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ORIGINAL REPORT

Use of menopausal hormones in the United States, 1992 through June, 2003[†,‡]

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SUMMARY

Purpose The Women's Health Initiative (WHI) study that documented an unfavorable benefit to risk ratio of Prempro and subsequently an increased risk of stroke with menopausal estrogen prompted us to investigate the use during 1992 through June 2003 of menopausal hormones in the United States.

Methods Two pharmaceutical research databases from IMS Health, the National Prescription Audit *Plus*™ and the National Disease and Therapeutic Index™, were accessed and analyzed.

Results The number of dispensed outpatient prescriptions for oral menopausal estrogens and oral combination estrogen–progestins increased 2.5-fold (153%) from 34.5 million dispensed in 1992 to a high of 87.3 million in 2000. For July 2002 through June 2003, the year following the publication of the results of the WHI trial, prescriptions for these products declined to 59.6 million, a 32% decrease from their peak in 2000. Prescriptions for transdermal estrogen and transdermal combination estrogen–progestin products increased from 5.2 million dispensed in 1992 to their peak of 8.3 million in 2000, and declined 10% to 7.5 million during July 2002 through June 2003. By contrast, prescriptions for oral menopausal progestins rose to 17.5 million in 1995 and then steadily declined. In the year after the WHI, prescriptions for oral progestins decreased 49% to 8.9 million from their peak in 1995. The earlier decline in oral progestin prescriptions was primarily due to the marketing in 1995 of the popular oral combination estrogen–progestin drugs.

Conclusions Prescriptions dispensed for menopausal hormones increased substantially between 1992 and peaked in 2000. By June 2003, prescriptions for oral menopausal estrogens and oral combination estrogen–progestins had declined by about one-third from their peak year. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — menopause; hormone replacement; conjugated estrogen; progestin; Premarin; Provera; medroxyprogesterone

INTRODUCTION

In July 2002, the Women's Health Initiative (WHI),[1] the first randomized prevention trial of postmenopausal hormones, reported that women with intact uteri who were receiving estrogen plus progestin (Prempro, 0.625 mg conjugated estrogen and 2.5 mg medroxyprogesterone acetate) were found to have an increased risk of invasive breast cancer, coronary heart disease, stroke, and pulmonary embolism and a decreased risk of colorectal cancer and hip fracture after an average follow-up duration of 5.2 years. The trial was terminated for the Prempro group but was continued for women with hysterectomies who were receiving menopausal estrogen until March 2004, when the estrogen arm was terminated because the hormone increased the risk of stroke and did not prevent heart attacks.[2]

The results prompted us to investigate the use of menopausal (perimenopausal and postmenopausal)

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hormones in women in the United States. Earlier research indicated a large secular increase in their use.[3–5] This article describes the use of these medications from 1992 through June 2003.

METHODS

National projected data on menopausal hormones were derived from two pharmaceutical marketing research databases purchased from IMS Health—the National Prescription Audit *Plus*™ (NPA *Plus*™) and the National Disease and Therapeutic Index™ (NDTI™). The NPA *Plus*™ provides national estimates of prescriptions dispensed by chain, independent, food store, mail order and long-term care pharmacies in the United States.[6] For the period 1996 through June 2003, IMS Health's pharmacy database consisted of approximately 34 000 reporting stores; the number of dispensed prescriptions was obtained from a sample of approximately 22 000 randomly selected stores and projected nationally. The pharmacies in the database account for 40% of pharmacy stores and represent 45% of prescription coverage, according to estimates by IMS Health. Although the NPA *Plus*™ sampling methodologies have changed over time (e.g. foodstore pharmacies were added to the sampling frame in 1992, and mail order and long term care pharmacies became accessible to the FDA in the latter part of the 1990s), the data have always been projected to obtain national prescription estimates.

Included in this report are drugs from the Uniform System of Classification (USC) class 52112, oral estrogens and class 52142, oral progestogens (also referred to as progestins); however, only generic and trade brands of menopausal estrogens and progestins but not other estrogens and progestins (such as oral contraceptives) were included. Data were also obtained from the USC classes 52115, transdermal estrogens, 52132, oral estrogen combinations and 52133 transdermal estrogen–progestin products. Data from the oral estrogen and combination estrogen–progestin tablet formulations were combined to determine the annual number of dispensed prescriptions for oral menopausal hormones in the United States during 1992 through June 2003. They also are presented separately in Figure 1. Prescriptions for transdermal products (including estrogen and combination estrogen–progestin) and for oral progestins were tabulated separately.

