Use of Hormone Replacement Therapy, 1998–2007: Sustained Impact of the Women's Health Initiative Findings

Barbara G Silverman and Ehud S Kokia

BACKGROUND: Trials of hormone replacement therapy (HRT) for prevention of chronic disease in postmenopausal women have suggested that the risks of treatment outweigh the benefits. The publication in 2002 of the Women's Health Initiative (WHI) study sparked a rapid decline in HRT purchases among American women.

OBJECTIVE: To examine the impact of the WHI findings on patterns of HRT use in Israeli women.

METHODS: We linked purchases of estrogen preparations from 1998 to 2007 by female Israeli health maintenance organization members aged 45 years and older to membership data. For each year, we calculated total annual purchases and rate of HRT utilization, characterized new users by age and mode of therapy, and examined rates of switching between modes of therapy.

RESULTS: Twenty percent of women aged 45 years and older purchased estrogen products in 2001, versus 10% in 2007 ($p < 0.001$; χ^2). Vaginally administered products accounted for a rising percentage of purchases, from 5% in 1999 to 18% in 2007. An increasing percentage of new users aged 55 years and older started with a vaginal product (62% in 1999, 82% in 2007). After 2002, new users of oral therapy discontinued use more quickly than those who started oral therapy before 2002. Tibolone accounted for an increasing percentage of oral drugs purchased (12% in 2003, 29% in 2007).

CONCLUSIONS: The WHI findings had a rapid and sustained impact on HRT utilization in a large population of Israeli women, including a sharp decrease in the rate of use, particularly of oral preparations, as well as reduced duration of therapy and increased use of vaginal preparations and tibolone as first choices for treatment.

KEY WORDS: hormone replacement therapy, Israel, pharmacoepidemiology.

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Prior to 2002, estrogen replacement therapy was widely recommended for the relief of menopausal symptoms, as well as for the prevention of osteoporotic fractures and heart disease.[1,2] Numerous observational studies had indicated a cardioprotective effect of postmenopausal hormone replacement therapy (HRT), although an increased risk of stroke was also observed.[3-5] Prior to 2002, HRT use in the US was widespread, although estimates of population rates of use varied. A telephone survey conducted in 1995 estimated that 37.5% of US women between the ages of 50 and 74 years used HRT.[6] Two studies extrapolated from drug purchasing data suggested rates among women aged 50–74 years of 33% and 41% in 1995 and 2000, respectively.[7,8] Use of HRT among Israeli women during the same time period appears to have been less prevalent than in the US; a 1998 telephone survey of Israeli women aged 45–74 years estimated that 17% were current HRT users.[9] HRT use among Israeli women aged 50–74 years attending family-practice clinics was, not surprisingly, somewhat higher, at 27%.[10]

The Women's Health Initiative (WHI) findings questioning the safety and efficacy of long-term estrogen therapy for prevention of chronic conditions were published in July 2002.[11] In response, the US Preventive Services Task Force and several professional groups and health maintenance organizations (HMOs) changed their guidelines for the use of HRT, reaffirming its value for treatment of menopausal symptoms but deemphasizing its use for prevention of chronic conditions.[12-16] It was recommended that symptomatic treatment be provided in the lowest effective dose and for the shortest time period possible.[17] In parallel with changing attitudes toward HRT,

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promotion of most types of hormone therapy by manufacturers also decreased.[18]

Studies have documented substantial reductions in the use of HRT in the US and other countries subsequent to the publication of the WHI findings.[7,8,19-24] These studies took a range of approaches to estimate changes in HRT use. Analyses of pharmaceutical marketing data and national patient care surveys highlighted the marked drop in prescribing of oral estrogen and estrogen/progestin combinations that occurred after July 2002, while noting little change in the use of vaginal preparations. The data used in these analyses were not person-level and did not allow for direct estimates of population use rates.[7,8,19] Cross-sectional surveys in the context of trials or routine medical care documented utilization at selected points in time but did not allow for longitudinal analysis.[21,22,25] Person-level drug purchasing data offer the opportunity to quantify purchases and describe users at specific points in time as well as the ability to track changes in therapeutic regimens over time.[20,23]

We examined HRT use among female members of an Israeli HMO from 1998 through 2007 to determine whether changes in the extent and patterns of use of the treatment occurred subsequent to changes in prescribing guidelines for this class of medications.

Methods

We used the pharmacy purchasing records of Maccabi Healthcare Services to examine use of estrogen replacement therapy (oral, transdermal, and vaginal products) in female members aged 45 years and older. Maccabi Healthcare Services is Israel's second-largest HMO, providing medical and preventive services to approximately 1.7 million members, 25% of the Israeli population. During the study period, the total population of HMO members grew from 1.3 million to 1.7 million, while the number of female members aged 45 years and older grew from 150,000 to 251,000.

