Continuation of Postmenopausal Hormone Replacement Therapy in a Large Health Maintenance Organization: Transdermal Matrix Patch versus Oral Estrogen Therapy

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Abstract

Objective: **To determine possible differences in continuation of postmenopausal estrogen replacement therapy among women initiating treatment with transdermal estradiol versus those initiating treatment with oral estrogen.**

Study Design: **A retrospective database search.**

Patients and Methods: **We analyzed estrogen use among 45- to 74-year-old women who filled index prescriptions for estrogen during 1996 for either once-a-week transdermal estradiol or daily oral estrogen. Prescription use was analyzed separately for each of 2 groups: 276 hysterectomized women who filled prescriptions for estrogen alone (ERT) and 4182 women who filled prescriptions for medroxyprogesterone acetate (MPA) with estrogen (HRT) on the same day.**

Results: **Risk of discontinuing therapy after 12 months ranged from 59% to 76% among the 4 subgroups: ERT with unopposed transdermal estradiol; ERT with unopposed oral estrogen; HRT with MPA-opposed transdermal estradiol; and HRT with MPA-opposed oral estrogen. The relative risk (RR) of discontinuation was significantly greater among women starting HRT with transdermal estradiol than among women starting oral estrogen (RR = 1.5; 95% confidence interval [CI] = 1.3 to 1.8). RR of discontinuation among women starting ERT with transdermal estradiol compared with women starting oral estrogen therapy was 1.3 (95% CI = 1.0 to 1.8).**

Conclusions: **Approximately 2 of 3 women who start either ERT or HRT discontinue therapy within a year, regardless of hysterectomy status. Furthermore, women who start ERT or HRT with a transdermal estradiol system are more likely to discontinue therapy.**

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Postmenopausal estrogen therapy is usually discontinued shortly after initiation, and few women use estrogen long enough to obtain any long-term health benefit. We previously showed that about half the women who start oral estrogen with progestin (hormone replacement therapy [HRT]) discontinue it within a year and that 75% to 80% stop within 3 years after starting.[1]

It has been hypothesized that women treated with transdermal estrogen systems will continue their use because the system serves as a visual reminder to continue treatment. In addition, transdermal delivery can maintain more constant levels of serum estradiol than can oral estrogen and may therefore control vasomotor symptoms better.[2] However, skin irritation[3] and the nuisance of wearing a skin patch may limit continuation of transdermal estrogen therapy.

Data on continuation rates with transdermal versus oral estrogen are conflicting. Cano surveyed estrogen use among postmenopausal women who

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attended the gynecology department at an academic center and reported that women who used transdermal estradiol were more likely to continue therapy than those who used pills.[4] Berman and coworkers examined estrogen prescription refills and medical records and reported that women using transdermal estrogen showed no statistically significant differences in discontinuation when compared with women using estrogen pills.[5] By contrast, we found that women who started HRT with an alcohol reservoir transdermal estradiol system twice weekly were 2.6 times more likely to discontinue HRT than women who started with oral estrogen.[6]

Recently, solid-matrix estradiol delivery systems have largely replaced the alcohol reservoir system. Solid-matrix patches provide excellent symptom control, allow superior adherence, cause few skin reactions, and may offer the convenience of once-a-week application.[7] We therefore designed the current study to compare continuation rates after treatment with solid-matrix transdermally delivered estrogen versus oral estrogen in postmenopausal women in a large health maintenance organization (HMO) who were starting treatment with either estrogen alone (estrogen replacement therapy [ERT]) or HRT. We hypothesized that the new estrogen matrix patch would be associated with better continuation and compliance compared with oral estrogen and that women who had undergone hysterectomy and were using ERT would have better continuation and compliance than women using HRT.

··· METHODS ···

Patient Selection

The study population consisted of 45- to 74-year-old women who had been continuous members of the Kaiser Foundation Health Plan (KFHP) in Northern California from 1995 through 1997 and whose health plan coverage provided prescriptions to members at a cost 80% or less of the average wholesale price. The study protocol was approved by the Kaiser Permanente Medical Care Program, Northern California, Institutional Review Board.

