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Utilisation of hormone replacement therapy in the United Kingdom. A descriptive study using the general practice research database

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Objective To determine prevalence and patterns of hormone replacement therapy (HRT) utilisation in women in the UK.

Design Prospective observational study.

Setting UK general practice.

Population Women from general practices throughout the UK.

Methods The study period was 1 January 1992 to 31 December 1998. Age-specific prevalence was calculated for each year. Trends in prescribing patterns were described over time. A sub-cohort of 'new starters' on HRT was identified to establish patterns of use, including duration of use and switching of preparations. Characteristics of the sub-cohort were compared with a reference group of non-HRT users.

Main outcome measures Prevalence, prescribing patterns and differences in characteristics between HRT users and non-HRT users.

Results Among women aged 45–64, prevalence of HRT use increased from 18.6% in 1992 to 27.7% in 1998. Secular trends were observed away from prescribing combined-sequential preparations and towards use of combined-continuous preparations. Among the prescriptions for combined HRT products, only 4.3% contained medroxyprogesterone acetate (MPA). A total of 45.7% of women without a record of a hysterectomy and 53.8% of women with a record of a hysterectomy used HRT for at least three years. When women were partitioned by year of starting HRT, there was a trend of increasing duration of use across the seven years. Some women without a record of a hysterectomy were receiving unopposed oestrogen without progestogen supplementation.

Conclusions Within the past decade, use of HRT has increased among women in the UK with large numbers of women using HRT for long periods and treatment often tailored to the individual.

INTRODUCTION

Hormone replacement therapy (HRT) is licensed for the alleviation of climacterial symptoms and for the prophylaxis of osteoporosis in peri/postmenopausal women. It is also believed to have other benefits such as increasing the woman's sense of wellbeing. Over the past decades, its use has increased considerably but there have been few studies on the way in which it is used in populations of women. Discussion of the interpretation of some of the recent studies concerned with its risks and benefits[1–9] is limited by the paucity of data describing its patterns of utilisation. For example, in the light of the recent Women's Health Initiative study (WHI),[1] it is interesting to know what proportion of women start taking HRT for the alleviation of climacteric symptoms and what proportion take it for osteoporosis prophylaxis. In addition, in view of the increasing risks with increasing duration of use, it is important to know the duration for which HRT is used in clinical practice. This investigation was designed to establish the prevalence, secular trends and patterns of HRT utilisation in the UK.

Many HRT preparations are currently available in the UK, the majority being of the conventional type, composed of continuously administered oestrogen, either alone (unopposed) or in conjunction with progestogen (opposed). It is recommended that women with a uterus receive combined (opposed) HRT to reduce the risk of endometrial hyperplasia.[10] HRT preparations vary by dose and type of oestrogen, by dose and type of progestogen and by method of administration (oral, transdermal or subcutaneous). Preparations involving continuous administration of progestogen (combined-continuous products) are so-called bleed-free as they are designed to diminish the monthly withdrawal bleeds associated with sequential progestogen administration, which are a major reason for non-compliance with treatment.[11] Tibolone is a synthetic steroid with weak oestrogenic, progestogenic and androgenic properties.[12] Its

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licensed indications are similar to those for HRT.[13] It is administered continuously as a single substance and is a 'bleed-free' product.

METHODS

The study was based on the UK General Practice Research Database (GPRD).[14,15] It contains the anonymised medical records of people within the UK National Health Service. Currently, about 3.6 million individuals are contributing to the database; historically, about 8 million have contributed. The database consists of coded records produced by general practitioners through the use of office-based computer software designed for the management of patient records in primary care. Information held on the system includes basic demographic details together with medical diagnoses and symptoms, detailed prescription data (includes name, quantity and dosage of the prescribed drug), hospital referrals and admissions and results of clinical investigations and tests, all of which are dated. Medical diagnoses and symptoms are entered and stored using the OXMIS (Oxford Medical Information System)[16] or Read coding systems.[17] The products prescribed are stored on the system as Prescription Pricing Authority (PPA) codes. Prescriptions are automatically issued when entered onto the system, thus virtually all are recorded. The recording of data from each practice is subject to quality control checks and each practice has been assigned an 'up-to-standard date' (the date the practice started contributing data deemed to be of 'good research standard' by the management of the GPRD).[15] Validation studies have shown the quality and completeness of the computer recorded data to be high.[18,19]

This study included all women on the GPRD who had had at least one prescription for HRT between 1 January 1992 and 31 December 1998 (study period). Women who were temporarily registered with the GP were excluded.