The patient information systems of Maccabi Healthcare Services are fully computerized and capture visits to hospitals, physicians, and other health professionals; prescription drug purchases; laboratory testing; and imaging studies. Available data regarding prescription drug purchases include identification numbers for the patient and prescribing physician, date and place of purchase, and drug classification number. Drug classification numbers identify the drug name, active ingredient(s), dosage, route, and number of units per package. We searched the pharmacy purchasing database for all purchases of products in the category of hormone replacement therapy, comprising: (1) oral medications, including estrogen-only and estrogen/progestin combinations, (2) vaginal preparations, including estrogen creams and suppositories, (3) transdermal products, including estrogen patches and gels, and (4) tibolone, a synthetic steroid that has been available in Israel since 2003, but is not included in the drug formulary that by law must be supplied to HMO members.

We used 3 separate approaches to assess the overall impact of changing knowledge regarding HRT on purchasing. First, we calculated total annual purchases of these types of medications by category and used these figures to calculate purchase rates and to examine time trends. In addition, we studied changes in the frequency with which women commenced therapy, as well as changes in the type of product (ie, oral, transdermal, vaginal) they used when starting therapy. A new user was defined as any woman in the target age group who made an HRT purchase after at least 1 year with no such purchases. The first drug purchased in the year was used to determine the type of estrogen therapy used to start treatment.

As a third indicator of changes in attitude toward the use of estrogen therapy, we examined the rate at which users of oral HRT medication discontinued treatment or switched to another type of product. For the purposes of this analysis, we defined discontinuation as 120 days without an oral medication purchase, even if the patient later began purchasing again. We calculated duration of therapy as the number of days elapsed from the date of the first purchase to the date of the last purchase, for any period with a break of less than 120 days between purchases. Switching from oral therapy was defined as a purchase of another type of HRT within 120 days of the last oral drug purchase. Each patient entered the analysis of discontinuation and switching only once, regardless of how many times she resumed and discontinued therapy.

Analysis of switching and discontinuation of therapy was limited to women who made at least 2 purchases of oral medication during the study period. We used autoregressive integrated moving average (ARIMA) time series analysis to assess trends in monthly HRT purchases over the period of the study. ARIMA analysis included an intervention variable to indicate purchases occurring after July 2002, when the WHI findings were widely published. Pearson's χ^2 tests were used to evaluate changes in HRT population purchasing rates and in the proportion of users commencing therapy with different treatment modalities. Life-table analysis was used to assess the impact of the calendar year in which treatment was started on duration of therapy. Follow-up for purposes of life-table analysis continued through December 31, 2007. Women who died or left the HMO within 120 days of their last purchase, as well as women whose last purchase was within 120 days of the last possible follow-up date, were censored from analysis as of the date of the last purchase. All analyses were conducted using SPSS version 14.0 (SPSS Inc., Chicago, IL). This project received approval from the HMO Helsinki Committee for Research Involving Human Subjects.

Results

ANNUAL PURCHASING

Purchases of oral estrogen replacement preparations among women aged 45 years and older peaked in 2001 and dropped steadily from 2002 onward. Purchases of transdermal estrogen lagged substantially behind those of oral estrogen in all years, peaked in 2002, and dropped thereafter. Vaginal estrogen products accounted for a rising percentage of estrogen purchases—from 5% in 1999 to 18% in 2007. Likewise, tibolone accounted for an increasing percentage of oral drugs purchased—from 12% in 2003, when it was first introduced in this population, to 29% in 2007 (Figure 1). In 2001, 20% of women aged 45 years and older had made at least one purchase of HRT. This figure dropped by 29% to 14% in 2003 ($p < 0.001$; χ^2), and further to 10% in 2007 (Figure 2). The most dramatic changes in utilization patterns occurred between 2001 and 2003.

During the period from January 2001 to July 2002, women aged 45 years and older made an average of 14,793 purchases of oral HRT per month; this figure dropped to 8982 for the period from August 2002 to December 2003. ARIMA analysis of monthly oral HRT purchases from January 1998 through December 2007 identified significant seasonal and autoregression components ($t = 8.5$ vs $t = 28.9$, respectively; $p < 0.001$), as well as a significant effect of the period of purchase (after vs before July 2002, $t = -2.8$; $p = 0.007$; model r^2 0.97). Mean monthly purchases of vaginal HRT products rose from 1197 for the period from January 2001 to July 2002 to 1287 for the period from August 2002 to December 2003. However, while ARIMA analysis of monthly purchasing of vaginal products for the entire study period (1998–2007) revealed seasonal and autoregression components ($t = 7.7$ vs $t = 17.6$, respectively; $p < 0.001$), period of purchase had no effect on purchasing volume in the model ($t = 0.821$; $p = 0.413$, respectively).