Using a computerized KFHP pharmacy database (Pharmacy Information Monitoring Service [PIMS]), we identified women on the basis of prescriptions filled: (1) once-a-week 0.05-mg solid-matrix transdermal estradiol (Climara®, Berlex, Wayne, NJ) between January 1, 1996, and June 30, 1997; (2) 0.625-mg conjugated equine estrogen (Premarin®, Wyeth Ayerst Pharmaceuticals, Philadelphia, PA) during 1996 ; and (3) 1.0-mg micronized estradiol (Estrace®, Bristol Meyers Squibb Company, Princeton, NJ) during 1996. From this group we selected first-time users, defined as women whose pharmacy records showed no prescription for any estrogen or progestin from January 1, 1995, until receipt of the index prescription. To correct for possible prescriber differences, we selected women who had been prescribed HRT by the same group of healthcare providers as had prescribed transdermal estrogen. Only women whose initial estrogen prescription was for 30 to 120 pills or 4 to 16 patches were included.

We next identified 2 further groups within the population of estrogen-using women: (1) the ERT group, which consisted of women with documented hysterectomy, and (2) the HRT group, which consisted of women who received an additional prescription for 2.5 mg, 5.0 mg, or 10 mg of medroxyprogesterone acetate (MPA) within 30 days of the initial estrogen prescription. On the basis of our previous studies, we considered concurrent prescription of 2.5 mg MPA an indicator for continuous combined HRT and concurrent prescription of 5.0 mg or 10.0 mg MPA an indicator for a cyclic monthly schedule.[1]

Data Collection

Using the PIMS database from all Northern California KFHP facilities, we assessed continuation of HRT with a previously described algorithm.[1] For all women, we assumed that estrogen was used every day of the month; we therefore calculated the days' supply (length of supply in days) as either the number of tablets dispensed or 7 times the number of patches dispensed. Using the calculated days' supply, we determined the time that a refill should occur. If no refill was recorded within 30 days after that date, we considered treatment to be discontinued. Switching the dosage or formulation of the estrogen was allowed, but switching the route of estrogen therapy was considered discontinuation. Follow-up for all subjects was stopped on June 30, 1998.

Statistical Analysis

Using a Cox proportional hazards model, we determined the hazard ratio (relative risk [RR]) and associated 95% confidence intervals (CI) for discontinuation. The RR was adjusted for the following factors: age; type of prescriber (obstetrician/gynecologist or other); cost of prescription (less than $10 per month or more than $10 per month); and, for HRT

users, type of MPA schedule (cyclic or combined continuous). We estimated survival distribution using the product-limit (Kaplan-Meier) method and assessed differences in this distribution for the study groups by using the log-rank test.[8] Analyses were performed with SAS® software (SAS Institute, Cary, NC). We calculated a measure of compliance for all subjects who filled 2 or more prescriptions for estrogen by dividing the total days' supply of estrogen (up to but not including the final prescription) by the number of days between receiving the first and final prescriptions.

··· RESULTS ···

Hormone Replacement Therapy

Among women who received HRT, a slightly higher percentage of older women used transdermal estradiol, whereas a higher percentage of younger women used oral estrogen (mean age [SD]: 55.3 [7.2] years for users of transdermal estradiol and 54.5 [7.1] years for users of oral estrogen) (Table). The 2 groups were similar with regard to prescription cost, prescriber type, and percentage of women receiving cyclic or continuous MPA. The mean lengths of follow-up were 8.0 months and 10.3 months for women using transdermal estrogen and those using oral estrogen, respectively.

After 12 months of follow-up, the probability of HRT discontinuation was 69% among users of transdermal estrogen and 61% among users of oral estrogen (Figure 1). Switching from the transdermal to the oral route accounted for 10% of patch discontinuations.

