Prevalence and Duration of Postmenopausal Hormone Replacement Therapy Use in a Managed Care Organization, 1990–1995

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OBJECTIVE: To determine the prevalence and duration of postmenopausal hormone replacement therapy (HRT) use and identify correlates of adherence to therapy.

DESIGN: Population-based cohort study.

SETTING: Staff-model health maintenance organization.

PARTICIPANTS: Female members, 40 years and older.

MEASUREMENTS AND MAIN RESULTS: Prevalence and duration of use were measured between 1990 and 1995. Duration was assessed by Kaplan-Meier and proportional hazards methods. Hormone replacement therapy use increased from 10.3% in 1990 to 20.7% in 1995. Greatest use (24%) occurred among menopausal women age 50 to 54 years. Less than 5% of women 75 and older used HRT. Among 1,680 first-time recipients of HRT, two thirds of initial prescriptions were written by internists. Thirty-eight percent discontinued HRT within 1 year. For the subset whose indication for therapy was ascertained, prevention of chronic disease was associated with a 33% 1-year discontinuation rate. Factors associated with longer duration of therapy included white race (relative risk [RR], 1.63; 95% confidence interval [95% CI], 1.32 to 2.02), younger age (RR, 1.02 per year; 95% CI 1.01 to 1.03), and changing the preparation or dose of estrogen (RR, 5.62; 95% CI, 4.33 to 7.25). The formulation (esterified estrogens 0.625 mg versus conjugated estrogens 0.625 mg) was also associated with greater duration of use; all other estrogens were, as a group, associated with shorter duration of use. Those who received their initial HRT prescription from an internist were more likely to continue therapy than those who received it from a gynecologist.

CONCLUSIONS: Despite increased use of HRT, only a minority of women in this population used HRT, and many of those discontinued therapy within 1 year.

KEY WORDS: menopause; hormone replacement therapy; estrogen; adherence; prevalence.

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Hormone replacement therapy (HRT) for menopause is associated with a decrease of as much as 25% to 61% in the incidence of coronary heart disease and osteoporotic hip fracture.^{1–4} While menopausal symptom management may be achieved with a short course of HRT, some benefits, such as prevention of osteoporosis, may only be derived with sustained use.^{5–8} Estimates of HRT use vary widely, from 2% to 49% of the studied populations, and methods for documenting use have relied almost exclusively on patient self-report.^{9–26} Determination of the duration of use has also been poorly characterized, ranging from a discontinuation rate of 7% to 76% at 1 year depending on definitions of use and discontinuation and methods of reporting.^{7,27} Correlates of HRT use, such as demographic characteristics, prescribing provider characteristics, and preparation of estrogen, have been reported, but the effects of these factors on adherence to therapy have not been well defined. Since the goal of HRT for some women is to achieve prolonged use, recognizing those factors that affect an individual's likelihood to continue therapy will assist clinicians in identifying methods for supporting adherence.

We used the automated medical and pharmacy records of Harvard Pilgrim Health Care to document the prevalence and duration of use in this managed care population and to identify correlates of greater adherence to therapy.

METHODS

Setting

Harvard Pilgrim Health Care is a mixed model health maintenance organization that included a staff-model Health Centers Division, with approximately 300,000 members from the greater Boston area. At the time of this study, the organization was known as Harvard Community Health Plan. During the period reported here, the organization maintained computerized pharmacy, medical record, and claims data for all members of 11 of the 14 staff-model health centers. The pharmacy record included medication name, dose, prescription date, provider name and specialty, amount dispensed, and patient zip code. Ninety percent of patients participated in the pharmacy benefit plan. Those who carried the pharmacy benefit paid \$5 to \$10 per prescription and, therefore, were more likely to use Harvard Pilgrim Health Care pharmacies for any prescriptions that have more than a nominal charge elsewhere.

Prevalence of HRT Use

For every 6-month period between 1990 and 1995, we determined the number of women, 45 and older, who

were members of the staff-model health centers with automated pharmacy and medical records and who subscribed to the pharmacy prepaid benefit program. Those who filled a prescription for any oral or transdermal estrogen preparation during these same time periods were designated HRT users for the purposes of prevalence calculations.

