

# National Use of Postmenopausal Hormone Therapy

## Annual Trends and Response to Recent Evidence

Adam L. Hersh, MD, PhD

Marcia L. Stefanick, PhD

Randall S. Stafford, MD, PhD

PATTERNS OF HORMONE THERAPY use among postmenopausal women in the United States ideally should reflect known risks and benefits. However, definitive information on these risks and benefits was lacking until recently. The Heart and Estrogen/Progestin Replacement Study (HERS)<sup>1</sup> and HERS follow-up (HERS II)<sup>2</sup> concluded that postmenopausal hormone therapy with combination oral estrogen/progestin offered no cardiovascular disease benefit among women with established disease. The estrogen plus progestin trial of the Women's Health Initiative (WHI)<sup>3</sup> demonstrated that hormone therapy with an estrogen/progestin combination caused increased risk of breast cancer and cardiovascular disease in postmenopausal women. These findings from randomized trials contrast with prior observational studies that suggested cardiovascular benefits.<sup>4-6</sup> Based on the quality of recent data, new guidelines recommend against routine hormone therapy use for chronic conditions,<sup>7</sup> and current users have been advised to taper doses toward discontinuation.<sup>8,9</sup>

Prior studies from nationally representative databases showed that in 1975, hormone therapy prescriptions peaked

**Context** Postmenopausal hormone therapy use increased dramatically during the past 2 decades because of a prevailing belief in its health benefits. Recent evidence from randomized trials published in July 2002 demonstrated adverse cardiovascular disease events and other risks with hormone therapy in the form of oral estrogen combined with progestin.

**Objective** To describe patterns of hormone therapy use from 1995 until July 2003, including the impact of recent evidence.

**Design, Setting, and Population** Two databases were used to describe national trends in hormone therapy use from January 1995 to July 2003. The National Prescription Audit database provided data on the number of hormone therapy prescriptions filled by retail pharmacies and the National Disease and Therapeutic Index database provided data on patient visits to office-based physicians during which hormone therapy was prescribed.

**Main Outcome Measures** Annual number of hormone therapy prescriptions and characteristics of visits to physicians during which hormone therapy was prescribed.

**Results** Annual hormone therapy prescriptions increased from 58 million in 1995 to 90 million in 1999, representing approximately 15 million women per year, then remained stable through June 2002. Adoption of new oral estrogen/progestin combinations, primarily Prempro, accounted for most of this growth. Obstetrician/gynecologists provided more than 70% of hormone therapy prescriptions, and more than one third of patients were older than 60 years. Following the publication of trial results in July 2002, hormone therapy prescriptions declined in successive months. Relative to January-June 2002, prescriptions from January-June 2003 declined by 66% for Prempro and 33% for Premarin. Small increases were observed in vaginal formulations and in new prescriptions for low-dose Premarin. If prescription rates observed through July 2003 remain stable, a decline to 57 million prescriptions for 2003, similar to the rate in 1995, is projected.

**Conclusions** Clinical practice responded rapidly to recent evidence of harms associated with hormone therapy. Since July 2002, many patients have discontinued hormone therapy or are tapering to lower doses.

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at 30 million.<sup>10-12</sup> Prescriptions subsequently declined to approximately 15 million in the early 1980s as evidence emerged showing an increased risk of endometrial cancer with unopposed estrogen use.<sup>10-12</sup> Prescription growth resumed as progestins were prescribed in combination with estrogen, and prescriptions for hormone therapy reached

36 million in 1992, representing approximately 6 million women and 17% of women older than 50 years.<sup>10</sup> More re-

**Author Affiliations:** Stanford Prevention Research Center, Program on Prevention Outcomes and Practices, Stanford University School of Medicine, Stanford, Calif.  
**Corresponding Author and Reprints:** Randall S. Stafford, MD, PhD, Stanford Prevention Research Center, Program on Prevention Outcomes and Practices, Stanford, CA 94305 (e-mail: rstafford@stanford.edu).