NEW ESTROGEN USERS

In 1999, a total of 9394 women were identified as new users of estrogen therapy (excluding tibolone). The number of new users per year declined to 8266 in 2003, then rose to 10,352 in 2006. Although the number of new users stabilized, the type of treatment used by new users changed markedly with time. Among new users in 1999, 60% started with oral, 10% with transdermal (patch or gel), and 30% with vaginal preparations. By 2007, the proportions of new users starting with each of these delivery methods were 24%, 8%, and 61%, respectively, representing significant changes in use of oral and vaginal products ($p < 0.001$, χ^2, Pearson's r for trend). Seven percent of new users in 2007 started treatment with tibolone (Figure 3). Choice of delivery method varied widely with age. In 1999, 78% of new users aged 45–54 years began treatment with oral medication; this figure dropped to 50% in 2003 and to

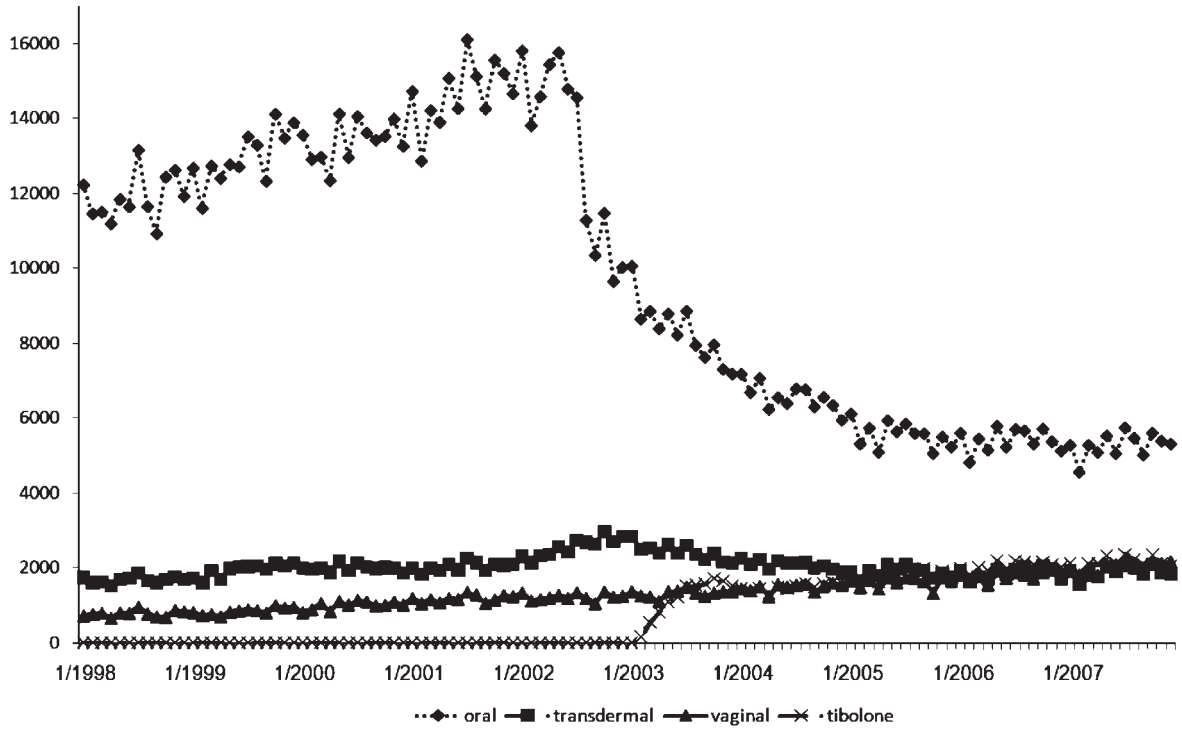

Figure 1. Purchases of hormone replacement therapy by type among women aged 45 years and older, Maccabi Healthcare Services, 1998–2007.

45% in 2007. Most new users aged 55 years and older started with a vaginal product (62% in 1999, 82% in 2007).

DISCONTINUATION/SWITCHING

Analysis of annual cohorts of new users of oral therapy demonstrated marked variation in percent adherence to therapy with year of initiation of treatment. Oral estrogen users who initiated therapy in 2002 or later tended to discontinue therapy more quickly than those starting in earlier years. Of users initiating therapy in 1999, 47% had a duration of therapy of longer than 1 year, and 33% longer than 2 years. The corresponding figures for users initiating therapy in 2005 were 34% and 29%, respectively (Figure 4). Median duration of therapy for the 1999 cohort was estimated at 319 days, compared with 178 days for the 2005 cohort ($p < 0.001$; log-rank test).