The second database, IMS Health, NDTI™ provides descriptive information on the patterns and treatments

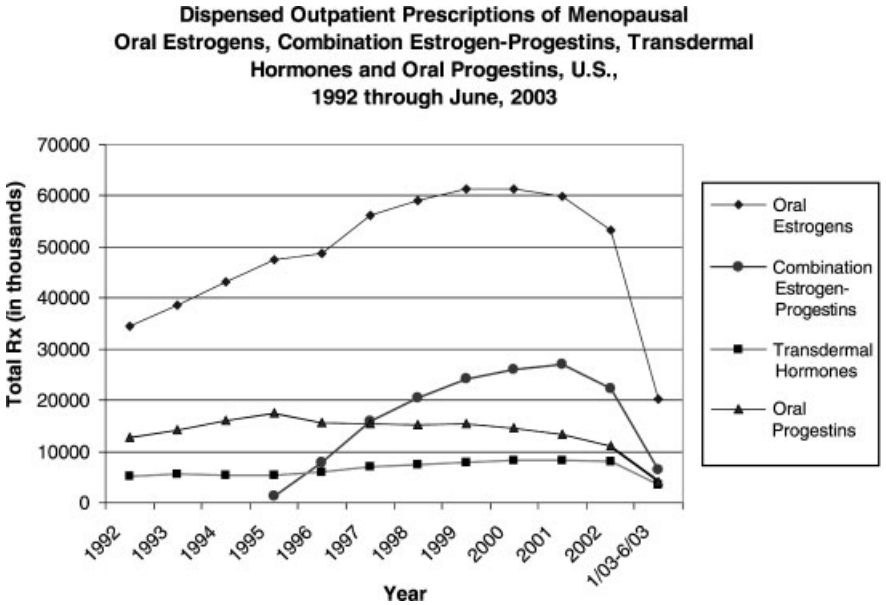

Figure 1. Oral estrogens: Premarin, Cenestin, Lanogen, Menrium, Milprem, PMB-200, PMB-400, Estrace, generic estradiol, Ogen, Ortho-Est, generic estropipate, Menest, Estratab; Combination estrogen–progestins: Prempro, Premphase, FemHRT, Activelle and Ortho-Prefest. Transdermal hormones: Climara, Vivelle, Vivelle-Dot, Estraderm, Alora, Esclim, Fempatch, generic transdermal estradiol and Combipatch. Oral progestins: Provera, Cycrin, Amen, Curretab, Prometrium and medroxyprogesterone. (*Source*: IMS Health, National Prescription Audit Plus, extracted July 2003.)

of diseases encountered in office-based medical practices in the United States.[7] Data are obtained from a panel of approximately 3000 participating office-based physicians who report on each patient–physician contact in the office, hospital, on the telephone or elsewhere, for two consecutive working days per calendar quarter. These data are also projected nationally. The sampling methodologies of the two databases are described elsewhere in more detail.[8]

By convention, the NDTI™ uses the term 'mentions' for drug reports. A mention refers to a drug in association with a diagnosis during a patient–physician contact. Mentions are not directly equivalent to prescriptions, since access to a drug product can be gained in a number of ways including written prescriptions, authorized refills, office samples, etc. However, we have found that for most drugs mentions are mostly associated with written prescriptions. For example, for 2001, 77% of mentions for Premarin were for issuance of a prescription or a prescription with a sample, 2% were for issuance of a sample, 8% had no prescription (or sample) issued that visit and 12% were unspecified as to disposition.[7] The category 'recommended' which is a small proportion of mentions for most drugs, was <1% for Premarin.

RESULTS

The number of dispensed outpatient prescriptions for oral menopausal estrogens and combination estrogen–progestins increased 2.5-fold (153%) from 34.5 million dispensed in 1992 to a high of 87.3 million in 2000. During the year following the publication of the WHI trial from July 2002 through June 2003, prescriptions for these products declined to 59.6 million, a 32% decrease from their peak in 2000 (Figure 1). Prescriptions for transdermal estrogen and transdermal combination estrogen–progestin products increased from 5.2 million dispensed in 1992 to their peak of 8.3 million in 2000, and declined 10% to 7.5 million during July 2002 through June 2003 (Figure 1). By contrast, prescriptions for oral menopausal progestins rose to 17.5 million in 1995 and then steadily declined (Figure 1). In the year after the release of the WHI findings, prescriptions for progestins decreased 49% to 8.9 million from their peak in 1995. The earlier decline in oral progestin prescriptions was primarily due to the marketing in 1995 of the popular combination estrogen–progestin drugs. Using linear regression modeling and analysis, we found that prescriptions for menopausal oral estrogens and estrogen–progestins, transdermal products, and oral progestins were statistically significantly lower in 2001–2003 than in their peak years 1999 or 2000.

The leading brand name and generic menopausal hormone products in 2002 were: Premarin, Prempro, estradiol, medroxyprogesterone, estropipate, Prometrium, FemHRT and Climara transdermal.

