TITLE

Hormone replacement therapy use in UK general practice: duration, discontinuation and women's experience

SHORT TITLE

HRT Use in UK General practice

UP TO 5 KEY WORDS:

HRT, Menopause, Quality of Life, Menopause Symptoms,

Introduction

The menopause is the stage in a woman's life when menstruation stops, permanently. It occurs with the final menstrual period and is usually diagnosed clinically after 12 months of amenorrhoea (1). Peri-menopause ends 12 months after the last menstrual period. The post-menopause begins when a woman has not had a period for 12 consecutive months, and continues throughout her life (1).The mean age of the natural menopause is 52 years (1), although this can vary between different ethnic groups (2).

The menopause has many effects on women's bodies: the most common symptoms being vasomotor symptoms: hot flushes (flashes) and night sweats. Other symptoms include mood changes, memory and concentration loss, urogenital atrophy, a lack of interest in sex, headaches, and joint and muscle stiffness (1). The health related quality of life (HRQoL) of women experiencing these symptoms may be severely affected (3). About 80% of women experience menopausal symptoms and of those 45% find the symptoms distressing (4). Hot flushes occur for 70-80% of peri-menopausal women and are most common in the first year after the final menstrual period (5), with 25% of these women being severely affected. Hot flushes may resolve in 2-5 years but the median duration is 7.2 years and can be longer, persisting beyond the age of 60 (6). In a US study women with daily vasomotor symptoms report 7 or more moderate to very severe vasomotor symptoms in a typical day (7). Vaginal symptoms occur in up to 30% of women in the peri-menopausal period and up to 47% of women during the post-menopausal period (7). Research shows that menopausal symptoms affect women in the workforce: about half working women over the age of 50 found it somewhat or fairly difficult to cope with their work because of menopausal symptoms and of those about 5% had severe and debilitating symptoms and were severely compromised in their ability to work (8). In summary the menopause is not a trivial change of life for women.

Menopause symptoms may prompt a woman to consult a health professional. The National Institute of Health and Care Excellence (NICE) in the United Kingdom (UK), has recently published a Clinical

Knowledge Summary (CKS) for the Menopause (1) based on the recently published (November 2015) Full Clinical Guideline NG23 (9). These emphasise the need for open discussion of risks and benefits of hormone replacement therapy (HRT) to manage symptoms and other approaches to menopause management, such as lifestyle modification.

The NICE guidelines (9) indicate initial menopause management options depend on the timing of the consultation, peri-menopause or post-menopause and whether the woman has her uterus or not. NICE guidelines (9) suggest advice should cover evidence for the benefits of combined HRT in controlling symptoms, along with likely health benefits (e.g. reduction in osteoporosis); the risks associated with combined HRT (oral and transdermal) explained, using the risk-benefit tables provided in the NICE guidelines. If HRT is the chosen option, guidelines state cyclical combined HRT should be used in peri-menopausal women and continuous HRT should be used in post-menopausal women.

There can be unwelcome effects related to HRT, such as breast tenderness, vaginal bleeding or spotting, fluid retention, leg cramps, nausea/sickness and headache/migraine. Differing symptoms may relate to oestrogen or progestogen or both (1,9). However these side-effects may settle after the first three months and NICE guidelines advise the health professional to encourage the woman to persist with treatment, but if these problems continue NICE guidelines (9) suggest switching mode of administration (oral to transdermal for example), HRT type, or (relative) dosage of hormones. (1)(9). HRT compliance is a crucial issue when treating post-menopausal women, since the beneficial effects of hormones may be reduced or lost if women do not adhere to treatment, so addressing the short term side-effects of HRT is important for improving compliance (10).

The purpose of the research presented here was to investigate rates of combined (cyclical or continuous) HRT use and HRT patterns in UK general practice in women ≥45 years to understand the reality of menopause management with HRT, using routine, electronic observational data and postal surveys. The specific objectives of this study were to: investigate the demographic and clinical

characteristics of women with a menopause diagnosis treated with HRT or not on HRT; drug therapy patterns for the management of menopause following initial HRT use and reasons and outcomes associated with discontinuation of HRT.