We defined switchers as women who purchased another form of estrogen therapy within 4 months of their last oral estrogen purchase. According to this definition, 5.3% of those discontinuing oral therapy switched to a transdermal preparation, 2.2% to tibolone, and 1.1% to a vaginal product. Proportion switching to vaginal or transdermal estrogen was highest in 2002 and 2003 (Table 1). Women who had recently discontinued oral therapy accounted for 19% of new users of tibolone in 2003, the first year the product became available. By 2007, this figure had dropped to 12%.

Discussion

Changes in drug utilization guidelines can lead to a number of responses in the community: cessation of treatment by current users, a drop in the proportion of the target population commencing use, and preference of users for products perceived as posing less hazard. Several studies have documented the substantial drop in prescribing and promotion of HRT in response to the new information and changes in prescribing guidelines.[7,8,18,19,25]

We analyzed utilization of HRT products in our HMO population. Our ability to link purchasing data on the basis of a unique member identification number allowed us to follow trends among users, thereby characterizing (1) new users, (2) changes in the formulation used to initiate therapy, (3) switching to alternate modes of therapy, and (4) changes in duration of therapy. Follow-up through December 2007 allowed us to determine whether the change in patterns of utilization seen immediately after the publication of the WHI findings was sustained. Our analysis demonstrated the following phenomena temporally related to the publication of the WHI findings in 2002: (1) a 22% drop in total HRT purchases between 2002 and 2003, (2) an initial drop and subsequent stabilization of the number of new users, (3) a major shift from oral to vaginal therapy among new users, but not among current users of oral medication, (4) reduced duration of oral therapy among

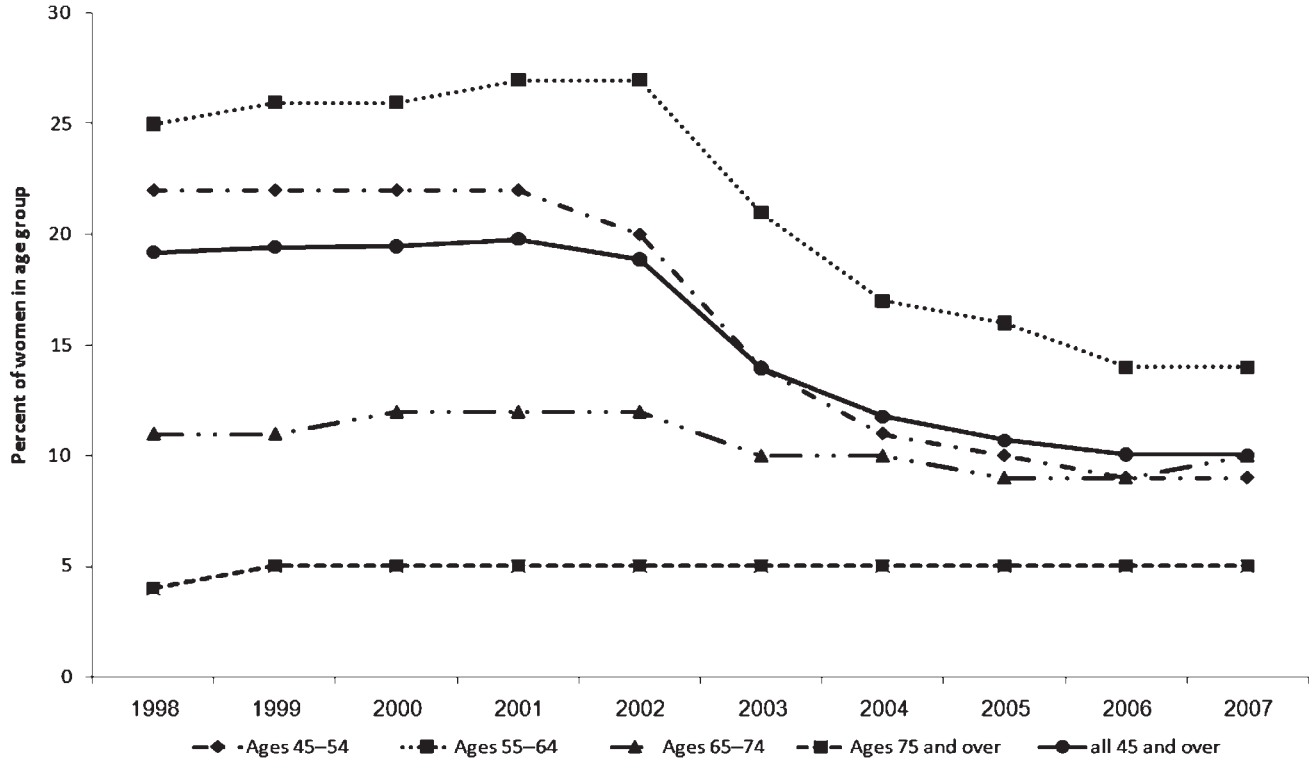

Figure 2. Rate of hormone replacement therapy use by age group, Maccabi Healthcare Services, 1998–2007.