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cent estimates of current hormone therapy use among women aged 50 to 74 years in 1995 ranged from 38% from a national telephone sample<sup>13</sup> to 40% in a large health maintenance organization.<sup>14</sup> These estimates suggest a large increase in hormone therapy use between 1992 and 1995, if these patterns reflect national practices.

National trends in hormone therapy use since 1995 have not been reported, and the impact of recent evidence on hormone therapy prescriptions in subsequent months is unknown. Our objective was to describe these trends using national data on hormone therapy prescriptions and patient visits to physicians during which hormone therapy was prescribed.

## METHODS

We used 2 nationally representative databases published by IMS HEALTH (Plymouth Meeting, Pa), an independent pharmaceutical research company, to describe national trends in hormone therapy use from January 1995 through July 2003. Information on hormone therapy prescriptions from pharmacies was obtained from the National Prescription Audit Plus (NPA). Information on visits to office-based physicians was obtained from the National Disease and Therapeutic Index (NDTI). Both databases use samples to estimate national patterns.

### Hormone Therapy Prescriptions

The NPA consists of a national random computerized sample of approximately 20 000 retail pharmacies, independent pharmacies, mail order pharmacies, and mass merchandise and discount houses. These stores are sampled from the company's pharmacy database of more than 29 000 stores, accounting for more than half of all retail pharmacies in the United States and constitute a nationally representative sample. The sample is resized on a semiannual basis. Pharmacy data are collected daily and reported in monthly aggregates with the prescription as the major unit.

National Prescription Audit Plus provided monthly data on the total number

of dispensed prescriptions provided to consumers (new plus refill) for all hormone therapy formulations and for individual brands. These include oral, transdermal, vaginal, and injectable estrogens; oral and transdermal combined estrogen/progestin; and oral estrogen/androgen. Injectable estrogens are not represented adequately in NPA because these prescriptions rarely are filled at retail pharmacies<sup>10</sup> and therefore are excluded.

Prescription data were organized into 6 categories: Premarin (conjugated estrogen) (Wyeth Pharmaceuticals, Collegeville, Pa); other oral estrogens and estrogen/androgen; Prempro (conjugated estrogen/medroxyprogesterone) (Wyeth Pharmaceuticals); other oral estrogen/progestin combinations; transdermal; and vaginal. The number of hormone therapy prescriptions was reported annually by category and in aggregate from January 1995 through July 2003. For January 2002 through July 2003, monthly totals were determined to examine the short-term impact of WHI and HERS II study findings on hormone therapy prescriptions. We report 2 annual totals for 2002: an annualized estimate based on January through June and an annualized estimate based on July through December. For 2003, the annualized total reflects the most recently available data through July. Estimated sampling errors for monthly dispensed prescriptions were available and 95% confidence intervals (CIs) were derived to indicate the reliability of our estimates.

The approximate number of women exposed to any form of hormone therapy annually from 1995 to 2003 was estimated based on the number of prescriptions filled. Based on prior reports<sup>10</sup> and NPA documentation, hormone therapy prescriptions averaged 6 per year, lasting approximately 2 months. Therefore, the number of women exposed to hormone therapy was estimated by dividing the total number of prescriptions for each year by 6.

### Physician Office Visits

The NDTI is a continuing survey providing nationally representative infor-

mation on patient visits to physicians and associated medication use. The sample consists of approximately 3500 physicians each calendar quarter stratified by specialty and geographic region, selected from the master lists of the American Medical Association and the American Osteopathic Association. National estimates for patient visits and associated medication use are derived from this sample and documented both quarterly and annually. For each patient encounter, physicians describe all diagnoses, indicate all newly prescribed or continuing medications used specifically for each diagnosis, and report a "desired action" for the medication. The desired action is the medication's intended physiological, symptom-relieving, or preventive role as reported by the physician. Each report of a medication constitutes a drug "mention." The data reflect the status of the medication at the completion of the visit. Therefore, visits to physicians during which a medication is discontinued are not captured and the physicians do not report the medication. Additional information provided by the reports includes patient age, physician specialty, and concomitant medications prescribed.