All prescriptions for systemic HRT (however administered) within the study period were identified. The duration of each prescription was calculated using information on the quantity and daily dose prescribed.

HRT products were grouped into 26 generic categories based on their constituents and form. Following this, periods of exposure to HRT were established for each woman. Since most patients would collect a prescription before the previous one has run its course (overlapping prescriptions), the exposure to this prescription was assumed to start the day after the previous one finished. When such 'overlapping' prescriptions were for the same generic product (i.e. continued therapy for the same product), total duration of exposure was the sum of the two individual prescription durations. Non-overlapping prescriptions were represented as separate periods of exposure. In this case, it was assumed that there was a gap in treatment. In cases where one generic product was prescribed during the logical exposure to another generic product, the exposure to the first product ('switched from') was truncated to the day of the prescription of the next product. A new period of exposure to the 'switched to' product was assumed to start on the subsequent day.

In some cases, prescribing patterns indicated it was likely that there was genuine simultaneous use of more than one generic product, rather than switching of products. To model such exposure, products were divided into four separate groups: (i) orally administered oestrogen-only therapy, (ii) other orally administered HRT, (iii) non-orally administered oestrogen therapy and (iv) other non-orally administered HRT. For example, it was deemed feasible for there to be genuine simultaneous use of a group (ii) product and a group (i) product ('top-up' oestrogen tablets). In a number of cases, prescribing of two products within the same group on the same day was considered feasible (e.g. a 50 μg oestradiol patch + 25 μg oestradiol patch to make a 75 μg oestradiol patch).

All prescriptions for separate progestogen products, licensed for use as the progestogen component of opposed HRT, were identified. Each woman's period of separate progestogen exposure was then established as previously described. If a woman received separate progestogen at the same time as receiving unopposed oestrogen, it was assumed that she was receiving combined therapy.

Age-specific annual prevalence figures of systemic HRT use were calculated. Among HRT users aged between 45 and 64 years, the proportion of women with a prescription for each of the different general regimens and forms of HRT was calculated in each of the years investigated. Regimens were divided into four categories: unopposed oestrogen, combined-sequential, combined-continuous and tibolone. Sub-group analyses were carried out to distinguish between women with or without a record of a hysterectomy; the absence of a record of a hysterectomy does not always mean that the woman has a uterus because the hysterectomy might have been done before the computer record started, and the GP might not have recorded this.

To establish whether prescribing of HRT varied by practice, all practices with at least 100 women aged between 45 and 64 years were identified. For each practice, the proportion of women using HRT in 1998 was calculated.

The study population in this investigation was dynamic. Women could join the practice and be registered on the database at any time during the study period. As a consequence, the data on the GPRD are censored (i.e. HRT exposure prior to registration with a practice is unknown), as is use after leaving the practice. A sub-cohort of women assumed to be 'new starters' on HRT during the study period was identified. These women were defined as those who had at least 12 months data before their first recorded HRT prescription and who were aged between 45 and 64 years at the time of that prescription. Women with evidence of HRT use prior to 1992 were excluded from the sub-cohort.

The sub-cohort of 'new starters' were followed up from the date of first HRT prescription until either the date they left the general practice or the date of last data collection from the practice, whichever was the earliest. Duration/discontinuation of HRT use and the proportion of women switching to a different generic product were calculated using a Kaplan–Meier Survival analysis in STATA 7.0,[20] censored on the last date of data collection or when the woman transferred out of the practice. For the purposes of the duration of use analysis, apparent gaps in treatment of less than 92 days were ignored. Since HRT is indicated for both short term symptom relief and for longer term osteoporosis prevention, women were partitioned into those with only one HRT prescription and those with at least two HRT prescriptions. Only women in this latter group were included in the duration/discontinuation and switching analyses.

Extent of continuous therapy was established for 'new starters' with more than one HRT prescription. This was calculated as the total days covered by HRT divided by the total days from the start of HRT use until the theoretical end date of the last HRT prescription.