new user cohorts, and (5) entry of tibolone as a treatment in parallel with the drop in estrogen-containing products, primarily as an option for new users of hormone therapy.

Current guidelines stress that while HRT may be appropriate for short periods of time and at the lowest possible dose for the relief of symptoms, it should not be used in women with a history of cardiovascular disease, breast cancer, uterine cancer, or venous thromboembolic events.[26] Increases in the proportion of women in our population who started therapy with a vaginal preparation, particularly among older women, may reflect increased attention to symptom relief, in concert with greater concern about the long-term effects of systemic hormone therapy. Total purchases of oral and transdermal HRT dropped, while purchases of vaginal preparations appear to have continued according to previously established trends. In addition, the number of new users and the percentage of new users starting therapy with an oral drug declined. While use of oral HRT among current users appears to decline with time, there was an especially pronounced drop among established users after 2002, indicating a tendency toward shorter duration of therapy with systemic agents.

Even prior to 2002, HRT utilization in our population appeared to be considerably lower than estimates from the US. Our estimate of a baseline prevalence of estrogen use of 20% (2001) is consistent with that of a 1998 telephone survey of Israeli women aged 45–74 years, which estimated that 17% were current HRT users.[9] Despite differences in baseline utilization between the 2 populations, the observed drop in utilization following the publication of the WHI findings correlates well with findings from US studies. An analysis of US pharmacy purchasing data estimated that approximately 42% of women aged 50–74 years were using HRT in 2001 and noted a precipitous drop in purchases by 2003.[7] In that study, data were not linked to the identity of the purchaser; therefore, longitudinal analysis of purchasing behavior of individuals was not possible. Data from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Care Survey also demonstrated a substantial decrease in the number of visits of women with HRT prescriptions between 2001 and 2003[19]; again, these studies were not designed to allow for person-level longitudinal analysis.

In a study of HRT use among women aged 50–74 years presenting for mammography, the self-reported rate of HRT use dropped 18% per quarter following the WHI publication in 2002.[25] Type of therapy was not addressed in this report. Analysis of data from a large US pharmacy benefits management company also documented increased discontinuation of therapy following the WHI publication, although switching to other forms of therapy was not considered.[27] In contrast to our findings and to the American