Annual data were obtained for patient visits during which hormone therapy was reported as either estrogen or estrogen/progestin combinations from 1995 through June 2003. For the sample sizes available, the 95% CIs around the estimates of visit characteristics are approximately  $\pm 10\%$ . To detect possible short-term changes in practice, we collected semiannual data for 2002 and 2003, reported in 6-month intervals, and data for January through June of 2002 and 2003. For each year, the desired action, the percentage of each formulation (oral, injectable, transdermal, and vaginal), physician specialty, and patient age were recorded.

### Simultaneous Use of Estrogen and Progestin

Data from NPA and NDTI were combined to estimate the overall number of women receiving hormone therapy as oral estrogen and progestin simulta-

neously. This population consists of 2 subgroups: women receiving combination formulations, such as Prempro, and women receiving estrogen and concomitant progestin as separate prescriptions. Both groups were designated collectively as estrogen/progestin. The estimate was obtained for oral estrogen/progestin combinations directly from NPA based on the number of prescriptions. The NDTI data were used to determine the frequency with which oral progestin was prescribed concomitantly with oral estrogen in 2001 and in 2003, which was 18% and 14%, respectively. The number of women receiving oral estrogen with concomitant progestin was obtained by multiplying this percentage by the total number of prescriptions for oral estrogen and oral estrogen/androgen from NPA. The sum of estrogen plus progestin combinations and estrogen with concomitant progestin constituted the total population of estrogen/progestin.

## RESULTS

In examining national data on annual trends in hormone therapy use based on prescriptions and physician visits, 3 phases of practice patterns are apparent. Prescriptions increased significantly between 1995 and 1999 following the introduction of oral estrogen/progestin combinations, then remained stable through the first 6 months of 2002 (FIGURE 1). Following the release of WHI and HERS II in July 2002, hormone therapy prescriptions declined in successive months through July 2003 (Figure 1 and FIGURE 2). Based on data from July 2003, hormone therapy prescriptions declined by 38% (95% CI, 37%-39%) overall relative to months prior to July 2002, with a decline of 74% (95% CI, 73%-75%) for Prempro. The percentage of women aged 50 to 74 years taking hormone therapy increased from 33% to 42% between 1995 and 2001. By July 2003, this exposure had declined to 28% of women in this age group.

### 1995-2002 Prescriptions

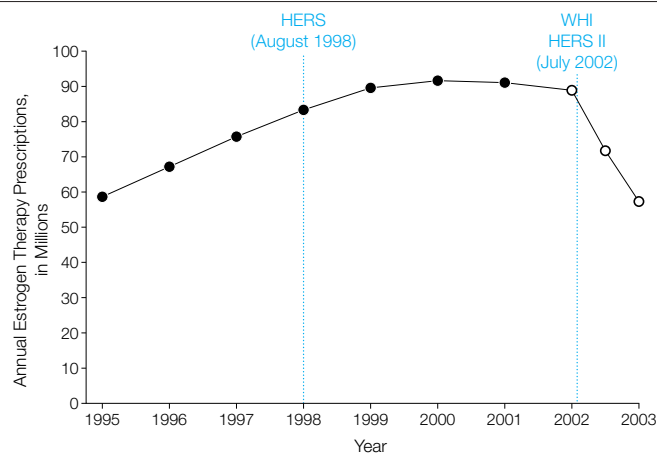
Between 1995 and June 2002, annual hormone therapy prescriptions in-

creased by 57% from 58 million in 1995 to 91 million in 2001 and annualized to 89 million for January through June 2002 (Figure 1, TABLE 1). Prescriptions remained relatively stable from January 1999 through June 2002, peaking at 92 million in 2000. In 1995, oral estrogens dominated hormone therapy prescribing (Table 1). Combined oral estrogen/progestin emerged in 1995 and prescriptions increased rapidly from 1.3 million (2% of hormone therapy) in 1995 to 24 million (26% of hormone

therapy) by 2001, accounting for more than 70% of the overall growth in hormone therapy prescriptions during this period (Table 1, FIGURE 3). While vaginal and transdermal prescriptions also increased during this period, the percentage of total prescriptions remained constant, ranging from 3% for vaginal to 8% to 9% for transdermal formulations (Table 1, Figure 3).

