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Formulations of hormone therapy and risk of Parkinson disease

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Abstract

Background—Hormone therapy (HT) is a class of medications widely prescribed to women in the Western world. Evidence from animal models and in vitro studies suggests that estrogen may protect against nigrostriatal system injury and increase dopamine synthesis, metabolism, and transport. Existing epidemiologic research indicates a possible reduced risk of Parkinson disease (PD) associated with HT use. The objective of this study was to evaluate PD risk associated with specific HT formulations.

Methods—Neurologist confirmed cases and age-matched controls were identified from Group Health Cooperative (GHC) of Washington state. Final analysis included 137 female cases and 227 controls. HT use was ascertained from the GHC pharmacy database, further classified as conjugated estrogens, esterified estrogens, and progestin.

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Results—Ever use of HT formulation demonstrated a suggested elevated risk with esterified estrogen use (OR, 3.1; 95% CI, 1.0–9.8), and no risk associated with conjugated estrogen use (OR, 0.6; 95% CI, 0.6–1.3). Restricting this analysis to prescriptions that included progestin further elevated the risk associated with esterified estrogen use (OR, 6.9; 95% CI, 2.1–22.9); again, no risk was associated with conjugated estrogen use (OR, 1.7; 95% CI, 0.6–5.0).

Conclusions—The findings from this study suggest an increase in PD risk associated with esterified estrogen use combined with progestin, and no risk associated with conjugated estrogen with progestin. These findings could have important implications for choice of HT in clinical practice.

Keywords

hormone therapy; estrogen therapy; Parkinson disease; neurodegenerative disease; epidemiology

INTRODUCTION

Women have consistently been observed to have a lower incidence of Parkinson disease (PD) compared to men.[1–4] The underlying biological basis of this observation has not been established, although some animal and human studies implicate a role for estrogen in protecting the nigrostriatal dopaminergic functions affected in PD,[5–7] and dopaminergic cells from neurotoxicant-induced damage.[7, 8] Gonadal steroids are lipophilic with a low molecular weight, thus allowing diffusion across the blood brain barrier. Putative neuroprotective mechanisms for estrogens' beneficial effects include anti-inflammatory activity[9] and increased dopamine synthesis, metabolism, and transport.[10–13] Correspondingly, estrogen therapy has been tested as a therapeutic approach to improve motor disability in parkinsonism males[14] and post-menopausal females.[15, 16]

Hormone therapy (HT) is commonly prescribed to women for treatment of menopausal symptoms, although use has decreased since the Women's Health Initiative reported increased risks for stroke and breast cancer in 2002.[17] The most common formulations of HT are esterified estrogens, often fabricated from soybeans and yams, and conjugated estrogens, derived from pregnant mare urine. The esterified estrogens are predominantly estrone, whereas conjugated estrogens are a mixture of more biologically active estrogens including 17β-estradiol, which has more than two-fold greater affinity for estrogen receptors than estrone.[18] This difference in estrogen form and potency, as well as inclusion of progesterone, may modify the association of hormone therapy and PD risk. Epidemiologic evidence evaluating exogenous estrogen use and risk of PD among women is mixed, with most studies showing either decreased risk or no association.[19–25] Prior research on hormone therapies for specific estrogen formulations and progesterone use and risk of PD is limited.[19, 20, 24, 26] The objective of this study was to examine the associations between use of different estrogen formulations, including concurrent use of progesterone, and PD risk among women enrolled in a population-based case-control study.