Doses of Premarin (the leading oral conjugated estrogen) ranged from 0.3 to 2.5 mg. In 2001, 64% of prescriptions were dispensed at 0.625 mg; 7%, 0.3 mg; 9%, 0.9 mg; 18%, 1.25 mg; and 1.4%, 2.5 mg. Thus in 2001, about 28% of women were dispensed Premarin at doses higher than the usually prescribed 0.625 mg. Doses of Provera (the leading oral medroxyprogesterone during the decade of the 1990s) ranged from 2.5 to 10 mg. In 2001, 52% were dispensed for 2.5 mg; 23%, 5 mg; and 25%, 10 mg. Average prescription sizes for most of the oral estrogens were for between 1 and 2 month supplies. For the year ending June 2003, average prescription sizes for most of the oral estrogens had decreased to supplies of about 1 month.

Compared with 1992, in 2001 there was a proportionate increase in older women prescribed Premarin (conjugated estrogen) and a proportionate increase in younger women prescribed Provera (Tables 1 and 2). The shift in Provera use to younger women reflects its decrease in use for management of menopausal symptoms. The decline in the use of oral progestins with Premarin (and vice versa) between 1992 and 2001 reflects the increase in popularity of the estrogen–progestin combination formulations that became available in 1995. A larger proportion of prescriptions for Premarin and Provera were for refills than for new prescriptions. Obstetrician–gynecologists were the primary prescribers of these medications (Tables 1 and 2).

DISCUSSION

With the passage from the childbearing years of the large cohort of 'baby boom' women, medications used for menopause were some of the most frequently-prescribed drugs in the United States during the final decades of the twentieth century. Although Premarin was approved by the FDA in 1942 for the management of menopausal symptoms and in 1986 for the prevention of osteoporosis,[3] menopausal hormones became popular for the prevention of cardiovascular disease and dementia. The popularity of these products was based on the results of observational epidemiological studies, recommendations of expert panels of physicians,[9] media reports and heavy advertising promotion. However, the use of menopausal hormones continued to be controversial because the

Table 1. Frequencies (%) of demographic characteristics of patient visits in which Premarin was mentioned and physician specialties of prescribers, U.S., 1992, 2001 and 2002

	1992	2001	2002
Age (years)			
<20	<1	0	<1
20–29	<1	<1	1
30–39	7	4	4
40–49	24	17	18
50–59	35	37	35
60–69	21	24	25
70–79	10	13	12
≥80	2	4	4
Therapy			
New	26	15	18
Continued	74	85	82
Concomitant drugs			
Used alone	56	76	79
Used with*			
Progestin, oral	36	14	13
Estrogen, oral	<1	<1	<1
Estrogen, vaginal	<1	2	1
Estrogen, transdermal	<1	<1	—
Calcium	2	5	4
Physician specialty			
Obstetrics–gynecology	61	65	66
Gen./family practice	19	15	13
Internal medicine	10	6	8
Osteopathic medicine	4	6	4
All others	6	8	9

*For the primary indication mentioned. All concomitant therapies are not provided.
Source: IMS Health, National Disease and Therapeutic Index™, 1992, 2001, 2002, extracted July 2002 and July 2003.

Table 2. Frequencies (%) of demographic characteristics of patient visits in which Provera was mentioned and physician specialties of prescribers, U.S., 1992, 2001 and 2002

	1992	2001	2002
Age (years)			
<20	2	2	2
20–29	6	13	13
30–39	11	14	14
40–49	28	17	27
50–59	34	31	30
60–69	14	16	10
70–79	5	7	4
≥80	0	<1	0
Therapy			
New	40	45	51
Continued	60	55	49
Concomitant drugs			
Used alone	26	39	46
Used with*			
Estrogen, oral	66	48	41
Estrogen, transdermal	4	1	2
Estrogen, vaginal	1	1	2
Calcium	2	2	1
Physician specialty			
Obstetrics–gynecology	71	75	77
Gen./family practice	15	15	11
Internal medicine	8	4	3
Osteopathic medicine	4	4	4
All others	3	2	5

*For the primary indication mentioned. All concomitant therapies are not provided.
Source: IMS Health, National Disease and Therapeutic Index™, 1992, 2001, 2002, extracted July 2002 and July 2003.