Age was significantly associated with HRT discontinuation: for each additional 5 years of age at start of follow-up, a woman's risk of discontinuation increased by 6% ($P < 0.001$). Prescription cost was also significantly associated with discontinuation (RR = 1.4; 95% CI = 1.1 to 1.8 for women who paid $10 or more per prescription versus women who paid less than $10 per prescription). Discontinuation risk was not influenced by type of prescriber (RR = 0.9; 95% CI = 0.8 to 1.1 for gynecologist versus other practitioner) or by HRT schedule (RR = 0.9; 95% CI = 0.9 to 1.0 for cyclic versus continuous combined HRT schedules).

The risk of discontinuation was higher among women starting HRT with transdermal estradiol than among those starting with oral conjugated estrogen therapy (RR = 1.5; 95% CI = 1.3 to 1.8). After adjustment for age, type of healthcare provider, progestin schedule, and prescription cost, the RR of discontinuation remained 1.5 (95% CI 1.3 to 1.8).

Compliance was equally high among users of transdermal and oral estrogen: median compliance

Table. Characteristics of 4182 Women Starting HRT, by Type of Estrogen Used

	No. (%) Women Using HRT		No. (%) Women Using ERT	
	Transdermal (n = 196)	Oral (n = 3986)	Transdermal (n = 85)	Oral (n = 19)
Age (yr):				
45-49	49 (25)	1091 (27)	41 (48)	93 (49)
50-54	57 (29)	1418 (36)	27 (32)	45 (24)
55-59	45 (23)	567 (14)	12 (14)	27 (14)
60-64	15 (8)	414 (10)	3 (4)	21 (11)
65-69	21 (11)	306 (8)	2 (2)	5 (3)
70-74	9 (5)	190 (5)	0	0
MPA schedule:				
Cyclic	81 (41)	1620 (41)	N/A	N/A
Continuous	115 (59)	2366 (59)		
OB/GYN Prescriber	175 (89)	3844 (96)	81 (95)	189 (99)
Prescription Cost <$10/mo	192 (98)	3918 (98)	85 (100)	189 (99)

HRT = hormone replacement therapy; ERT = estrogen replacement therapy; MPA = medroxyprogesterone acetate; OB/GYN = obstetrician/gynecologist.
N/A = not applicable.

was 101.4% for women using transdermal estrogen and 98.5% for women using oral estrogen.