METHODS

Study Subjects

Newly diagnosed idiopathic PD cases aged 35 and 89 years were identified (71% within 1 year of diagnosis, range up to 39 months) between 1992 and 2008 from Group Health Cooperative (GHC), a managed care organization in Washington State, as previously described.[27] Inclusion criteria were the presence of two of the four cardinal signs of PD: rest tremor, bradykinesia, postural instability, and gait disturbance. GHC neurologists' diagnoses were accepted. Three study neurologists (PDS, GMF, WTL) reviewed charts to verify diagnoses for cases not diagnosed by neurologists. Exclusion criteria were diagnoses of Alzheimer's disease, multiple sclerosis, or amyotrophic lateral sclerosis, evidence of multiple cerebrovascular events prior to symptom onset, use of confounding medications including antipsychotics, methyldopa, reserpine, and metoclopramide during the 12 months preceding onset, or evidence of another explanation for parkinsonism symptoms. Control subjects were GHC enrollees with neither medical records indicating nor self-reported history of physician-diagnosed neurodegenerative disease, including PD. As described previously[27], cases and controls were frequency-matched on age, gender, original year of GHC enrollment, and clinic location. The study procedures were approved by Institutional Review Boards at the University of Washington and Group Health Cooperative.

There was 72% participation of cases and 55% of controls among female subjects eligible for the study. Further exclusions included 34 case referrals from outside of GHC, and 9 cases and 6 controls with insufficient informed consent or missing data. One case and 2 controls were also excluded due to HT prescriptions prior to the age of 35. The final analytic dataset included 137 cases and 227 controls. Information was obtained on participants' lifestyle (e.g., smoking) and medical history from interviews, which occurred within a year of recruitment.

Medication history assessment

As detailed previously,[28] exposure to medications was ascertained from the GHC automated pharmacy database, which contains a computerized record for every drug dispensed at GHC pharmacies. Full prescription medication records were obtained for cases and controls from 1977 to 2003, including information on drug type, strength, and form, date and quantity dispensed, and, from January 1998 onward, dosing instructions. This analysis evaluated oral prescriptions only, including two formulations of estrogen, conjugated and esterified, and progesterone, which was further restricted to medroxyprogesterone acetate (henceforth referred to as progestin) because this synthetic formulation of progesterone was almost exclusively prescribed (>98%). We did not obtain data on HT prescribed outside of GHC; however, more than 95% of GHC members in this age group use GHC pharmacies to fill almost all prescriptions.[29] The GHC pharmacies switched the standard postmenopausal estrogen therapy from conjugated to esterified estrogen for current and new users of HT from 1992–1999, and then back to conjugated estrogen subsequently.[30] To account for a possible latency period in medication use and PD diagnosis, all medications filled within 5 years of the interview (a proxy of diagnosis date) were excluded.

Cumulative years of use were estimated by dividing the sum of the quantity of pills dispensed (known for all prescriptions) by dosing instructions (quantity of pills per day). Dosing instructions were missing for 67.7% of the 5,915 dispensations of HT (63.6% of cases, 71.4% of controls). For women with dosing information available on some prescriptions, we imputed missing dosing instructions, without knowledge of case/control status, by first carrying the dosing information forward and then backwards for the same person, drug formulation, and strength. There was no data on dosing instructions for any prescriptions for 19 cases (19/53; 36%) and 33 controls (33/76; 25%) with known HT prescriptions. These subjects, and those still missing dosing instructions after the imputation (26.7% of case prescriptions and 39.4% of control prescriptions), were assigned a weighted average for dosing instructions derived using drug formulation and strength, both known for all prescriptions and associated with dosing instructions. The most commonly prescribed strength of esterified estrogen was 0.625mg (87%; range 0.3–0.625) and conjugated estrogen was 0.625mg (66%; range 0.3–1.25). The dosing instruction for 0.625mg of esterified estrogen and 0.625mg of conjugated estrogen was 1 pill per day for 92.5% and 71.7% of those with known dosing information, respectively. Progestin use was incorporated into the models as a dichotomous (yes/no) variable, thus the missing dose information for these prescriptions was irrelevant.

Statistical analysis

We compared characteristics of cases and controls using t-tests for continuous variables, chi-square tests for categorical variables, and Fisher's exact tests when appropriate. To determine PD risk associated with HT use, odds ratios (ORs) and 95% confidence intervals (CIs) were computed from unconditional logistic regression models. The first level of analysis was an evaluation of PD risk by ever-use of conjugated or esterified estrogen only, compared to never use of any HT formulation. This was followed by ever-use of estrogen by formulation, with and without concurrent use of progestin, compared to never use of any HT formulation. Ever-use status was defined as one or more prescription by HT formulation and was restricted to ever-use of only one type of formulation. The next analysis estimated dose-response relations for cumulative length of use, defined as: 0, >0–2, and ≥2 years, by estrogen formulation and concurrent use of progestin compared to never-use of the formulation being modeled. Trend analyses used the median category values for length of use.