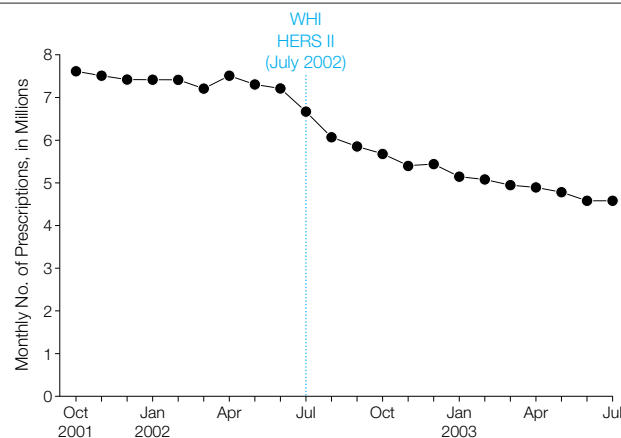
Since 1995, oral estrogen and oral estrogen/progestin collectively accounted for approximately 85% of hor-

**Figure 1.** Annual Number of US Prescriptions for All Forms of Hormone Therapy, 1995-2003



Annualized data for January to June 2002, July to December 2002, and January to July 2003 are included (open circles). Data are from the National Prescription Audit Plus, IMS HEALTH. HERS indicates Heart and Estrogen/Progestin Replacement Study; WHI, Women's Health Initiative.

**Figure 2.** Number of Monthly US Prescriptions for All Forms of Hormone Therapy, October 2001-July 2003



The 95% confidence intervals for monthly estimates are  $\pm 0.01$  million. Data are from the National Prescription Audit Plus, IMS HEALTH. WHI indicates Women's Health Initiative; HERS, Heart and Estrogen/Progestin Replacement Study.

hormone therapy. A single formulation dominated each category: Premarin among oral estrogen and Prempro among oral estrogen/progestin. Small declines in Premarin and Prempro prescriptions from 1999 and 2001 were associated with increases in use of other brands within oral estrogen and oral estrogen/progestin such that total prescriptions within these categories remained generally stable from 1999 to 2001 (Figure 3, Table 1). Based on the number of annual prescriptions, in 1995, 9.7 million women were estimated to have taken hormone therapy, increasing to 15 million annually between 1999 and 2001 (Figure 1, Table 1).

### 2002-2003 Prescriptions

**Overall.** When annualized, the number of prescriptions from January through June 2002 was similar to prior years, equaling 89 million (Figure 1). A decline in the number of monthly hormone therapy prescriptions initiated immediately following the publication of WHI<sup>3</sup> and HERS II<sup>2</sup> in July 2002 and continued in successive months (Figure 2). Hormone therapy prescriptions reached their lowest level in July 2003 (4.58 million; 95% CI, 4.57-4.59), 38% below mean monthly levels from January through June 2002. If this monthly rate remains constant for the remainder of 2003, the projected number of

hormone therapy prescriptions will be 57 million (Figure 1, Table 1).