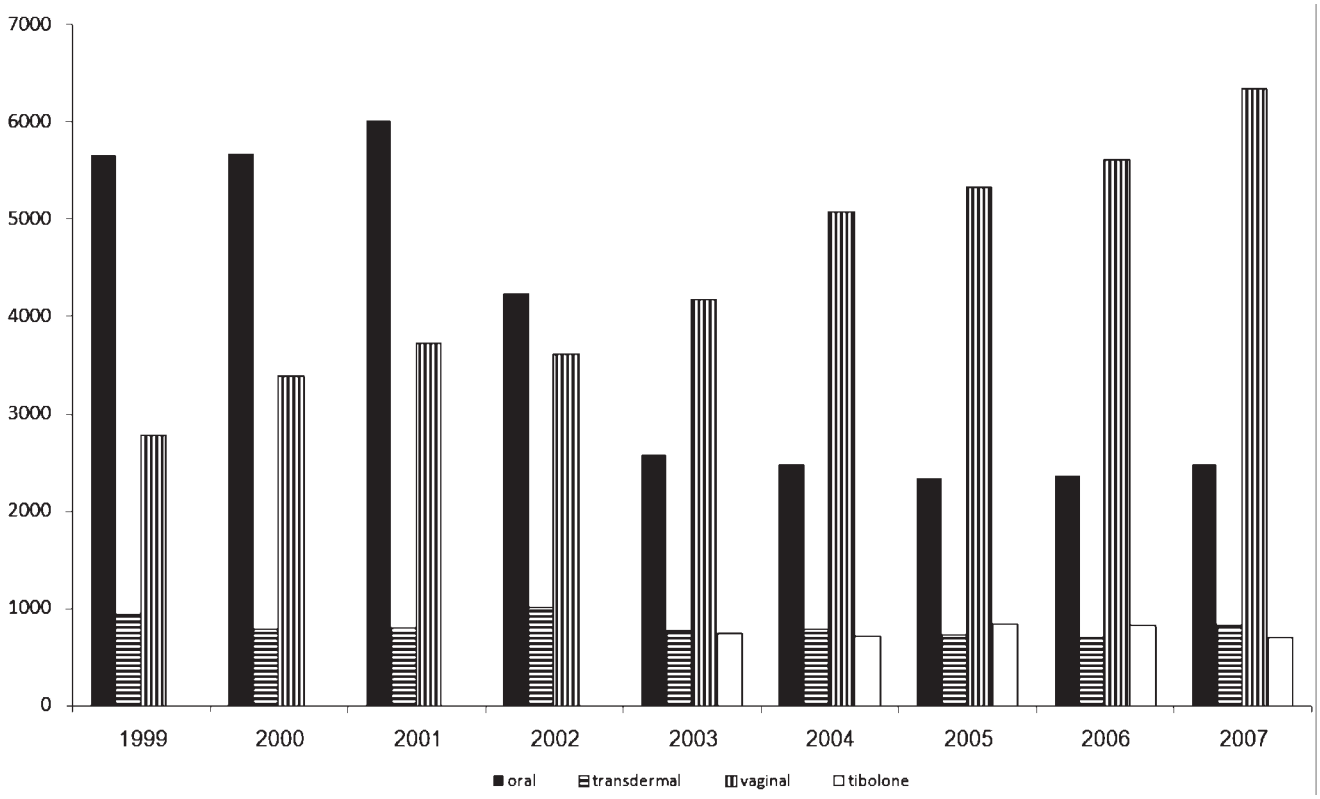

Figure 3. Administration method for new users aged 45 years and older of hormone replacement therapy, Maccabi Healthcare Services, 1999–2007.

studies cited, a longitudinal study of HRT use in the Netherlands documented little change after publication of the WHI findings. However, a sharp drop in the purchase of oral estrogens in late 2003 was noted, after publication of the findings of the British Million Women Study.[23]

In parallel with a decrease in the use of oral estrogen and estrogen/progestin combinations, we noted an increase in the use of tibolone, a synthetic steroid whose metabolites have estrogenic, androgenic, and progestagenic properties. Tibolone has been shown to provide relief of hot flushes/sweating comparable to that provided by HRT; the effect of the drug on cardiovascular and breast cancer risk is less clear.[13,28] A recent clinical trial of tibolone in women with osteoporosis found it to be associated with a reduced risk of fractures and breast cancer but an increased risk of stroke.[29] Although tibolone is not included in the formulary of Israeli HMOs, Maccabi Healthcare Services offers a 50% discount on the purchase of tibolone to members with supplemental insurance (86% of women aged ≥45 y). Other members may choose to purchase this drug at full price without the purchase appearing in the Maccabi Healthcare Services database. Therefore, we may have underestimated the degree to which tibolone has become accepted.

Our analysis has several limitations. We focused on purchases covered by the HMO, rather than physician prescriptions or actual drug use. Furthermore, we limited our analysis to purchasing behavior and did not attempt to link trends in utilization to health outcomes. Since our analysis equated a discontinuation of purchasing with cessation of therapy, we could not separately analyze the effects of physician and patient decision-making on changes in utilization. However, because patients may choose at times not to fill prescriptions they have received, purchasing data are a more reliable indicator of actual utilization than prescribing data in that patients are unlikely to continue purchasing a drug they do not use. In addition, it is theoretically possible for members to purchase medications outside of the system, resulting in underestimation of HRT utilization. However, prescription drug coverage with a modest copayment (generally 15% of the cost of the drug) is an important benefit available in the standard services that must be provided by all HMOs, and it is unlikely that women would choose to pay full price for prescription medications.

We defined sustained usage as a pattern of purchasing without a break of greater than 120 days. We chose this approach, rather than a calculation of adherence to therapy, to identify time points at which therapy clearly appeared to have ceased, while allowing for less than perfect adherence. Because the analysis considered a range of products, and differences in packaging and dosage make it difficult to establish the number of days of therapy included in a package, we chose the last date of purchase as the endpoint of therapy rather than adding an arbitrary number of days to the calculated duration of therapy. This approach may underestimate the true duration of therapy. However, since we used the same method to calculate treatment duration