For all 'new starters', the date of first HRT prescription was designated as the index date. To assess differences in the characteristics of HRT users and non-HRT users, each user was matched to up-to-three reference women, of the same year birth, who were registered on the database over the index date, with at least 12 months data following the practice 'up-to-standard' date and with no record of HRT use at any point. The proportion of women with a record of the following variables, prior to the index date, was established and the odds ratio for each was calculated using a matched conditional (fixed effects) logistic regression: diabetes, hypertension, hyperlipidaemia, acute myocardial infarction, heart failure, angina, stroke, venous thromboembolism, breast cancer, endometrial cancer, osteoporosis, hysterectomy, oral contraceptive use, cigarette smoking and body mass index (using recorded heights and weights). In addition, unconditional logistic regression was carried out to establish whether 'new starters' with only a single recorded HRT prescription differed from those with multiple HRT prescriptions with respect to the same characteristics.

Table 1. Percentage of HRT users. Values are given as *n* (%).

Generic	HRT users
CEE only	59,833 (24.0)
Oestradiol* only	66,333 (26.6)
CEE + MPA	13,334 (5.4)
CEE + NG	93,698 (37.6)
CEE + either progestogen	100,445 (40.3)
Oestradiol* + MPA	3860 (1.5)
Oestradiol* + NG/LNG	26,671 (10.7)
Oestradiol* + NEA	62,370 (25.0)
Oestradiol* + DYDRO	3959 (1.6)
Oestradiol* + any progestogen	82,688 (33.2)
Tibolone	24,616 (9.9)
Any (all users)	249,034 (100)

CEE = conjugated equine oestrogens; MPA = medroxyprogesterone acetate; NG = norgestrel; LNG = levonorgestrel; NEA = norethisterone acetate; DYDRO = dydrogesterone.
The categories are not mutually exclusive, a woman may have received a prescription for more than one type of product hence the figures do not necessarily total 100%.
* Includes analogues of oestradiol.

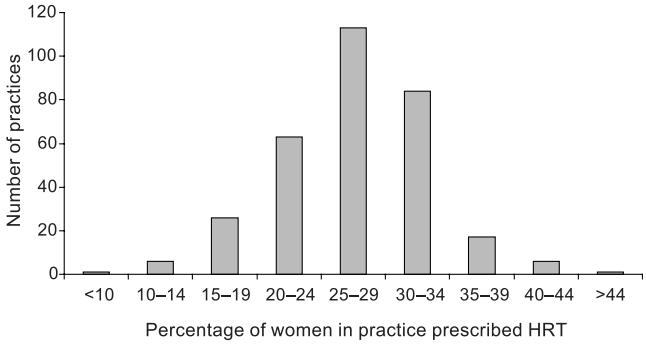

Fig. 1. Percentage of women aged 45–64 in 1998, prescribed HRT, by practice.

RESULTS

Between 1 January 1992 and 31 December 1998, about 2.3 million prescriptions for systemic HRT were identified, prescribed to about 247,000 women. Of these, 35,383 (14.5%) had received only one prescription. The mean number of prescriptions per user was 9.5 (range 1–149), for which the mean duration was 98.4 days (SD 50.4). Oral preparations were the predominant form of HRT, accounting for 76.8% of all prescriptions. Others were administered as transdermal patches, 21.9%; subcutaneous implants, 0.7%; transdermal gels, 0.5%; and injections, <0.1% (Table 1).

Three hundred and seventeen practices were identified with at least 100 women aged between 45 and 64 years in 1998. Prescribing varied by practice as can be seen in Fig. 1.

Among women aged 45 years and over, the prevalence of HRT increased between 1992 and 1998 as shown in Fig. 2. Among women aged between 45 and 64 years, prevalence of HRT use increased from 18.6% in 1992 to 27.7% in 1998; an increase of 49%. In all years, the highest usage was among women aged between 50 and 54 years (28.2% in 1992 to 36.1% in 1998).