To determine the prevalence of use, the total number of women age 45 and older who filled at least 1 prescription for any oral or transdermal estrogen preparation during each 6-month period between January 1, 1990 and December 31, 1995 was divided by the number of menopausal enrollees age 45 and older. Prevalence of use was determined for the entire population as well as for each 5-year age group.

The proportion of women in each 5-year age group presumed to be menopausal was derived from data prospectively collected by Treolar.²⁸ While all women 55 and older were assumed to be menopausal, Treolar stated that 58% of women age 45 to 49 and 95% of women age 50 to 54 are menopausal. Because Treolar's data only account for naturally menopausal women and the majority of menopausal women between 40 to 45 are likely to have experienced surgical menopause, it was not possible to generate an accurate estimate of the number of menopausal women for this age group. Therefore, we did not compute the prevalence of HRT use for women younger than 45.

Duration of HRT Use

For analyses of duration of adherence, women 40 years of age and older who used the Harvard Pilgrim Health Care pharmacy as part of the prepaid benefit program were eligible if they received their care at centers with automated full text medical records and were not receiving fertility medications. We identified all recipients of first prescriptions for any oral or transdermal estrogen preparation between October 1, 1989 and December 31, 1992. First-time recipients were defined as those whose first estrogen prescription occurred at least 1 year after first use of pharmacy or clinical services. Discontinuation of estrogen was defined as a gap of at least 180 days in dispensing of estrogen despite continued use of other clinical or pharmacy services. Fewer than 2.2% of the 15,614 total estrogen dispensings had gaps of greater than 180 days between dispensings, and dispensings after a 180-day gap were omitted from analyses. Refill status was reviewed through June 1993 in order to observe the refill behavior of all cohort members for at least 180 days.

The primary outcome was total days on therapy. Each individual's total number of days was calculated as the sum of days from the first HRT dispensing through the last HRT dispensing plus the quantity of pills dispensed with the final prescription, since typical HRT prescribing recommendations are for a single tablet per day. Use of a second estrogen was defined as any change in the dose or preparation of estrogen during the course of therapy. Because information about the actual instructions provided to patients was not available from the automated medical

record, only those receiving 2.5 mg of medroxyprogesterone were assumed to be using a continuous regimen.

Median household income was estimated by 1990 U.S. Census data for zip codes. Twenty-two percent of patients were missing race data. We performed 2 analyses, the first classifying those with missing race as white (the status of 74% of those with documented race) and the second classifying them as nonwhite. Only the first analyses are presented, since the 2 were not meaningfully different.

Duration of use was assessed by Kaplan-Meier curves.²⁹ Patients who continued to fill prescriptions in the last 180 days of observation time were defined as continuing users and were censored for the purpose of survival analysis. Proportional hazards models and Kaplan-Meier curves compared by log-rank tests were used to describe univariate and multivariate correlates of longer adherence to therapy.³⁰ Proportional hazard assumptions were tested for all covariates associated with the outcome in multivariate models. Medication type was treated as a time-varying covariate, as 25% of the population experienced a change in dose or preparation of estrogen during the course of therapy. Multivariate analyses were stratified by health center to control for unmeasured confounding. SAS Statistical Software was used for all analyses except interobserver κ determinations made using STATA. The hazard ratios estimated by proportional hazards regression were reported as risk ratios for ease of interpretation.

Chart Review

We reviewed 110 randomly selected full text medical records from each of the following 3 groups: patients who filled a single prescription only, patients who filled more than a single prescription but for 1 year or less, and patients who filled prescriptions for more than 2 years. The sample size provided 80% power to detect a 2-tailed difference of 20% or greater in indication for therapy with a type I error of 0.05. Ten percent of the charts were randomly selected for review by a second reader to determine interobserver agreement on data abstraction and assignment of indication for therapy ($\kappa = 0.94$, indicating excellent agreement). After eliminating those younger than 40 and those who had exposure to fertility medications, a total of 279 were eligible for analysis. Kaplan-Meier curves, log-rank tests, and χ^2 statistics were performed to identify whether the indication of prevention was associated with greater duration of use. We defined anyone who had medical record documentation of taking HRT for prevention of heart disease, management of cholesterol, prevention of osteoporosis, or for a family history of heart disease or osteoporosis as taking estrogen to prevent the long-term consequences of estrogen deficiency.