All multivariate models were adjusted for duration of enrollment in GHC. Additional adjustments were considered and retained if covariates confounded the risk estimates by more than 10%, and the log likelihood chi-square statistic was statistically significant ($p<0.05$). Covariates of interest included smoking (>100 cigarettes in lifetime), race (non-Hispanic Caucasian, yes/no), coffee consumption (≥6, 2–5, 0–1 cups per day), education (≥high school), personal history of estrogen-related cancers, and family history of PD. Progestin was considered as a covariate in models that did not include progestin as a main effect. Where noted, models were mutually adjusted for use of other HT formulations. All analyses were performed using SAS v9.3 (Cary, NC).

RESULTS

Cases and controls did not differ with respect to age, length of GHC enrollment, education, race, coffee consumption, or history of estrogen-related cancers. The mean age at time of interview was 68 years old. Ever having smoked was frequent in the controls ($p<0.01$), and family history of PD was greater in the cases ($p<0.01$).

In an initial analysis, there was no association between ever-use of either estrogen formulation and risk of PD (OR, 0.8; 95% CI, 0.4–1.7; data not shown). Evaluating PD risk by type of formulation, adjusted for duration of enrollment at GHC, smoking (>100 cigarettes in lifetime), and progestin use (ever), demonstrated a suggested increased risk with ever-use of esterified estrogen (OR, 3.1; 95% CI, 1.0–9.8) and no risk with ever-use of conjugated estrogen (OR, 0.6; 95% CI, 0.3–1.3), compared to no HT use (Table 2). Further evaluation of HT formulation with concurrent progestin use, adjusted for duration of enrollment at GHC and smoking (>100 cigarettes in lifetime), resulted in significantly elevated PD risk associated with ever-use of esterified estrogen (OR, 6.9; 95% CI, 2.1–22.9), compared to no HT use. PD risk associated with ever use of conjugated estrogen showed no significant risk with concurrent progestin use (OR, 1.7; 95% CI, 0.6–5.0).

Esterified estrogen use, concurrent with progestin use, demonstrated a monotonic dose-response trend for cumulative years of use ($p=0.021$) (Supplemental Data Table 1); there was an increased risk of PD associated with ≥2 years of cumulative use compared to no use of esterified estrogen with progestin, adjusted for duration of enrollment at GHC, smoking (>100 cigarettes in lifetime), and cumulative years of use of other HT formulations (OR, 3.4; 95% CI, 1.2–9.5). Conjugated estrogen therapy, concurrent with progestin use, did not demonstrate a dose-response trend ($p=0.612$). However, there was a decreased risk of PD associated with ≥2 years of cumulative use of conjugated estrogen, without concurrent use of progestin, compared to no use of conjugated estrogens without progestin, adjusted for duration of enrollment at GHC, smoking (>100 cigarettes in lifetime), and cumulative years of use of other HT formulations (p-trend = 0.037; OR, 0.3; 95% CI, 0.1–0.9).

Family history was significantly associated with PD in all models ($p<0.01$), but including this covariate did not modify the risk estimates. Inclusion of self-reported estrogen-related cancer (breast, uterine, or ovarian) in the risk models, to assess confounding by indication, did not modify the results, although the number of cancer cases was low (cases, n=8; controls, n=11). In consideration of changes in HT use patterns following reported adverse findings by the Women's Health Initiative in 2002, a sensitivity analysis restricted HT prescriptions to those prior to 2002; risk estimates modeled similar to those reported in Table 2 were not materially different (conjugated estrogen only, OR, 0.6; 95% CI, 0.3–1.3, and esterified estrogen only, OR, 4.4; 95% CI, 1.3–15.7).

