the association of Parkinson disease with age at menopause, type of menopause, and estrogen replacement therapy (ERT), Benedetti et al. *(45)* used the medical records linkage system of the Rochester Epidemiology Project and identified 75 pairs of women with Parkinson disease and age-matched control subjects between 1976 and 1975. Whereas ERT was inversely associated with risk of Parkinson disease (odds ratio: 0.47) and women with Parkinson disease had experienced early menopause (≦46 yr) more frequently than control subjects, neither were statistically significant in this sample. However, the investigators did find a significant association between prior hysterectomy (with or without unilateral oophorectomy) more often than control subjects *(45)*. Taken in isolation, it is unclear whether the abrupt onset of menopause and withdrawal of hormones is causative, suggesting that an overall matrix of exposure may not be as important as the timing of estrogen exposure.

A Symptomatic Role for Estrogen?

In parallel to basic studies, some clinical studies also support a modulatory role of estrogen independent of a neuro-

protective role. However, studies are conflicting, with some emphasizing that the modulation is prodopaminergic, whereas others show estrogen to be antidopaminergic. Early case reports in particular suggested that estrogen was antidopaminergic and worsened Parkinson disease and improved dyskinesias (chorea associated primarily with hyperdopaminergic states). These data sharply contrast with several recent reports, that suggest a prodopaminergic effect of estrogen. The apparent discrepancy between the early findings and the recent ones may be related to the doses of estrogen used for hormone replacement, which are currently much smaller. However, even some recent studies have not all shown a prodopaminergic or beneficial response to estrogen. Further, while nigral DA loss is the causative agent for Parkinson disease, other transmitter systems are involved with and modulate nigrostriatal function. As clinical worsening with Parkinson disease is felt secondary to misfiring in two parallel loops of physiologic function, termed the *direct* and *indirect pathways (46)*, nondopaminergic modulation at different stages along the pathway, such as via modification of *N*-methyl-D-aspartate, may also change the expression of Parkinson disease.

Retrospective Studies

Case reports, in particular, are conflicting. Most reports of premenopausal women with Parkinson disease suggest that there is menstrual worsening of Parkinson disease and a need for more L-dopa during the perimenstrual period when estrogen levels are low. Of 12 premenopausal women with Parkinson disease, 90% had worsening of Parkinson symptoms before their period, including a reduction in the duration of the L-dopa effect *(47)*. Further, some patients increased their dose of L-dopa during the perimenstrual state *(48)*. By contrast, others have reported worsening of parkinsonism and improved dyskinesias with estrogen treatment *(49–52)*. After treatment with conjugated estrogen, Bedard et al. *(50)* reported a woman whose parkinsonism markedly worsened and the dyskinesias completely abolished after treatment with exogenous estrogens. Conversely, cessation of estrogen therapy has also been reported to worsen Parkinson symptoms and increase motor fluctuations *(7)*.

In our study of postmenopausal women with early Parkinson disease, we compared those who had taken hormone replacement therapy (HRT) with those who had never taken HRT. Those who had undergone HRT had improved motor scores as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) *(8)*. We performed a retrospective chart review of women with presumed idiopathic Parkinson disease for less than 5 yr who were not taking L-dopa at their first visit, and compared parkinsonian scores for women with early Parkinson disease who had never taken HRT with those who had *(8)*. Ever having undergone HRT was associated with a better UPDRS score, and hence milder parkinsonism, whereas longer duration of disease and older age at onset were associated with worse motor scores. We also found that the older the age at onset, the greater the effect of estrogen. This effect may reflect that estrogen levels are lower in the older population, and, therefore, ERT exerts the most beneficial effect in this group. Older women may have been exposed to exogenous hormones longer and thus could have experienced a milder course of Parkinson disease. Alternatively, estrogen may delay or reduce the onset such that Parkinson disease is detected later. Our study did not show a higher age at onset in the estrogen-treated group; it was, in fact, lower by 5 yr than the no-estrogen group. This suggests either that estrogen may have a symptomatic benefit via modulation of the nigrostriatal pathway, or that estrogen may have a neuroprotective effect, with women taking estrogen having milder disease. The latter hypothesis is supported by the previously described gender discrepancy of men having more Parkinson disease, but as women age (and become more hypoestrogenic), the relative frequency of disease in women approaches that of men.