Human Subjects

All investigations were performed with permission of the Harvard Pilgrim Health Care Human Studies Committee.

RESULTS

Prevalence of HRT Use

There was an average of 20,714 menopausal women, 45 and older, eligible for filling a prescription for HRT during each 6-month period from 1990 to 1995. During this time, the prevalence of use of HRT increased from 10.3 to 20.7% (Fig. 1). Figure 2 represents the mean proportion of each 5-year age group using HRT during the 6-year period observed. Peak estrogen use occurred between ages 50 and 54, with a maximum of 23.7% of the eligible women in that age group receiving HRT during the first half of 1995. Hormone replacement therapy use was negligible among those 75 and older; less than 5% of the 75 to 79-year-old group filled prescriptions for HRT, and less than 2% of those 80 and older filled HRT prescriptions.

Duration of HRT Use

There were 1,680 women identified as first-time recipients of HRT between October 1, 1989 and December 31, 1992. Patient, provider, and medication characteristics are reported in Table 1. Twenty-five percent of the first-time estrogen users discontinued therapy within 100 days,

as indicated by the solid line of the Kaplan-Meier curve (Fig. 3). An additional 13% stopped during the remainder of the first year, yielding a cumulative discontinuation rate of 38% at 1 year. After 1 year, the rate of discontinuation slowed considerably, reaching 51% at 3 years.

Correlates of Duration of HRT Use

Predictors of longer adherence to therapy are listed in Table 2. We assessed the following potential predictors of adherence: age; median household income; race; number of medical encounters in the year prior to starting therapy; exposure to pap smears, mammograms, and bone densitometry in the year prior to starting therapy; type of estrogen; inclusion of a progestin in the regimen; change in the regimen during the course of therapy; specialty and gender of the provider of the original prescription. All were individually significantly associated with duration of use except number of medical encounters, bone densitometry, and provider specialty. The factors that remained significantly associated with longer duration after adjustment for all of the univariate predictors just described were younger age, white race, change in estrogen preparation or dose during the course of therapy, receiving an initial

* Eligible women represents the average female membership, age 45 and older, for three months before and three months after the date reported, assuming a 90% participation in the pharmacy benefit program, and estimating that 57% of those 45-49, 95% of those 50-55 and 100% of those > 55 are menopausal.

FIGURE 1. Prevalence of hormone replacement therapy use among menopausal women 45 and older, 1990-1995.

FIGURE 2. Proportion using hormone replacement therapy by age, 1990–1995.

HRT prescription from an internist rather than a gynecologist, and specific estrogen preparation used.

We repeated this analysis excluding all patients who filled only a single prescription to eliminate those who discontinued immediately. Again, younger age, white race, change in estrogen dose or preparation, provider specialty, and specific estrogen preparation used remained significantly associated with longer duration among the 1,320 women who filled 2 or more prescriptions.

Among specific estrogen preparations, the 9% initially prescribed esterified estrogens (Estratab) 0.625 mg had the longest duration of use, followed by the majority who received conjugated estrogens (Premarin) 0.625 mg and those who received any other preparation. Test of proportional hazard assumptions indicated that the association of esterified estrogens with duration of use became stronger with time, while the effect of experiencing a change in estrogen therapy, although still associated with duration of use, was not as strong an association 1 year after beginning therapy.

For the 1,253 (75%) who used medroxyprogesterone, a separate multivariate analysis, including a variable for continuous versus cyclic therapy, was performed. Thirty-three percent of those who filled a prescription for a progestin were using 2.5 mg of medroxyprogesterone; all others were presumed to be receiving cyclic therapy. The type of regimen (cyclic vs continuous), based on this limited definition, was not a significant predictor of duration

of use (log-rank $P = .28$) and did not change the overall results of the multivariate analysis.