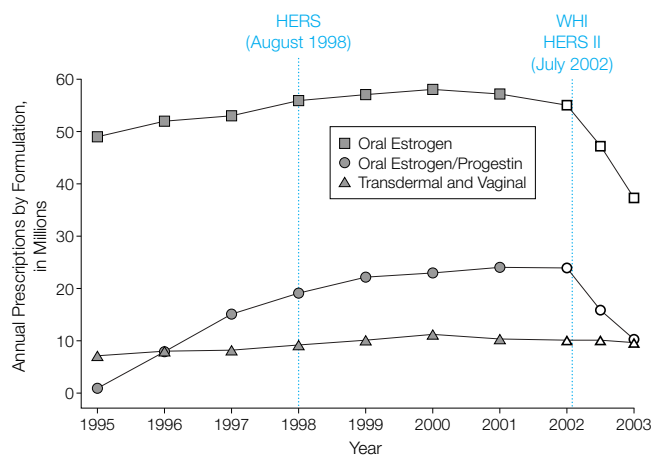
**Specific Formulations.** The decline in hormone therapy prescriptions varied by formulation but was concentrated most heavily among oral estrogen and oral estrogen/progestin (Figure 3). Premarin and Prempro prescriptions alone accounted for 80% of the overall decline observed between July 2002 and July 2003. To illustrate this trend, monthly prescriptions were compared for hormone therapy during the 6-month periods between January to June 2002 to January to June 2003 (FIGURE 4). Prescriptions for Prempro in 2003 declined by 66% (95% CI, 65%-67%) relative to 2002, reaching a monthly low of 386 000, a level last seen in 1996. Prescriptions for Premarin declined by 33% (95% CI, 32%-34%) during this period, reaching a monthly low of 1.8 million, a level below monthly rates from 1995. Although overall prescriptions for oral Premarin declined, new prescriptions for Premarin, 0.3 mg, a lower-dose estrogen than that used in WHI, increased by 6% during the second half of 2002. This increase, however, was not sustained in 2003. Recent trials had a lesser impact on other hormone therapy formulations, with smaller declines observed for all other oral estrogen (23%), all other oral estrogen/progestin (18%), and transdermal formulations (14%) (Figure 4). Vaginal formulations did not decline during this period; however, use of this formulation remains limited overall, and the small increase (7%) did not exceed the confidence limits of the estimates.

**Table 1.** Annual Dispensed US Prescriptions for Hormone Therapy and Estimated Number of Women

|                               | No. in Millions |             |             |             |             |
|-------------------------------|-----------------|-------------|-------------|-------------|-------------|
|                               | 1995            | 1997        | 1999        | 2001        | 2003*       |
| Premarin                      | 38.2            | 38.7        | 40.7        | 38.1        | 23.0        |
| Other oral estrogen           | 11.2            | 14.1        | 17.5        | 18.7        | 14.2        |
| Prempro                       | 1.1             | 12.9        | 19.7        | 18.8        | 5.3         |
| Other oral estrogen/progestin | 0.2             | 1.5         | 2.1         | 5.2         | 5.0         |
| Transdermal                   | 5.4             | 6.4         | 7.1         | 7.4         | 6.1         |
| Vaginal                       | 2.2             | 2.2         | 2.5         | 2.8         | 3.3         |
| <b>Total Prescriptions</b>    | <b>58.3</b>     | <b>75.8</b> | <b>89.6</b> | <b>91.0</b> | <b>56.9</b> |
| No. of women                  | 10              | 13          | 15          | 15          | 10          |

\*2003 includes annualized figures based on January through July 2003. Data are from the National Prescription Audit Plus, IMS HEALTH.

**Figure 3.** Annual Number of US Prescriptions for Hormone Therapy by Formulation, 1995-July 2003



Annualized data for January to June 2002, July to December 2002, and January to July 2003 are included (open symbols). Data are from the National Prescription Audit Plus, IMS HEALTH. HERS indicates Heart and Estrogen/Progestin Replacement Study; WHI, Women's Health Initiative.

### 1995 Through June 2002 Patient Visits

The percentage of overall visits for hormone therapy involving oral estrogen/progestin combinations increased from 5% in 1995 to more than 28% in 2001 and the first half of 2002, similar to trends described above for prescriptions. We observed variation in patient age between visits for estrogen/progestin and estrogen (TABLE 2). Patients 60 years or older were more common among visits during which estrogen was prescribed, while



patients younger than 60 years were more common among visits during which estrogen/progestin was prescribed. Oral hormone therapy formulations predominated and most visits were to obstetrician/gynecologists (Table 2). Physicians reported prescribing hormone therapy primarily for treatment of menopausal symptoms (>90%), with osteoporosis (4%) and cardiovascular disease prevention (1%) reported at low levels.