DISCUSSION

The results of this case-control study demonstrate differences in risk of PD in women associated with use of routinely prescribed specific HT drugs. A notable strength of this study was the ability to consider disease modifying effects associated with specific HT

formulations. Other studies have treated HT as a single exposure, without differentiating formulation types.[19–26] The most notable finding was increased PD risk associated with esterified estrogen use in combination with progestin, and no risk associated with conjugated estrogen combined with progestin.

The role of estrogens in the pathogenesis of PD is unclear. Animal models and in vitro studies suggest a neuroprotective effect of estrogen on the dopaminergic system by anti-oxidant activities and modulation of dopamine receptor function that increase cell survival and enhance neurogenesis and synaptic transmission.[7, 31–33] Null findings in previous studies have been described as unsupportive of the hypothesis that estrogen and estrogen hormone products reduce PD risk.[34] However, our observed difference in risk of PD between conjugated estrogen and esterified estrogen may be explained by the estrogenic activity of the two formulations. The conjugated estrogen formulation is predominantely17β-estradiol, which has more than two-fold greater affinity for estrogen receptors than estrone, the predominant form of estrogen in esterified estrogen.[18, 31, 35, 36] In addition, 17β-estradiol, but not estrone, has been demonstrated to be neuroprotective against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), an established neurotoxicant which selectively destroys dopaminergic neurons of the substantia nigra,[35, 36] and more effective at inhibiting α-synuclein aggregation.[37] Thus, the increased risk of PD associated with esterified estrogen use compared to the null risk associated with conjugated estrogen use may be due to a relatively decreased neuroprotection from esterified estrogen after menopause. Likewise, the findings for conjugated estrogen use may be attributed to the continuation of the neuroprotective effects of estradiol after menopause. However, the risk of PD associated with esterified estrogen use was greater than expected for reasons that are unknown. As such, some mechanism unrelated to estrogen potency may explain the association between esterified estrogen use and increased risk of PD.

The increased risk of PD associated with estrogen and progestin ”combined” HT compared to subjects with no HT use was not entirely unanticipated. Rodent studies have demonstrated that estrogen and natural progesterone are protective against MPTP neurotoxicity.[38, 39] However, synthetic progestin is not considered neuroprotective and, when co-administered with estrogen, has been shown to attenuate neuroprotective effects associated with estrogen alone.[40, 41] The Nurses’ Health Study reported an increased risk of PD with use of progesterone only, although this was based on only 4 cases.[24] Prior studies evaluating combined HT therapy compared to no HT use in post-menopausal women have reported no associations with PD.[19, 24] Although, a recent cohort study by Liu et al.[26] reported an increased risk of PD with combined HT compared to no HT use in post-menopausal women. Progestin therapy is often given to women with an intact uterus taking long-term estrogen to prevent uterus hyperplasia or neoplasia. Estrogen therapy without concurrent use of progestin is likely indicative of prior hysterectomy. Previous studies on PD risk associated with hysterectomy status have reported mixed findings.[19, 21, 22, 24, 26] Unfortunately, we do not have natural or surgical menopause information available to help clarify the underlying etiologies of the observed findings. Cautious interpretation is recommended when comparing PD risk for the same HT formulation with or without progestin.

A reduced risk of PD has been demonstrated consistently among cigarette smokers,[42] and less consistently associated with caffeine consumption.[27, 42–44] The Nurses' Health Study reported a modifying effect of HT with smoking and caffeine use.[20, 24] Caffeine use was not significant in any model from this study. Smoking was significant in all models ($p<0.01$) as a main effect but not as an interactive term. Nicotine has been demonstrated to inhibit estrogen-mediated neuroprotection,[45] and decrease serum estrogen levels.[46] The mechanism by which the nicotine confounded risk associated with HT use in this study is not known.