Chart Review

Medical record review for the stratified random sample of HRT users revealed that the most commonly cited reason for prescribing HRT was hot flashes (52% of all reviewed charts; 40% of those who filled a single prescription, 67% of those who filled more than one prescription but for less than 1 year, and 49% of those who filled prescriptions for 2 or more years).²³ Twenty percent had no documentation of the indication for therapy.

Prevention was documented as at least one consideration for starting medication in 22% of charts. Of those who filled only 1 prescription, 13% had documentation of using HRT for prevention; of those who filled more than one prescription but for no more than 1 year, 19% had similar documentation; and of those who filled prescriptions for 2 or more years, 31% of the charts indicated that prevention was at least one reason for starting HRT ($\chi^2 = 9.3$, $P = .01$).

For those for whom prevention was an indication for therapy, 33% discontinued HRT at 1 year, compared to 53% who discontinued therapy at one year if prevention was not cited in the medical record (log-rank test $P = .003$). Figure 3 shows the Kaplan-Meier curves for the chart review subset, superimposed on the curve for the

Table 1. Characteristics of 1,680 First-time Hormone Replacement Therapy (HRT) Users

Patient Characteristics	n (%)
Median age, y	52
Median household income*	\$40,715
Median clinical encounters in year before starting HRT	8
Race	
African American	165 (10)
Asian	18 (1)
Hispanic	35 (2)
White	1,097 (65)
Not recorded	365 (22)
Mammogram in year prior to starting HRT	1,049 (62)
Pap smear in year prior to starting HRT	1,620 (96)
Bone densitometry in year prior to starting HRT	71 (4)
Prescriber's specialty (first dispensing)	
Internal medicine	1,106 (66)
Obstetrics/gynecology	508 (30)
All others	66 (4)
Prescriber's gender (female)	776 (46)
Initial medication type	
Conjugated estrogens 0.625 mg	1,362 (81)
Esterified estrogens 0.625 mg	146 (9)
All others	172 (10)
Progestin plus estrogen	1,253 (75)

*Based on 1990 U.S. Census zip code data.

entire cohort of 1,680 women, comparing those who took HRT for prevention with those who did not have such documentation in their medical record.

DISCUSSION

The key findings of this investigation include the low, but increasing, prevalence of HRT use, the large minority who discontinue therapy within the first year, and the association of younger age, type of estrogen, change in estrogen regimen, specialty of the initial prescribing physician and white race with persistent HRT use. In the subset of charts reviewed, a documented indication of using HRT for prevention was associated with greater adherence to therapy.

As shown in previous studies, women in the 50 to 54 year age group were most likely to use HRT.^{21,31,32} However, only 24% of the women in this study group used HRT. Virtually no women in the age groups most at risk for osteoporotic hip fracture and coronary artery disease, age 75 and older, used HRT. Lower prevalence of HRT use by older women has been well documented in other reports^{20,22,33-36} and may be explained by a number of factors, including reluctance to experience endometrial bleeding, fears of cancer, and concerns about interaction with other medications. The approximate doubling of HRT use during the 6-year period

suggests increased acceptance of HRT in this population, consistent with prevalence changes in other populations.³⁷

These data are consistent with the findings of the Massachusetts Women's Health Study, a longitudinal population-based survey of over 8,000 Massachusetts women between 1983 and 1986. In that population, 16% used HRT at any time.¹⁸ However, studies in other communities have documented substantially higher use of HRT,^{13,14} suggesting regional variation in HRT use. An analysis of estrogen use reported in the National Health and Nutrition Examination Survey (NHANES) documents relatively lower use of HRT in the Northeast (60.3% ever-use in the West vs 37.6% ever use in the Northeast).³⁷ Derby and colleagues documented prevalence of use in 2 southeastern New England communities in 1989 to 1990 as 10.9%,³⁸ and the Black Women's Health Study noted the lowest use of HRT in the Northeast.³¹

Among those who initiated HRT, a substantial proportion discontinued within 1 year. Several other studies have documented discontinuation rates in the 30% to 40% range at 1 year, supporting the findings in this population.^{26,39-41} The association of increasing age with shorter duration of use suggests that age may be a marker for the need for better decision support efforts for the older patient who chooses to initiate HRT.^{37,41}