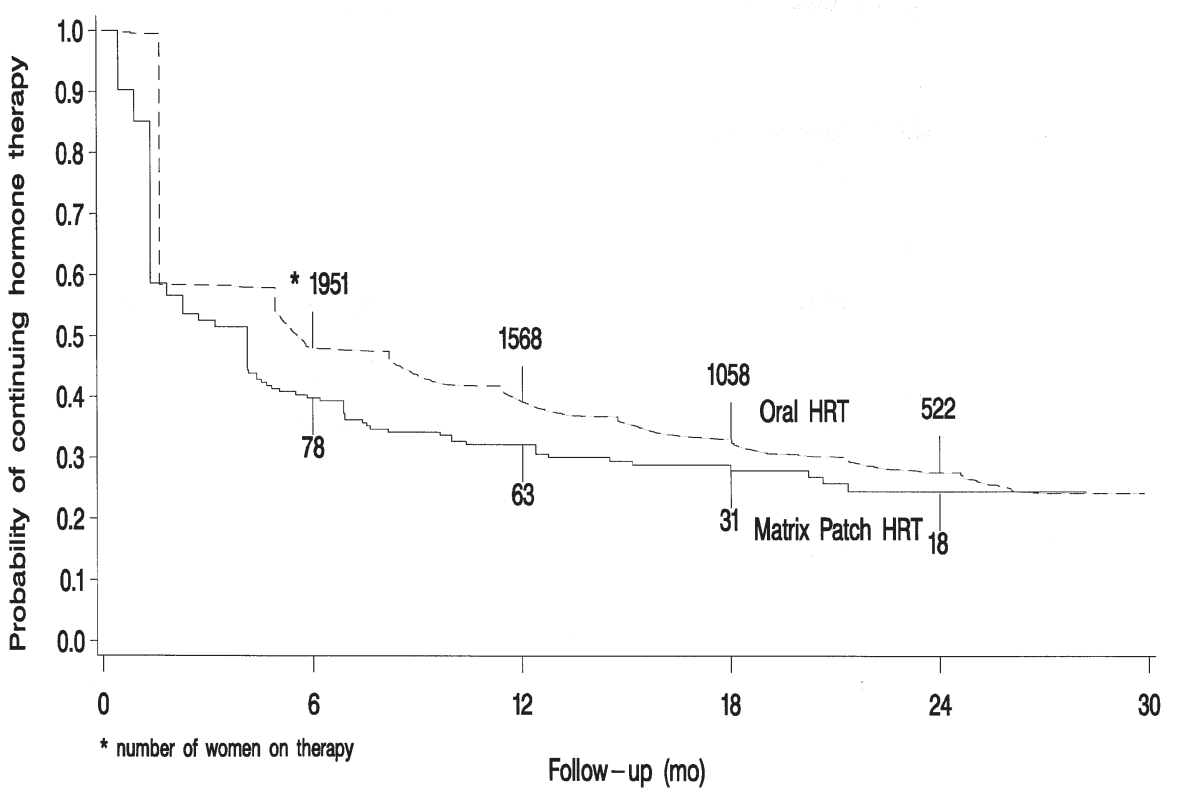
Estrogen Replacement Therapy

Women who received ERT were, on average, 4 to 5 years younger than women who used HRT. Among women receiving ERT, the mean (SD) ages were 50.5 (4.8) years and 51.6 (5.7) years for transdermal estradiol and oral estrogen treatments, respectively. The 2 groups were similar with regard to prescription cost and prescriber type. Mean lengths of follow-up were 8.6 months and 10.6 months for women using transdermal estrogen and oral estrogen, respectively. After 12 months of follow-up, the probability of discontinuation among women receiving ERT was 67% for the transdermal route and 59% for the oral route (Figure 2). Switching from the transdermal to the oral route accounted for 18.6% of patch discontinuation.

Age, type of prescriber, and prescription cost did not appear to influence discontinuation of ERT. The RR of discontinuation among women starting ERT with transdermal estradiol compared with those starting oral estrogen was 1.3 (95% CI = 1.0 to 1.8). Adjustment for age, type of healthcare provider, and prescription cost did not alter RR. Compliance was equally high among users of transdermal and oral estrogen: median compliance was 100.6% for users of transdermal estrogen and 99.4% for users of oral estrogen.

Although we previously showed that 90% of women who continue to use estrogen obtain refills within 30 days of the exhaustion of their drug supply,[1,6] we performed an additional sensitivity analy-

Figure 1. Probability of continuing postmenopausal estrogen-medroxyprogesterone therapy (HRT) throughout a 30-month follow-up period between January 1996 and June 1998 among 45- to 74-year-old women in the Kaiser Foundation Health Plan. Discontinuation of therapy was defined as failure to refill prescription within 30 days of the scheduled exhaustion of the prescribed estrogen supply.