Our study was conducted in a well-characterized population, and included incident PD cases with data on smoking and other PD risk factors. Long-term historical pharmacy data, available from as far back as 1977, allowed for exposure lagging without concern of recall bias by the subject. Additionally, accessibility to three decades of exposure records allowed for an evaluation of HT use with respect to case status. Our dose-response analysis should be interpreted carefully as dosing instructions, not available until 1998, were missing for 67.7% of the prescription records evaluated. The missing dosing instruction data was imputed based on drug formulation and strength (both were known for all prescriptions) from other prescriptions for the same person, or assigned based on drug formulation and strength for all prescription records (dosing instructions were consistent for 92.5% and 71.7% of the most common drug strengths of conjugated estrogens and esterified estrogens, respectively). Although these metrics may offer reasonable estimations of the dosing instructions, the large amount of missing data should be considered when reviewing these findings. Our results conceivably reflect dispensing pattern differences between cases and controls; as such, incomplete data may be an explanation for these findings. HT prescriptions outside of GHC pharmacies may have occurred due to copayments, changes in health benefits, or other unknown factors. However, a study evaluating reliability of the GHC pharmacy database reported kappa estimates of 0.75–0.83 when comparing automated pharmacy records and self-reported HT (n=3610).[47] GHC policy dictated major secular trends in the most commonly used formulations over time, thus characteristics of cases and controls should not distribute differentially in regard to formulation. Likewise, confounding due to different indications for the HT prescriptions, including preclinical symptoms of PD, is unlikely to vary by case/control status.

The sample size for the current study is modest, but the findings may contribute to the understanding of PD pathogenesis mechanisms and could ultimately have important implications for clinical recommendations of HT prescriptions. Replication in a larger study with complete exposure history, including available dosing instruction data, to substantiate our findings is recommended.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of women at the time of the interview, and HT use: Parkinson disease cases and controls

	Cases (n=137)	Controls (n=227)	p-value
Age (years), mean (SD)	68.6 (9.0)	68.7 (9.6)	0.86
Length of GHC enrollment (years), mean (SD)	22.1 (10.9)	24.0 (12.0)	0.13
Education (≥ high school), n (%)	130 (95%)	215 (95%)	0.94
Race (non-Hispanic Caucasian), n (%)	128 (93%)	210 (93%)	0.74
Smoking (>100 cigarettes in lifetime), n (%)	45 (33%)	108 (48%)	<0.01
Caffeine (coffee), n (%)[a]			
0–1 cups per day	81 (59%)	127 (56%)	0.64
2–5 cups per day	48 (35%)	89 (39%)	
>6 cups per day	8 (6%)	10 (4%)	
Breast cancer (self-reported), n (%)	6 (4%)	10 (4%)	0.99
Uterine (cervical) cancer (self-reported), n (%)	2 (1%)	1 (<1%)	0.30
Ovarian cancer (self-reported), n (%)	0 (0%)	0 (0%)	.
First-degree relative with PD, n (%)[b]	16 (14%)	7 (4%)	<0.01

[a] data missing for n=1 control subject; test statistic includes all categories

[b] data missing for 21% of the subjects

Table 2

Hormone therapy use in women and risk of Parkinson disease; ever use

	Case	Control	OR (95% CI) Crude	OR (95% CI) Adjusted[a]
no HT use	84	151	1.0 (Ref)	1.0 (Ref)
Conjugated estrogen use only	17	42	0.7 (0.4–1.4)	0.6 (0.3–1.3)
Esterified estrogen use only	16	7	4.1 (1.6–10.4)	3.1 (1.0–9.8)
Combination	20	27	1.3 (0.7–2.5)	1.0 (0.4–2.7)
no HT use	84	151	1.0 (Ref)	1.0 (Ref)
Conjugated estrogen use only				
With progestin	7	8	1.6 (0.6–4.5)	1.7 (0.6–5.0)
Without progestin	7	26	0.5 (0.2–1.2)	0.5 (0.2–1.2)
Esterified estrogen use only				
With progestin	12	4	5.4 (1.7–17.2)	6.9 (2.1–22.9)
Without progestin	4	2	3.6 (0.7–20.0)	3.0 (0.5–16.9)
Combination*	23	36	1.1 (0.6–2.1)	1.4 (0.7–2.6)

[a] adjusted for duration of enrollment at GHC, and smoking (>100 cigarettes in lifetime); plus progestin use (ever) in the top model

* Note: 3 cases and 8 controls had prescriptions for both conjugated estrogens with and without progestin, and 1 control had prescriptions for esterified estrogen with and without progestin