cardiovascular disease prevention indication was based on surrogate endpoints and epidemiological studies that had conflicting results.[10,11] In July 2002, the WHI, a large randomized trial, reported increases in breast cancer, coronary heart disease, stroke and pulmonary embolism in the Prempro (estrogen plus progestin) arm after 5¼ years of treatment.[1] In May 2003, the WHI investigators reported that estrogen plus progestin did not have a clinically meaningful effect on health-related quality of life.[12] Later that month, the authors of the Women's Health Initiative Memory Study reported that estrogen plus progestin therapy increased the risk for probable dementia in postmenopausal women aged 65 years or older and did not prevent mild cognitive impairment in these women.[13] In June 2003, the WHI Investigators reported that the women who developed invasive breast cancer following use of estrogen plus progestin exposure had larger and more advanced breast cancer at diagnosis than those in the placebo group.[14] In August 2003, investigators of the United Kingdom's Million Women Study[15] disclosed that current users of menopausal hormone preparations had statistically significantly increased risks of breast cancer of 1.3-fold for current users of estrogen only products and 2-fold for users of estrogen–progestogen products. The relative risks were significantly increased separately for oral and transdermal preparations, and the risk increased with increasing total duration of use. In March 2004, the menopausal estrogen arm of the WHI trial that was continued for women with hysterectomies was terminated because estrogen increased the risk of stroke and did not prevent heart attacks.[2]

Meanwhile, as the data in this and other reports[3–5] suggest, a large proportion of U.S. women has been exposed to a variety of menopausal hormones. We applied the age and sex information from NDTI™ and the dispensed prescription data from NPA *Plus*™ to obtain age and sex distributions for prescriptions dispensed. Since 87.3 million prescriptions of oral menopausal estrogens were dispensed in 2000[6] of which about 80% or 70 million prescriptions were dispensed

to women 50 and older,[7] and assuming that prescriptions were for about a 2 month supply (six prescriptions per year), we estimate that 11.7 million women were treated with oral menopausal estrogens in 2000 (70 million rxs/6 rxs per year). This group of exposed women comprised about 28% of the 42.1 million U.S. women who were 50 years and older in 2000[16] (or 37% of the 31.7 million 50–74 years old). If we add in the 8.3 million prescriptions for transdermal estrogen and transdermal estrogen–progestin products in 2000, about 13.1 million women [11.7 million treated with oral rxs + (8.3 million rxs/6 rxs per year)] comprising 31% of the 42.1 million women 50 years and older (or 41% of the 31.7 million 50–74 years old) were treated in year 2000. Considering the increase in use over time, the estimated prevalence of menopausal hormone use of 41% of 50–74 year old women in 2000 is consistent with the 38% prevalence of use found in a random-digit telephone survey conducted in 1995.[17] For the year ending in June 2003, when average prescription sizes dropped to about one per month,[7] we estimated that the number of women 50 and older who used oral and transdermal menopausal estrogens was 4.6 million (59.6 million prescriptions $\times$ 0.80 prescribed to women 50 and older) + 7.5 million = 55.2/12 prescriptions per year) amounting to about 11% of the 42.1 million women 50 years and older (or 15% of the 31.7 million women 50–74 years old). Since these estimates are quite sensitive to the average number of prescriptions per year, they should be used with caution.

The data presented in this article are limited by the following methodological considerations: the NPA *Plus*™ data are based on prescriptions rather than exposed women; the data do not address duration of use; and although the data are projected to cover the entire U.S., the sampling schemes are not statistical samples so the results may not be representative. Furthermore, the sampling schemes have changed over time and these changes could affect the trend data. The mail order and long-term care channels were added during the 1990s; however, they constitute a relatively small proportion of total prescriptions and inclusion of these channels is in the direction of greater population coverage and more accurate estimates. Despite these limitations, the large sample size of the prescription data is predictive of a high likelihood of valid results. Similarly, the descriptive information from the NDTI™ for Premarin and Provera are based on large numbers of patient–physician visits that result in narrow confidence intervals and accurate estimates.

The IMS Health data are purchased by pharmaceutical companies, the FDA, and other government agencies to obtain timely national drug use information. The IMS Health databases yield results that are generally consistent with other surveys (e.g., the random digit phone survey of hormone replacement use[17] mentioned above) and health databases.[18] The data presented in this manuscript show as reality the anticipated decline of menopausal hormone prescriptions following the release of the WHI study results.

KEY POINTS

- Prescriptions for menopausal hormones increased substantially between 1992 and 2000, reaching a peak in 2000.
- For the period July 2002 through June 2003, the year following the publication of the results of the WHI trial, prescriptions of oral menopausal estrogens and combination estrogen–progestins declined about 32% from their peak in 2000.
- Prescriptions for transdermal menopausal hormones and oral menopausal progestins also declined during this period.
- In 2000, an estimated 41% of U.S. women 50–74 years old were exposed to menopausal hormones; for the year ending June 2003, the proportion had dropped to an estimated 15%.
- These data demonstrate the effect of the WHI in decreasing the prescribing of menopausal hormones in the United States.

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