HRT = hormone replacement therapy

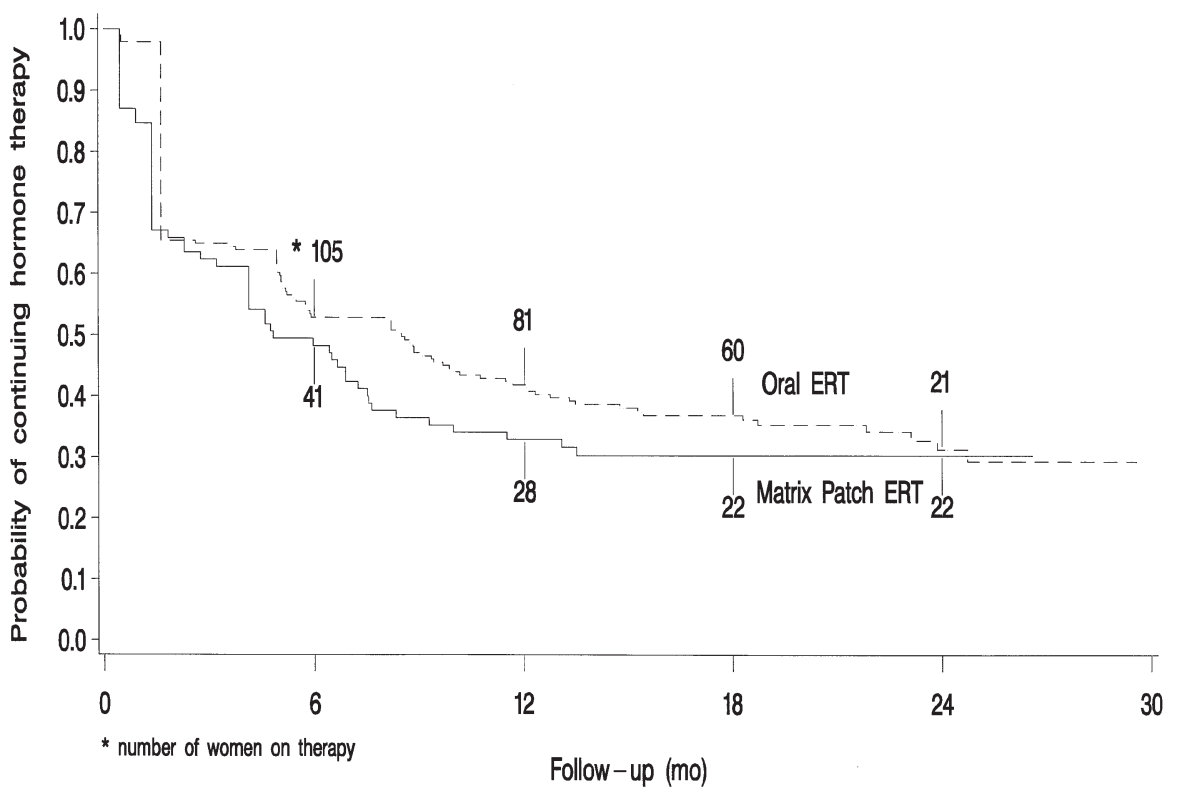
sis of discontinuation that tested the effect of using an interval of 60 days (instead of 30 days) between exhaustion of prescribed drug supply and receipt of refill. Probability of discontinuation at 12 months was about 10% lower in all subgroups, but the difference in discontinuation between users of transdermal versus users of oral estrogen did not change (data not shown).

··· DISCUSSION ···

In this study we found that 2 of 3 women who began estrogen treatment discontinued it and that hysterectomy did not alter the rate of discontinuation. In addition, we discovered that women who use a transdermal solid-matrix estrogen patch have a higher probability of discontinuation than do women who start oral estrogen therapy. Most discontinuation represented patients stopping ERT or HRT altogether, but about 25% of the patch discontinuations represented a switch to an oral estrogen formulation. In fact, the difference in discontinuation for the oral versus the transdermal routes could be explained by women switching from patch to oral estrogen.

In randomized, double-blind clinical trials of HRT, the rates of discontinuation obtained for women assigned to receive oral or transdermal estrogen have been similar and low. In a 3-year, double-blind, randomized clinical trial in which women received 0.625 mg of oral conjugated

Figure 2. Probability of continuing postmenopausal therapy with estrogen alone (ERT) throughout a 30-month follow-up period between January 1996 and June 1998 among 45- to 69-year-old women in the Kaiser Foundation Health Plan who had undergone hysterectomy. Discontinuation of therapy was defined as failure to refill prescription within 30 days of the scheduled exhaustion of prescribed estrogen supply.