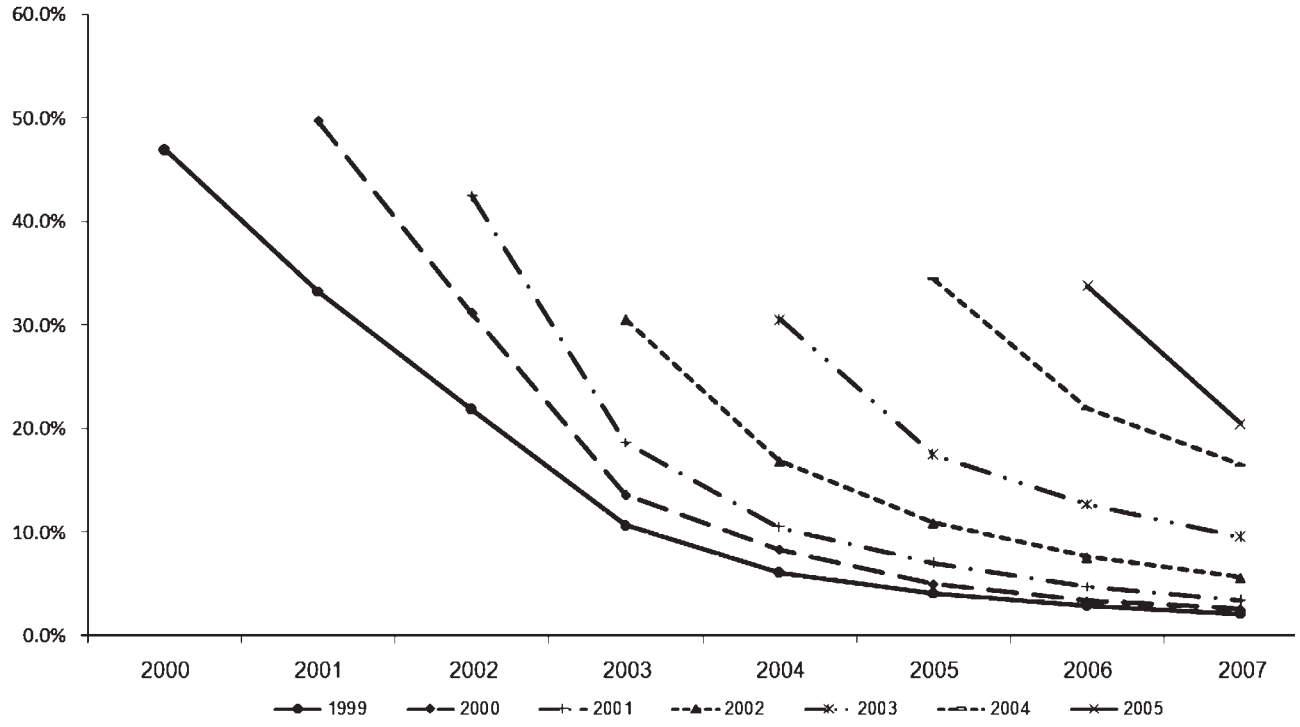

Figure 4. Percent adherence to oral estrogen therapy by year of initiation of treatment, 1999–2005 new user cohorts, Maccabi Healthcare Services.

for the entire study period, the potential underestimation of duration of therapy is not likely to have affected our finding that treatment duration declined dramatically in later cohorts of new users. Finally, as noted above, our data may underestimate the rate of tibolone use since, unlike the remainder of the medications studied, this product is not included in the standard formulary.

We documented a rapid drop in the proportion of women aged 45 years and older using HRT following the publication of the WHI findings, as well as marked shifts in the type of treatment used and the duration of therapy. Our analysis of a large stable population allowed longitudinal analysis of HRT use, enabling not only a survey of drug purchasing trends, but also estimates of utilization rates in the target population over a period of several years. Longitudinal data also allowed us to characterize new users by age and mode of therapy, and to examine switches between modes before and after 2002. The decrease in overall HRT use in our population can be attributed both to discontinuation by current users and a reduction in the number of new users. This reduction was sustained through the end of December 2007. The finding of increased tibolone use is likely due to patient and provider perceptions of this product as a safer alternative to traditional HRT. Continued surveillance will be required to determine whether this trend continues and to assess the long-term health impact of tibolone use.

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Table 1. Switches to Other Hormone Therapy Among Women Discontinuing Oral Estrogen[a]

Year of Last Oral Purchase	Pts. Discontinuing Oral Product (n)	Pts. Switching to Vaginal Product (%)	Pts. Switching to Transdermal Product (%)	Pts. Switching to Tibolone (%)
1999	1,347	0.7	5.0	0.0
2000	2,212	1.1	3.8	0.0
2001	2,509	1.0	5.2	0.0
2002	4,033	1.3	9.3	0.3
2003	2,181	1.6	6.2	8.8
2004	1,350	1.5	4.4	5.8
2005	1,225	0.9	5.5	5.3
2006	1,176	1.2	4.1	4.0
2007	2,654	0.3	1.0	0.9
All years	18,687	1.1	5.3	2.2

[a]Maccabi Healthcare Services, 1999–2007.