Between 1992 and the end of 1998, the proportion of HRT users prescribed preparations containing conjugated equine oestrogens (CEE) combined with norgestrel decreased significantly from 42.0% in 1992 to 20.3% in 1998 (Table 2). This was accompanied by increases in the use of combined preparations containing oestradiol with medroxyprogesterone acetate (MPA), norethisterone

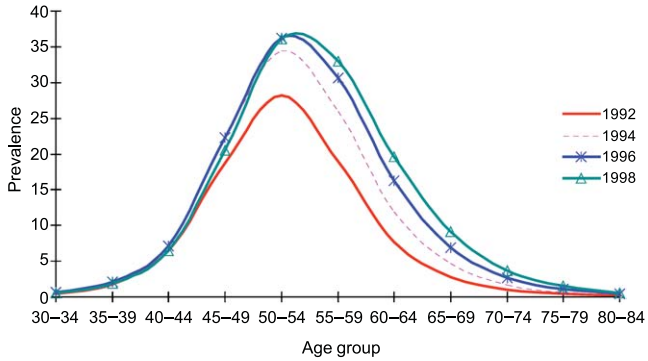

Fig. 2. Prevalence of HRT use by age and calendar year.

acetate (NEA) and dydrogesterone (DYDRO) and in preparations containing CEE with MPA. A decrease in the proportion of HRT users prescribed CEE alone was seen over this period, which was accompanied by an increase in the proportion prescribed oestradiol alone.

The proportion of users in each year, aged between 45 and 64 years, with at least one prescription for a particular HRT regimen is shown in Table 3, stratified by hysterectomy status. Among HRT users without a record of a hysterectomy, use of combined-sequential products was predominant in all years, although, proportionally, use of these products decreased with each subsequent year. This was accompanied by an increase in use of combined-continuous therapy. The use of tibolone remained relatively constant over the seven years. In 1992, 10.1% of HRT users without a record of a hysterectomy had at least one prescription for unopposed oestrogen without progestogen supplementation. By 1998, this had decreased slightly to 9.2%. A total of 32.1% (79,876) of HRT users had a record of a hysterectomy. Among these, unopposed oestrogen remained the predominantly prescribed regimen in all years.

A total of 92,615 'new starters' on HRT were identified. Of all new starters, 3651 (3.9%) had a record of osteoporosis, osteoporotic fractures, degenerative changes to the spine or bone density checks within the six months preceding the first HRT prescription and/or the first 6 months thereafter. A total of 39,943 (43.1%) had a record of menopausal symptoms in these 12 months straddling the first HRT prescription date. Looking at their entire medical records, 14,216 (15.3%) of new starters had a record of osteoporosis-related bone disease ever, whereas 63,189 (68.2%) had a record indicating menopausal symptoms at some point in their medical records. These categories are not mutually exclusive: 24,962 (27.0%) had no record of menopausal symptoms or osteoporosis anywhere in their medical notes; 5023 (20.1%) of these received one HRT prescription only.

Table 2. Proportion of HRT use by type of oestrogen and progestogen (women aged 45–64).

% HRT users	1992	1993	1994	1995	1996	1997	1998
CEE alone	21.3	21.8	22.1	21.6	20.2	19.3	18.3
Oestradiol* alone	18.3	17.6	18.5	20.1	20.8	22.2	23.0
CEE + NG	42.0	39.3	37.7	34.0	28.9	24.2	20.3
CEE + MPA	0.2	0.2	0.3	0.4	4.0	7.3	9.2
Oestradiol* + NG/LNG	8.1	8.2	8.3	8.4	7.1	6.7	6.1
Oestradiol* + MPA	–	–	–	0.5	1.9	2.2	2.0
Oestradiol* + NEA	15.3	16.4	16.2	19.3	21.0	21.5	22.3
Oestradiol* + DYDRO				0.1	1.4	2.4	2.7
Tibolone	6.9	7.4	7.9	7.7	6.5	5.9	5.8

CEE = conjugated equine oestrogens; MPA = medroxyprogesterone acetate; NG = norgestrel; LNG = levonorgestrel; NEA = norethisterone acetate; DYDRO = dydrogesterone.

The categories are not mutually exclusive, a woman may have received a prescription for more than one type of product hence the figures for each year do not necessarily total 100.

* Includes analogues of oestradiol.

Table 3. Prescribing of different HRT regimens to women with and without a record of a hysterectomy.