Retrospective studies have been limited in that they have assessed the role of exogenous estrogen use at only one sampling point, and did not address progression well, and because they did not assess endogenous estrogen levels *(5,8)*. As an extremely potent hormone, estrogen may confer an effect in low doses, so it is necessary to assess endogenous levels in postmenopausal women and men to appropriately test the hypothesis that estrogen may account for gender differences.

Observational Studies

In an effort to assess the role of sex steroids in influencing Parkinson disease in premenopausal women, Komplioti et al. *(53)* performed a 5-wk study correlating changes in the UPDRS with hormonal changes in the menstrual cycle in young women with parkinsonism. They did not show significant fluctuation during the cycle. This suggests that prior case reports were overreporting menstrual fluctuations. Alternately, a change may not have been seen because of the underlying milder disease status of the women, or an overall low baseline UPDRS, such that if the effect of hormonal fluctuation is mild, it may not be noticed in this less disabled group.

Interventional Studies

Although interventional studies avoid the major problem of subject bias that plagues retrospective studies, they have been limited and preliminary. In a 2-wk double-blind crossover study, 10 parkinsonian women treated with high-dose 17β-estradiol (in the form of a 0.1mg/d estradiol patch) had a 30% reduction in the threshold dose of L-dopa required to improve motor symptoms. However, they did not have a change in measures of motor function, including "on" time and an abbreviated parkinsonism rating scale *(54)*. Although this was not associated with a statistically significant increase in dyskinesias or decrease in "off" time, the number of patients who were ultimately included in the analysis was small (eight), and the trend was toward increasing dyski-

nesias. Because the investigators used high-dose estradiol for a short period of time, it is unclear how this relates to the lower doses of estradiol, or estrone/estradiol oral combinations used in clinical practice. Strijks et al. *(55)* also performed a placebo-controlled, randomized, 8-wk double-blind trial using 2 mg of 17β-estradiol. The mean age of the women was 64, with average disease duration of 8.6 yr. By contrast, they did not find a significant change in the UPDRS or subjective patient interview *(55)*. However, they had a small sample size, with seven individuals in the treatment group, and therefore limited power to detect a small change in the short duration of the study. While the first study shows that estradiol affects the needed L-dopa dose requirement, collectively, these studies suggest that estrogenic compounds have a limited symptomatic benefit.

In a much larger double-blind placebo-controlled trial, 20 women were assigned to treatment with 0.625 mg/d of oral Premarin and 20 were assigned to the control arm. The women treated with Premarin showed significant improvement in the motor portion of the UPDRS, as well as less mean "off" time and more "on" time *(9)*. This is consistent with a possible role of decreased COMT transcription, which would increase available DA and prolong the "on" time, therefore arguing for a symptomatic role of estrogen. Unfortunately, all these studies are limited by their short duration and small sample size.

Finally, there are other nonhormonal mechanisms for gender differences in Parkinson disease. These are diverse, including developmental striatal differences and pharmacologic differences that may not be directly related to estrogen. For example, women require less L-dopa than men, yet have more dyskinesias *(4,5)*. While this may be attributable to a hormonal difference, it may be related to metabolism of L-dopa, because women have different enzymatic activities in major enzymes responsible for DA degradation in the brain *(56)*.

Selective Estrogen Receptor Modulators and Parkinson Disease

An alternative to continuous stimulation of all ERs (i.e., brain and uterus simultaneously) is the selective estrogen receptor modulators (SERMs). SERMs are an attractive clinical option, because they offer the possibility of the benefits of receptor stimulation or antagonism in targeted tissues such as the brain, but not in other tissues, such as endometrial and breast tissue. Early data with the SERM raloxifen suggests that it may also be neuroprotective. Using the MPTP model, Grandbois et al. *(57)* demonstrated less DA depletion in MPTP-treated animals pretreated with raloxifen. Additional effects of the SERMs are well reviewed by Cyr et al. *(41)*. If antiparkinsonian effects in the brain can be demonstrated, then SERMs have a potential role in the treatment of Parkinson disease. Unfortunately, few data are available regarding the effects of SERMs in the brain. Women with breast cancer treated with tamoxifen had worsened cognition, suggesting that there may be an antiestrogenic effect in the brain since estrogen is associated with increased cognition *(58,59)*. However, it is unclear whether parallels to parkinsonism are relevant, because the brain may be heterogeneous in its response to tamoxifen. Therefore, further analysis of the effects of tamoxifen and raloxifene on the nigrostriatal system are warranted.