The association between specific HRT formulation and duration of use was unexpected. Although the association was reasonably strong and increased in magnitude in the multivariate analysis and over time, less than 10% of all women, all of whom received their care at a minority of health centers, received esterified estrogen as their initial HRT prescription. Thus, we cannot dismiss the possibility that other unmeasured factors accounted for the observed differences. Since the effect was large, we believe the subject deserves additional study, ideally using a double-blind, randomized trial to compare the medications. Without such data, it is not possible to know whether better side effect profile, symptom relief, or other properties of the medication could account for the greater adherence.

Exposure to medroxyprogesterone and method of administration (cyclic vs continuous) did not appear to have a deleterious effect on adherence, despite assumptions about the negative side effect profile associated with its use.^{42,43} Micronized progesterone was not available at the time of the period studied. Other studies have confirmed that hysterectomized women are more likely to adopt HRT^{16,18,22,23,32,34,35,37,38,44-46} and some have established greater duration of HRT use in this population.¹⁸ We were unable to evaluate use by hysterectomy status since it was unreliably recorded in the medical record. Although the association between endometrial carcinoma and unopposed estrogen was already well established,⁴⁷ some physicians may have prescribed it to women with an intact uterus. Further, some clinicians at the time of this study may have prescribed progestins to women despite hysterectomy because of suggestions in the literature that progestins might protect against breast cancer.⁴⁸ There-

FIGURE 3. Time to discontinuation of hormone replacement therapy (HRT).

fore, any assumption that lack of exposure to a progestin is an acceptable marker for having had a hysterectomy would be of limited utility.

Other investigations have supported an association between continuous regimens and improved compliance with therapy.^{49,50} We cannot exclude the possibility of misclassification bias as a factor contributing to the lack of association between form of administration (cyclic vs continuous) and duration, as dose alone is not the only determinant of the frequency with which women take progestins. Although dispensed quantity data were available, provider prescribing recommendations were not. Hence, we were unable to determine absolutely whether form of administration is associated with duration.

Women who received more than 1 estrogen preparation during the course of continuous therapy had longer duration of use. While no information is available as to why patients or providers decided to switch either dose or preparation, these data imply that adjustments in an HRT

regimen led to greater adherence. Untoward effects of HRT have been well documented and not all women achieve symptom relief at comparable doses.⁵¹⁻⁵⁵ Patients and providers who opt to make changes in therapy rather than discontinue treatment at the onset of side effects or if symptom relief is inadequate not surprisingly achieve substantially greater adherence; however, such adjustments may simply represent greater commitment on the part of the patient, provider, or both to maintaining HRT, greater expertise on the part of the prescriber who is familiar with alternative regimens, or greater opportunity to change simply due to longer duration of use.

Our demographic data, albeit limited, indicate that race was a more important determinant of duration of use than income, which had only borderline association with duration after adjustment (RR, 1.12; 95% CI, 0.99 to 1.26). The NHANES survey, among others, supports an association between white race and HRT use.^{36,37} However, some investigations have not confirmed an association between

Table 2. Proportional Hazards Model of Correlates of Greater Duration of Use of Postmenopausal Hormone Replacement Therapy

	Adjusted Risk Ratio*	95% Confidence Interval
Age	0.98	0.97 to 0.99
White race	1.63	1.32 to 2.02
Estrogen preparation		
Conjugated estrogens 0.625 mg	Reference	—
Esterified estrogens 0.625 mg	2.32	1.66 to 3.24
All other estrogens	0.52	0.41 to 0.66
Change in preparation during course of therapy	5.62	4.33 to 7.25
Provider specialty†		
Internist	Reference	—
Gynecologist	0.84	0.71 to 0.99
All other providers	0.74	0.51 to 1.09

*Adjusted for median household income; number of medical encounters in year prior to starting HRT; pap smear, mammography and bone densitometry in the year prior to starting HRT; use of a progestin; prescriber gender. All variables were significantly associated with duration of use in unadjusted analyses except bone density testing, number of medical encounters in the year prior to starting therapy, and provider specialty.