	% Women						
	1992	1993	1994	1995	1996	1997	1998
HRT users without a record of a hysterectomy							
Unopposed oestrogen	10.1	10.1	9.9	9.9	9.5	9.2	9.2
Combined sequential	83.8	82.5	82.0	80.0	74.8	70.0	65.1
Combined continuous	–	–	0.1	4.7	14.0	20.3	24.7
Tibolone	9.3	10.1	10.9	10.6	9.1	8.3	8.1
HRT users with a record of a hysterectomy							
Unopposed oestrogen	91.5	93.2	94.0	94.9	95.3	95.5	95.6
Combined sequential	10.5	8.1	6.4	5.3	4.4	3.6	3.1
Combined continuous	–	–	–	0.2	0.6	0.9	1.0
Tibolone	1.4	1.4	1.3	1.3	1.1	1.1	1.1

The categories are not mutually exclusive, a woman may have received a prescription for more than one type of product hence the figures for each year do not necessarily total 100. Also a woman was eligible for inclusion in both categories of hysterectomy status if she had had a hysterectomy within the year of the study.

It was possible to match 91,204 of the new starters to up to three non-HRT users for comparison (mean age 50.9, SD 4.48). New starters on HRT were significantly less likely to have a prior record of diabetes, hypertension, acute myocardial infarction, heart failure, stroke, venous thromboembolism, breast cancer or endometrial cancer than non-users (Table 4). They were significantly more likely to have a record of osteoporosis, hysterectomy, hyperlipidaemia and prior oral contraceptive use than non-users. HRT users were more likely to be smokers than non-HRT users and were less likely to have a body mass index of less than 20 or greater than 29. However, non-HRT users were significantly less likely to have information on these factors recorded.

For the new starters, 16.8% (15,574) had only a single HRT prescription. These women were significantly more likely than new starters with multiple HRT prescriptions to have a prior record of angina (adjusted OR 1.2 95% CI 1.0, 1.3) and were more likely to be current smokers (adjusted OR 1.1 95% CI 1.1, 1.2). They were significantly less likely to have a record of a hysterectomy (adjusted OR 0.6 95% CI 0.6, 0.7) or osteoporosis (adjusted OR 0.7 95% CI 0.6, 0.8).

Table 4. Characteristics of HRT users and non-HRT users. Values are given as *n* (%), crude OR [95% CI] and adjusted OR [95% CI].

Characteristic	HRT users ($n = 91,195$)	Non-users ($n = 150,745$)	Crude OR [95% CI]	Adjusted* OR [95% CI]
Diabetes*	1294 (1.4)	2860 (1.9)	0.8 (0.7, 0.8)	0.7 (0.7, 0.8)
Hypertension*	8628 (9.5)	14,777 (9.8)	1.0 (0.9, 1.0)	0.9 (0.9, 1.0)
Hyperlipidaemia*	2000 (2.2)	2511 (1.7)	1.4 (1.3, 1.4)	1.3 (1.3, 1.4)
Acute myocardial infarction	403 (0.4)	736 (0.5)	0.9 (0.8, 1.0)	–
Heart failure*	113 (0.1)	343 (0.2)	0.6 (0.5, 0.7)	0.6 (0.4, 0.7)
Angina	1488 (1.6)	2230 (1.5)	1.1 (1.1, 1.2)	–
Stroke*	315 (0.4)	813 (0.5)	0.7 (0.6, 0.7)	0.6 (0.5, 0.7)
Venous thromboembolism*	974 (1.1)	2031 (1.4)	0.8 (0.7, 0.9)	0.6 (0.6, 0.7)
Breast cancer*	25 (0.03)	243 (0.2)	0.2 (0.1, 0.3)	0.2 (0.1, 0.2)
Endometrial cancer*	68 (0.1)	178 (0.1)	0.6 (0.5, 0.8)	0.3 (0.2, 0.4)
Osteoporosis*	1725 (1.9)	564 (0.4)	5.2 (4.7, 5.7)	5.5 (4.9, 6.0)
Hysterectomy*	21,617 (23.0)	13,746 (9.1)	3.1 (3.0, 3.2)	3.2 (3.2, 3.3)
Oral contraceptive use*	5123 (5.6)	6476 (4.3)	1.3 (1.3, 1.4)	1.4 (1.4, 1.5)
Body mass index				
<20	2696 (3.0)	3828 (2.5)	0.9 (0.9, 1.0)	–
20–29	54,466 (59.7)	70,692 (46.9)	1.0 (ref)	–
30–39	10,779 (11.8)	16,749 (11.1)	0.8 (0.8, 0.9)	–
40+	987 (1.1)	2467 (1.6)	0.5 (0.5, 0.6)	–
Unknown	22,267 (24.4)	57,009 (37.8)	0.5 (0.5, 0.5)	–
Cigarette smoking				
Non-smoker	49,888 (54.7)	73,440 (48.7)	1.0 (ref)	–
Smoker	21,596 (23.7)	14,308 (9.5)	2.2 (2.1, 2.3)	–
Former smoker	4812 (5.3)	6078 (4.0)	1.2 (1.1, 1.2)	–
Unknown	14,899 (16.3)	56,919 (37.8)	0.4 (0.4, 0.4)	–