Role of Other Sex Hormones

Other sex steroids, in particular progesterone and testosterone, may also mediate gender differences in Parkinson disease. Testosterone and 17β-estradiol are intimately linked, and testosterone may alter the nigrostriatal system primarily, or as an estrogen precursor. Further, because these precursors are present in adipose tissue and levels vary with gender and age, the endogenous levels of estrogen also vary according to gender and age *(60)*. During development, estrogen is synthesized through aromatization of testosterone in many brain regions. Testosterone deficiency has been reported in up to 35% of men with Parkinson disease *(61)*; therefore, primary testosterone deficiency, or secondary estrogen deficiency (as testosterone is aromatized to estradiol), may also contribute to gender differences. While most basic research has focused on estrogen, other sex steroids have also been implicated in the nigrostriatal gender differences. Sex-specific differences in the topography and functionality of the GABA systems in the substantia nigra were found to be dependent on the sex hormone testosterone *(62)*.

Because unopposed exogenous estrogen therapy in postmenopausal women is associated with increased risk of uterine malignancy, estrogen therapy is often combined with progesterone. Studies of the effects of progesterone on Parkinson disease are limited. Because the role of progesterone in Parkinson disease is poorly understood, but the risk of unopposed estrogen use is present, the few clinical trials of estrogen in Parkinson disease have been limited to 8-wk trials of unopposed estrogen *(9,55)*. It is unclear whether estrogenic effects would increase with time, and longer duration efficacy studies are needed.

Dementia and Parkinson Disease: A Role for Estrogen?

There are additional pragmatic reasons for studying estrogen in Parkinson disease. First, approx 20–40% of individuals with Parkinson disease will develop dementia *(63,64)* and approximately two-thirds of early Parkinson disease patients will have abnormal cognitive function on neuropsychologic testing *(65–67)*. Estrogen replacement in postmenopausal women has been implicated in improvement in cognitive function *(58,59,68,69)* and is inversely associated with in Parkinson disease *(44)*; therefore, even if a strong role for estrogen in the modulation of Parkinson disease is not demonstrated, estrogen may decrease the development of dementia in women with Parkinson disease. Second, despite recent data from the Women's Health Initiative *(70)* that will lead

to many women discontinuing HRT, HRT is a commonly prescribed therapy, so physicians prescribing HRT should be aware of possible benefits and side effects for their parkinsonian patients.

Conclusion

The implications of possible estrogenic antiparkinsonian effects are tremendous. Because Parkinson disease may afflict as many as 1 in 100 adults over the age of 60 *(14)*, if estrogen or estrogen-like compounds can act to enhance DA synthesis or synaptic transmission or can decrease the cell death in this disease, then they have the potential for significant public health impact. Multiple mechanisms have been reviewed: DA agonists are one of the primary compounds used in symptomatic treatment of Parkinson disease; therefore, if estrogen modulates DA receptor activity, it has pharmacologic potential for symptomatically improving Parkinson disease. Parkinson disease is a degenerative disorder, and apoptosis may be responsible for induction of cell death or may be a final path in the cascade of cell death. If estrogen is antiapoptotic in brains with increased susceptibility to Parkinson disease, it may either slow the progression of Parkinson disease or prevent Parkinson disease if susceptible individuals are identified. However, clinical data lag behind basic scientific data, and from this limited data it is suggested, but not proven, that exogenous estrogen may symptomatically improve Parkinson disease, as well as be neuroprotective. Prior to the initiation of clinical trials for possible neuroprotection, the relative symptomatic benefit of estrogen must be determined. This may be done through carefully designed clinical trials or assessment of biomarkers, such as with single-photon emission tomography or positron emission tomography neuroimaging or through a combination of both. Despite the wealth of basic science data, clinical data regarding the symptomatic or neuroprotective effect are limited. Additional study, including evaluation of the role of the SERMs in Parkinson disease, is warranted.

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