†Specialty of the provider of the initial HRT prescription.

race and HRT use⁵⁶; others have found a relatively high rate of HRT use (33%) among African-American women.³¹ Lower utilization of HRT among women of color could be attributed to a number of factors. African-American women are less likely to develop osteoporosis and consequently may be less likely to take HRT for long-term prevention. Other possible explanations include less provider support for women of color using therapy, less inclination on the part of African-American women and other ethnic minorities to use medications not well studied in their racial group, and different side-effect profiles of these medications in women of color. Although race information was unavailable for 22% of the study sample, analyses assigning those with missing race as all white or all nonwhite both revealed race to be a significant correlate of duration of use. Our analyses were limited by the fact that income data was estimated from the patient's zip code and census data.

Although women whose indication for therapy was prevention of chronic disease took HRT longer than other women, the discontinuation rate for the prevention group was only marginally better than for the entire population overall (33% vs 38%). This suggests that, even for the most motivated to adhere, taking HRT for protracted periods is a challenge. Since other studies confirm that women are more likely to initiate therapy for symptoms than for prevention, the vast majority of HRT initiators in this population are unlikely to derive the long-term preventive benefits of such therapy.^{22,23,26,57}

Much of the observational data supporting the benefits of estrogens have been criticized as not generalizable because estrogen users were more likely to participate in other healthy behaviors such as preventive screenings.^{23,38,46} Our data suggest that such behavior cannot discriminate between those likely to sustain or discontinue estrogen use. However, we had information only on

health care utilization behavior such as Pap smears, and not on other behaviors such as exercise.

Other studies have suggested that the use of bone densitometry has a positive influence on patients' willingness to take HRT.^{39,58-61} Our data provide no meaningful information about the influence of bone densitometry because of the low frequency of exposure to bone densitometry (4%).

Those who received their first prescription from internists were more likely to continue therapy than those who received prescriptions from gynecologists. In this managed care organization, general gynecologic care and menopause counseling originated with internists. It is conceivable that only those with complications related to menopause, possibly a group at risk for discontinuing HRT, would have been referred to a gynecologist for care. It is also possible that internists had a higher threshold for prescribing, thereby selecting a sample more likely to continue. Greendale and Seto documented that female providers in the same geographic location were more likely to prescribe HRT than male providers.^{62,63} They did not, however, describe the effect of prescriber gender on length of patient adherence to therapy.

Utilization, as measured by ambulatory visits, was not associated with HRT use, in contrast to findings in the Massachusetts Women's Health Study.¹⁸

These results must be interpreted with recognition of several limitations. These data are derived from an ambulatory managed care population and may not generalize to other systems of health care delivery. The only other study in a managed care organization that measured discontinuation of use at 1 year with similar definitions of discontinuation documented the same proportion stopping (38%).⁷

Our definition of HRT exposure probably represents an overestimation of use. Both because we included all pills in the last refill in our calculation of days on therapy and because we defined a continuous user as someone who filled at least 1 prescription within 180 days of the

prior prescription, we can assume that regular, sustained use of HRT is even lower than that reported here.

While automated data allow detailed tracking of prescription refill behavior, the database cannot account for anyone who may have filled prescriptions outside the pharmacy drug plan and cannot confirm that a patient actually took her medication. Moreover, automated data do not allow for incorporating information about the patient-provider interaction and other influences on patients' decisions about stopping and starting these medications. Because the average monthly cost of HRT is approximately 4 times the required typical copay of the Harvard Pilgrim Health Care pharmacy (\$20 vs \$5), women would have been unlikely to fill prescriptions at outside pharmacies.

These data suggest that, in this managed care population, specific subgroups, such as older women and women of color, were at risk for premature discontinuation of HRT. If the goal for specific women is to maximize duration of HRT use, such as for prevention of heart disease or osteoporosis, programs to support adherence could be targeted at those most at risk for discontinuation. Further exploration of best methods for supporting patient adherence to therapy will be necessary to ensure optimal utilization of these medications.

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