* Variables included in the final model. Note: BMI and smoking were not included because the proportion of women for which information on these variables were unknown, significantly differed between HRT users and non-users.

Figure 3 shows the proportion of new starters discontinuing HRT treatment over time after starting treatment, partitioned by hysterectomy status. Of women without a record of a hysterectomy, 17.4% discontinued therapy within six months of starting treatment, while of those with a record of a hysterectomy, 15.9% had discontinued. After three years from starting treatment, 39.8% of women without a record of a hysterectomy were still using HRT, while of women with a record of a hysterectomy, 44.7% were still using HRT.

Among new starters with only one HRT prescription, there was little change in the mean age that treatment was started; remaining 52 years from 1992 through to 1997 and being 51 years in 1998. The proportion of new starters in each year with only one prescription increased over the seven years from 12.0% in 1992 to 36.3% in 1998. Among women with more than one prescription, there was an upward trend of increasing duration of use with each successive year as shown in Table 5 (i.e. women who started HRT in 1995 were using HRT for longer periods than women who started in 1992).

Overall, 15.5% (11,965) new starters with more than one HRT prescription switched generic product at least once. Of these, the mean number of switches was 1.2 (SD 0.5, range 1–7) per user. The mean number of different generic products used was 1.6 (range 1–10). Figure 4 shows the proportion of new starters switching HRT regimens over

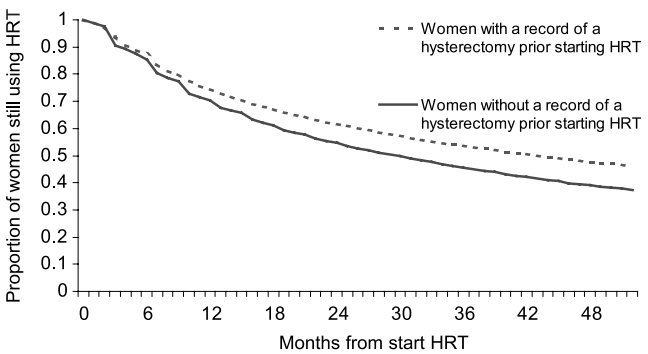

Fig. 3. Duration/discontinuation of HRT use.

Table 5. Proportion of new starters still using HRT after *n* months from starting treatment.

Months from start HRT	1992	1993	1994	1995	1996	1997	1998
6	0.89	0.89	0.89	0.90	0.91	0.90	0.93
12	0.75	0.75	0.74	0.77	0.77	0.77	0.89
18	0.66	0.66	0.65	0.68	0.68	0.70	–
24	0.59	0.59	0.58	0.61	0.62	0.67	–
30	0.53	0.52	0.53	0.56	0.58	–	–
36	0.49	0.48	0.49	0.52	0.55	–	–
42	0.44	0.44	0.45	0.49	–	–	–
48	0.41	0.41	0.42	0.46	–	–	–
54	0.38	0.39	0.40	–	–	–	–
60	0.36	0.36	0.38	–	–	–	–