### Patient Visits in January to June 2003

The percentage of visits for estrogen/progestin declined from 29% during the first half of 2002 to 21% during the first half of 2003 (Table 2). We observed changes in the hormone therapy formulations prescribed, with a decline in oral formulations and an increase in vaginal preparations during this period. No changes were noted in the reported desired action or in the physician specialty. Small changes in patient age relative to prior years were noted, with a small decline in the percentage of women older than 60 years using hormone therapy (Table 2).

### Estrogen Plus Progestin Use

Of the estimated 15 million women who were prescribed hormone therapy in 2001, oral estrogen plus progestin was estimated to account for 5.6 million women, representing 42% of oral hormone therapy and 38% of hormone therapy overall. Furthermore, an estimated 67% of these women were older than 60 years and 6% were 75 years or older. If patterns observed through July 2003 remain constant throughout the year, estrogen plus progestin use would decline by 56% to 2.5 million women in 2003, representing 33% of oral hormone therapy and 25% of hormone therapy overall. No major changes in the age distribution of women prescribed oral estrogen plus progestin was observed.

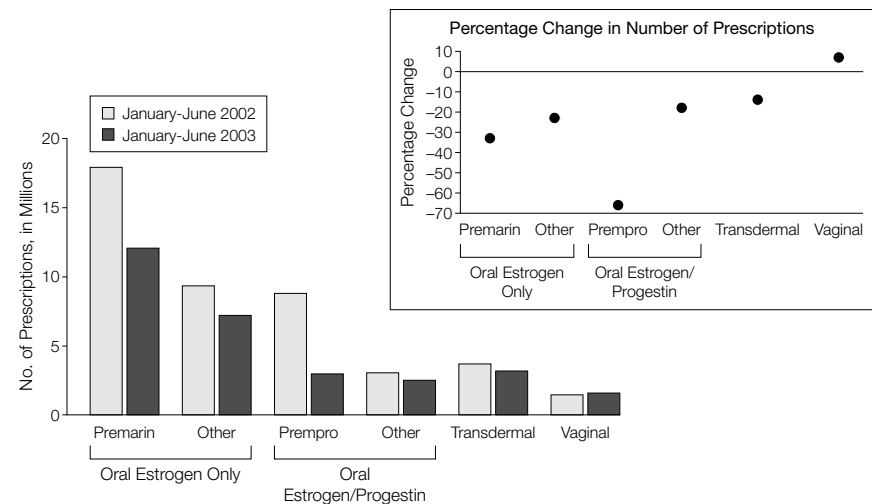
### COMMENT

Our results based on national hormone therapy use data showed 3 suc-

cessive patterns since 1995. From 1995 to 1999, annual hormone therapy prescriptions increased, primarily because of the adoption of oral estrogen/progestin combinations. Between 1999 and June 2002, hormone therapy prescriptions stabilized at approximately

90 million annually. Following publication of HERS II<sup>2</sup> and WHI<sup>3</sup> in July 2002, hormone therapy prescriptions declined substantially, with the largest decline among oral estrogen and estrogen/progestin. The overall number of hormone therapy prescriptions in

**Figure 4.** Number of and Percentage Change in US Prescriptions for Hormone Therapy Between January-June 2002 and January-June 2003 by Formulation



Data are from the National Prescription Audit Plus, IMS HEALTH.