ERT = estrogen replacement therapy

equine estrogen, the cumulative rate of discontinuation was about 20%.[9] In a 2-year, double-blind, randomized trial of women who had a hysterectomy and used a reservoir system for receiving estradiol transdermally, the rate of discontinuation was about 21%.[10] Thus, discontinuation rates in clinical practice are considerably higher than those in clinical trials. Several factors may account for this. Women selected for clinical trials are usually well educated, highly motivated, and seriously committed to seeing the research project through to completion. In addition, these women receive considerable support, education, and encouragement from a dedicated research team.

In our study, it is possible that less compliant patients were prescribed a patch rather than a pill. An alternative hypothesis is that women who received the patch were likely to have asked for it, which indicates greater knowledge about HRT and, consequently, a higher likelihood of being compliant. In a survey of estrogen use among postmenopausal women who attended an academic center gynecology department, Cano reported that women who used an alcohol reservoir system for delivering estradiol transdermally were more likely to continue therapy than those who used estrogen pills.[4] However, the results of this study were not adjusted for age, hysterectomy status, type of progestin schedule, or previous use of HRT. By examining both a database of estrogen prescription refills and medical records, Berman and coworkers[5] found that women who used an alcohol reservoir system for delivering estrogen transdermally showed no statistically significant differences in discontinuation when compared with women who took estrogen orally. On the basis of prescription refills, we previously found that women who started HRT with an alcohol reservoir estradiol delivery system were 2.6 times more likely to discontinue than women who started with oral estrogen.[6] When compared with those results, our current study shows smaller differences in discontinuation between transdermal and oral estrogen therapy, suggesting that the newer matrix transdermal delivery system is more likely to be continued than the older reservoir system. Additional support for this belief is our finding, during a similar duration of follow-up, that approximately 10% of women who stopped transdermal HRT switched from the solid-matrix system to oral estrogen, whereas 25% of similar women switched from the alcohol reservoir system to oral estrogen.[6]

A strength of our study was that we were able to examine prescription records of a population of women who had equal access to physicians and pharmacies and who received their estrogen prescriptions at relatively low cost and from the same group of healthcare providers. The PIMS database provided an objective and accurate method of tracking pharmacotherapy use. We consider it unlikely that women would use pharmacies outside the health plan, because the prescription cost for HRT at outside pharmacies would be several times higher. Moreover, prescription underreporting would be unlikely to cause bias toward one or the other estrogen regimen.

We did not examine reasons for discontinuing estrogen use. Possible explanations are inconvenience of wearing a skin patch, inadequate symptom control, and skin irritation. However, we believe that these are not important factors in these women's decision to stop ERT or HRT. Even though newer solid-matrix transdermal estrogen delivery systems have a lower risk of troublesome skin reactions, improved adhesion, and overall better patient acceptance [3,11-13] than do the alcohol reservoir systems, we still observed a high rate of discontinuation. In addition, discontinuation rates were similar among women who had a hysterectomy, suggesting that neither cyclic nor unscheduled bleeding is a critical factor in most women's decision to stop estrogen therapy.

These results, obtained at KFHP, an HMO in Northern California, may not be generalizable to women in other locales or in other managed care systems. In an analysis of a large prescription benefit management company that served numerous health plans across the country, Faulkner and coworkers[14] found noncompliance rates similar to those in this study—among 28,718 women who started ERT or HRT, 54.4% were noncompliant at 1 year. However, geographic differences were noted in that study; compared with women in the East or Midwest, women in the West were about 10% more compliant, whereas women living in the South were about 20% less compliant.

Our results confirm other study results that showed that in usual clinical practice, the likelihood of women continuing HRT beyond the first several months is low.[1,6,14] We conclude that transdermal estrogen does not seem to improve continuation of therapy. Efforts must be directed at understanding the reasons behind this early discontinuation of HRT.

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