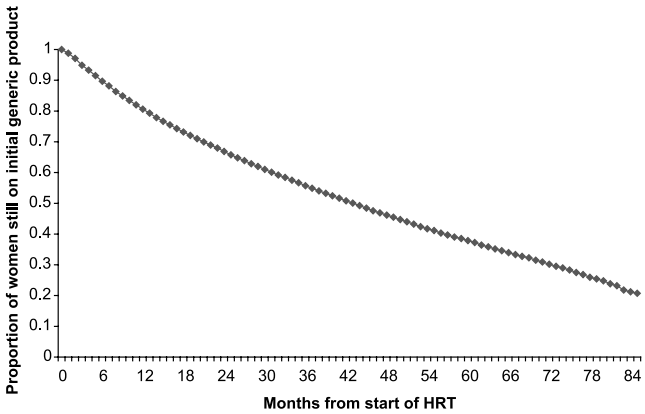

Fig. 4. Proportion of women still on the same generic product initially prescribed.

time after starting treatment. After six months, 10% of women had switched to a different generic formulation and after three years, 43% had switched.

For the new starters, 77,070 (83.2%) had more than one HRT prescription. Among these, the mean coverage was 94.8% (SD 8.5). A total of 15.6% were receiving HRT continuously without a gap in treatment (100% adherence). A total of 84.1% had continuous use for $\geq$90% of the total potential period of coverage.

DISCUSSION

Between 1992 and 1998, the prevalence of HRT use rose from 18.6% to 27.7% among women aged between 45 and 64 years; an increase of 49%. Unopposed CEE and unopposed oestradiol preparations were prescribed to a similar number of HRT users, although over the seven years of the study, there was a decline in the proportion of HRT users receiving unopposed CEE, accompanied by a decrease in the proportion receiving unopposed oestradiol. Of the combined preparations, those containing NG/LNG or NEA were the most frequently prescribed. Relatively small proportions of HRT users received combined preparations containing MPA or DYDRO. A significant trend away from prescribing preparations containing CEE combined with NG was seen, as was a decrease, albeit less striking, in the use of oestradiol combined with NG/LNG. These were accompanied by increases in prescribing of preparations containing oestradiol combined with NEA, MPA or DYDRO. A trend away from prescribing combined-sequential regimens was observed along with increasing use of the newer combined-continuous regimens. A wide spectrum of use was observed regarding duration and discontinuation of use, and it was found that some women with a uterus still received oestrogen replacement therapy without progestogen supplementation.

Recent findings from the WHI suggest an increased risk of breast cancer associated with long term HRT use. In addition, neither Heart and Estrogen/Progestin Replacement Study (HERS) nor the Women's Health Initiative (WHI) could not confirm a preventive effect on acute myocardial infarction.[1–3] This may result in a decrease in HRT use. Since, at present, more than a quarter of all women in the age group 45–64 are using HRT, the impact of WHI and HERS on public health and the NHS budget may be substantial. This impact will be both in terms of direct costs of HRT prescribing and in terms of indirect costs with, potentially, increasing numbers of hip fractures and decreasing numbers of breast cancer. If any decrease in HRT use only occurs in those women using it to prevent osteoporosis (i.e. for long duration), then the impact on public health and the NHS budget will be limited to a relatively small proportion of women.

The GPRD is a population-based database of primary health care practice in the UK. Selection bias is minimised as the database is considered to be representative of the UK population.[15] It has the advantage of holding data collected at the time of the event, including demographic information, clinical events and prescriptions. The majority of women receive their HRT prescriptions directly from their GP within the primary care setting. A small proportion of prescriptions may be given within hospitals and from specialist menopause clinics, which may not be recorded by the GP.

Since women could enter or leave the cohort at any time, HRT use outside the period a woman is registered is unknown. Also, it is important to note that women who had had a hysterectomy prior to registration may have been misclassified as having a uterus if this was not recorded, thus the proportion of women with a uterus prescribed unopposed oestrogen will be overestimated. It was not possible to establish primary and secondary non-compliance in this study because the recording of prescriptions on the database reflects prescriptions issued by the physician, rather than collection and/or uptake of the drug. We found that the proportion of women prescribed HRT varied by practice. This may be due to the personal views of the physician regarding HRT and/or the geographical area of the practice since socio-economic status[21] and ethnicity have been linked to HRT use[22]; such information is not available from the GPRD.