**Table 2.** Comparison of US Physician Visits During Which Hormone Therapy Was Reported

|                         | % of Visits |      |       |       |
|-------------------------|-------------|------|-------|-------|
|                         | 1995        | 2001 | 2002* | 2003* |
| Estrogen                | 95          | 72   | 71    | 79    |
| Estrogen/progestin      | 5           | 28   | 29    | 21    |
| Formulation             |             |      |       |       |
| Oral                    | 87          | 86   | 85    | 74    |
| Transdermal             | 7           | 9    | 9     | 11    |
| Injectable              | 4           | 2    | 2     | 3     |
| Vaginal                 | 2           | 3    | 4     | 12    |
| Specialty               |             |      |       |       |
| Obstetrics/gynecology   | 66          | 73   | 74    | 73    |
| General/family practice | 19          | 16   | 15    | 15    |
| Internal medicine       | 12          | 9    | 8     | 8     |
| Other                   | 3           | 2    | 3     | 4     |
| Patient age, y          |             |      |       |       |
| Estrogen                |             |      |       |       |
| <60                     | 64          | 59   | 59    | 62    |
| 60-74                   | 28          | 30   | 30    | 30    |
| ≥75                     | 7           | 11   | 11    | 8     |
| Estrogen/progestin      |             |      |       |       |
| <60                     | 78          | 71   | 72    | 76    |
| 60-74                   | 19          | 25   | 24    | 21    |
| ≥75                     | 3           | 4    | 4     | 3     |

\*2002 and 2003 are based on annualized figures for January through June of each of those years. Data are from the National Disease and Therapeutic Index, IMS HEALTH.

January 2003 was comparable with monthly figures from 1995.

Our findings suggest a rapid response to clinical trial evidence and revised guidelines. Many women have discontinued hormone therapy, especially those using Premarin and Prempro. The small increase in low-dose Premarin suggests that tapering of dosages is occurring as well. This example shows effective information dissemination of scientific evidence and clinical guidelines to patients and physicians, which has resulted in prompt changes in clinical practice. In addition, the subsequent media cascade undoubtedly enhanced dissemination. Our findings support prior literature suggesting that physicians may rapidly abandon well-established therapies when studies demonstrate harm.<sup>15,16</sup> Whether acting alone or with the involvement of physicians, patients also played a major role in the decline in hormone therapy use that we observed. The less dramatic changes in the use of other hormone therapy formulations (transdermal, vaginal, oral brands other than Premarin and Prempro) may reflect less certainty among physicians and patients about the generalizability of recent findings.

Growth in hormone therapy use from 1995 to 1999 primarily was attributable to oral estrogen/progestin combinations, a newly available formulation. Our results show that this formulation attracted new patients who previously had not received hormone therapy, suggesting an influence of pharmaceutical innovation targeting convenience on medical practice patterns and market expansion. We observed a similar trend following the introduction of alendronate, the first oral daily bisphosphonate, in which identification and treatment of osteoporosis increased significantly in subsequent years.<sup>17</sup> The availability of combination therapy for women with a uterus also might explain the increase in the percentage of visits for hormone therapy to obstetrician/gynecologists relative to that of internists.

Although HERS did not immediately impact hormone therapy prescrip-

tions, growth stabilized soon thereafter as additional studies,<sup>18,19</sup> preliminary results from WHI,<sup>20,21</sup> and an influential guideline<sup>22</sup> were reported. This period may have set the stage for the decline in hormone therapy use following the publication of the WHI results. Features of the WHI trial design also likely enhanced its impact relative to prior studies. The WHI studied primary prevention of cardiovascular disease events, which applies to a wide range of women. Given the importance attached to breast cancer,<sup>23,24</sup> the inclusion of breast cancer outcomes in WHI may have further influenced recent trends. In this regard, it will be interesting to determine the longer-term impact of the more recent (May 2003) findings of a 2-fold increase in dementia<sup>25</sup> and a somewhat negative effect on global cognitive function<sup>26</sup> in the estrogen plus progestin arm of the WHI Memory Study (WHIMS).

Although physicians reported prescribing hormone therapy primarily for relief of menopausal symptoms, recent trials addressed chronic disease prevention. More than one third of women taking estrogens and one quarter of women taking estrogen/progestin were older than 60 years. Many of these older patients may have initiated hormone therapy use previously for symptom relief and continued subsequently for disease prevention. Despite the small decrease in the proportion of older women among visits for hormone therapy, substantial numbers of younger women also discontinued therapy. The abandonment of hormone therapy has important clinical implications for treatment of vasomotor symptoms and fracture prevention. Some women whose vasomotor symptoms return may reconsider treatment alternatives that may include lower-dose hormone therapy along with herbal products. For women at risk of osteoporosis, bisphosphonates may sustain benefits in bone mineral density achieved by prior hormone therapy use.<sup>27</sup> For all women discontinuing hormone therapy, nutrition and physical activity for osteoporosis prevention are essential.