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Uso de Terapia de Reemplazo Hormonal, 1998–2007: Impacto Sostenido de los Hallazgos de Iniciativa de Salud de las Mujeres

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EXTRACTO

TRASFONDO: Estudios sobre terapia de reemplazo hormonal (HRT) para prevención de enfermedad crónica en mujeres postmenopáusicas sugieren que los riesgos del tratamiento sobrepasan los beneficios. La publicación del estudio Iniciativa de Salud de las Mujeres (WHI) en 2002 provocó un rápido descenso en las compras de terapia de reemplazo hormonal entre las mujeres norteamericanas.

OBJETIVOS: Examinar el impacto de los hallazgos de WHI sobre patrones de uso de terapia de reemplazo hormonal en mujeres israelitas.

MÉTODOS: Comparamos las compras de preparaciones de estrógeno por miembros femeninos de organizaciones de mantenimiento de la salud (HMO) de 45 años o más desde 1998–2007 con datos sobre membresía. Para cada año calculamos el total de compras anuales y la tasa de utilización de terapia de reemplazo hormonal, caracterizamos las usuarias nuevas por edad y modalidad terapéutica, y examinamos los cambios entre modalidades terapéuticas.

RESULTADOS: Veinte por ciento de las mujeres de 45 años o más compraron estrógenos en 2001, comparado con 10% en 2007 ($p < 0.001$, χ^2). Los productos vaginales presentaron un aumento en el porcentaje de compras, de 5% en 1999 a 18% en 2007. Un porcentaje creciente de usuarias nuevas de 55 años o más comenzaron con un producto vaginal (62% en 1999, 82% en 2007). Después de 2002, las usuarias nuevas de terapia oral la descontinuaron más rápido que anteriormente. Se atribuye a Tibolona el porcentaje creciente de medicamentos orales comprados (12% en 2003, 29% en 2007).

CONCLUSIONES: Documentamos el impacto rápido y sostenido de los resultados de WHI en la utilización de terapia de reemplazo hormonal en una población grande de mujeres israelitas, incluyendo una caída marcada en la tasa de uso, particularmente de preparaciones orales, duración reducida de la terapia y aumento en uso de preparaciones vaginales y Tibolona como primeras selecciones para tratamiento.

Traducido por Ana E Vélez

L'Utilisation d'Hormonothérapie Substitutive, 1998–2007: Impact Prolongé des Résultats de l'Initiative Pour la Santé des Femmes

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RÉSUMÉ

INTRODUCTION: Les études portant sur l'hormonothérapie substitutive (HTS) dans le but de prévenir certaines complications chez les femmes ménopausées, suggèrent que les risques sont supérieurs aux bénéfices. La publication des résultats de l'Initiative pour la Santé des Femmes (ISF) en 2002 entraîna un rapide déclin des ventes de ces produits aux États-Unis.

OBJECTIFS: Examiner l'impact des résultats de l'ISF sur l'utilisation d'HTS par les femmes Israéliennes.

DEVIS EXPÉRIMENTAL: Nous avons analysé les achats de préparations d'estrogènes pour la période de 1998–2007 par les femmes de 45 ans et plus, membres d'une organisation de gestion des soins de la santé, et relié ces à achats à l'ensemble de la population membre de l'organisation. Pour chaque année, nous avons calculé le total des achats et le taux d'utilisation d'HTS. Nous avons caractérisé les nouvelles utilisatrices selon leur âge et le type de traitement et avons examiné les changements de thérapies.

RÉSULTATS: Vingt pourcent des femmes de 45 ans et plus ont acheté des estrogènes en 2001, contre 10% en 2007 ($p < 0.001$, χ^2). L'utilisation de produits pour administration vaginale a augmenté de 5% en 1999 à 18% en 2007. Une proportion plus grande d'utilisatrices de 55 ans et plus ont débuté la thérapie par un produit pour administration vaginale (62% en 1999, 82% en 2007). Après 2002, les nouvelles utilisatrices de thérapie orale ont cessé la thérapie plus rapidement qu'avant. Parmis les produits oraux, la tibolone est plus utilisée qu'avant (12% en 2003, 29% en 2007).

CONCLUSIONS: Nous avons documenté un effet rapide et prolongé des résultats de l'ISF sur l'utilisation d'HTS chez une large population de femmes Israéliennes. Les observations incluent une baisse importante du taux d'utilisation, en particulier des préparations orales, une réduction de la durée de traitement, et une augmentation de l'utilisation de produits pour administration vaginale et de tibolone comme premier choix de traitement.

Traduit par Suzanne Laplante