The prevalence of use is similar to that reported in a previous study using a small subset of the GPRD.[23] Using prescription data from 15 contributing practices in the former Oxford, South West and North West Thames Regions, Lawrence *et al.* reported the prevalence of HRT use in 1992 to be about 15%, among women aged between 45 and 64 years. Our figures are also similar to those reported by Townsend.[24] Using prescription data from England, Scotland and Wales, the prevalence of HRT use in 1994 among women aged between 40 and 64 years was reported to be 21.5% (our figure for this age group and year was 20.1%). As seen in our study, Townsend also described a decline in use of conjugated oestrogens plus progestogen; 46.2% in 1989 to 29.4% in 1994, along with a rise in use of

oestradiol plus progestogen; 9.4% in 1989 to 17.2% in 1994. In our study, 66.2% of HRT users had used CEE with or without progestogen. These preparations accounted for 74.8% of all HRT prescriptions (data not shown). Although CEE preparations are the most frequently prescribed preparations in the UK, they are not as predominant as in the US.[25,26] Oestradiol is an endogenous female oestrogen, which is currently a component of several HRT preparations. Our results show that these are becoming increasingly favoured by physicians in the UK, over those containing CEEs, which are structurally less similar to the oestrogens produced by the human ovary.[27] Our study also demonstrates the differences between the UK and the US in the progestogens prescribed in combined HRT. In our study, only 4.3% of the prescriptions for combined HRT preparations contained MPA as the progestogen while in the US, MPA is by far the most frequently prescribed progestogen in combined HRT.[25,26] The increasing prevalence of newer combined-continuous regimens is a likely explanation for the observed trend away from prescribing combined-sequential regimens. These offer a desirable alternative for women seeking to avoid withdrawal bleeds.

The wide spectrum of use observed regarding duration, discontinuation and switching is not surprising when considering differences in the indication for use (climacteric symptoms or osteoporosis), variation in onset, duration and severity of climacterial symptoms. Individuals may also differ in tolerance or desire to try newly launched products. We found that women without a record of a hysterectomy discontinued with treatment earlier than those with a record of a hysterectomy. Possibly, this is because women who have had an early hysterectomy, which can be accompanied by a bilateral oophorectomy, will have started HRT at an earlier age, and also possibly because women on oestrogen-only HRT have no progestogen-related side effects. The fact that 45.7% of women without a record of a hysterectomy and 53.8% of women with a record of a hysterectomy were using HRT for at least three years suggests that large numbers of women are using HRT for long periods and questions widely held beliefs to the contrary. Interestingly, our results showed that women are using HRT for increasingly longer periods; a finding that may have important public health implications.

It is recommended that women with an intact uterus who receive oestrogen replacement therapy should receive progestogen supplementation to reduce the risk of endometrial hyperplasia. We found that in 1992, 10.1% of HRT users without a record of a hysterectomy had received unopposed oestrogen. This figure decreased slightly in each subsequent year to 9.2% in 1998. As previously mentioned, these figures must be viewed with caution due to potential misclassification of hysterectomy status among women who had a hysterectomy in the left censored period. The downward trend is consistent with under-recording of hysterectomies. However, a previous study by Wilkes and Meade,[28] reported that out of 218 general practitioners who filled in a research questionnaire, 31 (15%) said they had prescribed unopposed oestrogen to women who had not had a hysterectomy, with 8 of these saying that it was sometimes tolerated better.

Observational studies investigating use of oestrogen replacement therapy are limited in drawing conclusions about causal associations with disease outcomes due to potential bias from uncontrolled confounding, in that HRT users may differ from non-HRT users in ways that may affect their disease outcome. This has been the subject of much discussion in studies investigating the association of HRT with coronary heart disease. In this study, HRT users were significantly different to non-HRT users with respect to the characteristics studied. Since the recording of data may have been differential between users and non-users of HRT, all of the figures should be interpreted with some caution, especially those for body mass index and smoking; non-HRT users were significantly less likely to have information on these lifestyle factors recorded.

CONCLUSION

Our results show the growing use of HRT in clinical practice in the UK. A wide spectrum of use exists with regards to patterns of use, with large numbers of women continuing with treatment for long periods. In the majority of women on HRT, the recorded indication for HRT prescribing is symptom relief whereas about 15% of women have a record indicating, or suggestive of, osteoporosis.

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