Prescriptions for hormone therapy peaked in 2000-2001 at 91 million, corresponding to an estimate of approximately 6 million women using oral estrogen plus progestin. Using this estimate and applying the updated adverse event rates reported by WHI for coronary heart disease,<sup>28</sup> breast cancer,<sup>29</sup> and stroke<sup>30</sup> and the rate originally reported for pulmonary embolus,<sup>3</sup> we estimate that in 2001, 14 500 adverse events were attributable to oral estrogen plus progestin, with 3500 cardiovascular disease events, 2000 breast cancers, 4000 strokes, and 5000 cases of pulmonary embolism. Although the attributable risks may be small, this contrasts with prior estimates that survival benefits outweighed risks.<sup>31</sup> If hormone therapy prescription rates from through July 2003 remain constant, we estimate a 56% decline to 6500 adverse events for 2003.

Our estimate for hormone therapy use in 1995 differs somewhat from prior reports. One study estimated that 38% of postmenopausal women were current hormone therapy users based on a telephone survey of postmenopausal women between ages 50 and 74 years.<sup>13</sup> Based on US Census data,<sup>32,33</sup> our estimate for the number of hormone therapy exposures corresponds to 33% of women aged 50 to 74 years and 27% of women older than 50 years in 1995. An important source of bias in the prior study was that participants were more highly educated than nonparticipants,<sup>13</sup> a characteristic that is associated with increased use of hormone therapy. Nonetheless, a significant increase in hormone therapy use occurred between 1992 (when an estimated 17% of women older than 50 years were exposed<sup>10</sup>) and 1995. Another study reporting that 40% of women older than 50 years were prescribed conjugated equine estrogen<sup>14</sup> may not be generalizable to the US population because this study was conducted in a large managed care organization. Using our estimates, the percentage of women between ages 50 and 74 years exposed to hormone therapy increased from 33% in 1995 to 42% in 2001.

We acknowledge several limitations of our analysis. The NPA lacks patient

demographic and clinical information, including concomitant prescriptions. The NDTI provided this information and our results incorporate information from both sources. Both databases are nationally representative and showed similar trends, lending support to this approach. Our estimate of the number of women receiving hormone therapy was based on an assumption of the average prescription length that may not apply to all formulations and brands. We were unable to stratify hormone therapy use on specific parameters, such as patient age or physician specialty, to examine trends according to these variables, which limits the depth of our analysis. The NDTI data capture patient-physician encounters during which hormone therapy was reported as a treatment. Therefore, we were unable to obtain specific data on characteristics of

patients who visited physicians and discontinued hormone therapy. The NPA underestimates prescriptions for injectable estrogens, leading to a possible underestimate of overall hormone therapy use. However, use of injectable estrogens since 1995 is low based on NDTI data and therefore is unlikely to represent a significant bias.

In summary, we described 3 phases of hormone therapy use since 1995. The recent sharp and continuing decline in hormone therapy prescriptions appears to be an appropriate response to evidence substantiating cardiovascular disease harms and breast cancer risk associated with estrogen/progestin. Future patterns of hormone therapy use remain uncertain but will likely be shaped by multiple influences including professional and public attitudes toward risks and benefits, the outcome

of the estrogen-only arm of WHI, and pharmaceutical marketing.

**Author Contributions:** Dr Stafford had access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Hersh, Stafford.

*Acquisition of data:* Hersh, Stafford.

*Analysis and interpretation of data:* Hersh, Stefanick, Stafford.

*Drafting of the manuscript:* Hersh, Stafford.

*Critical revision of the manuscript for important intellectual content:* Hersh, Stefanick, Stafford.

*Statistical expertise:* Hersh, Stafford.

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*Study supervision:* Stafford.

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