Methods

Study Design

The study consisted of two parts, a retrospective observational study using The Health Improvement Network (THIN) database examining women's characteristics and treatment patterns (database study), and a survey via postal questionnaire exploring reasons and outcomes associated with discontinuation of HRT (survey study).

Database Study

Data Source

The THIN database contains pseudonymised electronic primary care health records from UK general practices and as of May 2015 contained records from over 14 million patients, of which over 3.43 million were actively registered from 648 general practices. The age and gender profile of the active patient population in THIN has been shown to be comparable to the UK population (11,12).

Study Population

The study population comprised women ≥45 years who first received an oestrogen and progestogen containing hormone therapy (study-HRT) between 1st January 2006 and 13th January 2010[1]. To compare demographic and clinical characteristics, women treated with a study-HRT were matched 1:1 with women not treated with HRT, who were registered at the same practice, aged over 45 years

[1] The HRT products that are the subject of this research are assumed to be indicated for management of menopause symptoms.

and whose age was within ± 2 years of their matched subject. Index date was assigned as the date of the first prescription of a study-HRT. Untreated matched subjects were assigned the same index date as their treated matched subject.

Subjects were required to have ≥12 months of baseline data prior to index date and ≥24 months of follow-up data from index date. Women were excluded if they had a history of hysterectomy or breast or uterine cancer, were pregnant during the study period, or had reported breast pain or bleeding in the 12 months prior to index date.

Study Variables

Treatment patterns examined included treatment duration, time between menopause diagnosis and first prescription for a study-HRT, and treatment changes. A treatment phase began at the first prescription of the medication and ended at the estimated end date of the last prescription. Prescriptions were included in a treatment phase if there was <14 days between the estimated end date of the previous prescription and the next prescription date. Treatment patterns investigated include: first study-HRT prescribed at index date, switching of study-HRT, add-on therapy to study-HRT, re-start of study-HRT and discontinuation of study-HRT.

Error! Reference source not found. illustrates changes to first-line therapy for the management of menopause. A switch was defined as a therapy change after the end of a treatment phase, including different study-HRT, non-study HRT and non-HRT. Changes to route of administration or strength were considered a switch for study-HRTs. A prescription for another product (study-HRTs, other non-study HRTs or non-HRTs) within a treatment phase of a continuing therapy was considered an add-on therapy. Re-start of therapy was defined as initiation of therapy after an interval of ≥6 months between treatment phases. Women with an interval of ≥6 months between the end of the last treatment phase and end of follow-up were considered to have discontinued treatment.

Other study variables include demographic characteristics (age, smoking status, Townsend score), menopause status (menopause diagnosis, time between diagnosis and treatment) and medical conditions related to menopause recorded in the 12 months prior to index date, including sleep problems, osteoporosis, low bone density, vulvar vaginal atrophy, vaginal dryness and depression.

Survey Study

Data Source

Surveys were obtained using THIN Additional Information Services (AIS) using the encrypted identity of the practice and patients. THIN AIS deciphered the practice code and sent a list of pseudonymised patient codes to the GP who sent the questionnaire to the women. Women returned their completed questionnaire to their GP who removed any identifiable information before returning to THIN AIS. Researchers were sent the questionnaire with the original pseudonymised patient ID to allow linkage to information obtained from the database study.

Survey Subjects

Survey subjects were selected from those prescribed study-HRT in the database study, were active in THIN between September 2012 and June 2013 and had at least one prescription for a study-HRT during this period to capture women who were either still receiving HRT or just discontinued HRT when the questionnaire was administered. Women were asked to consent to the study and whether they were receiving HRT at the time of completion. Depending on the responses, survey subjects were divided into two groups: currently taking HRT and discontinued HRT.

Survey Questionnaire

For women who discontinued HRT, reasons for discontinuation were further explored. Additionally, HRQoL was assessed using the Menopause Rating Scale (MRS) which has been shown to be a reliable way of measuring and comparing menopause related HRQoL (14). MRS scores are split into 11

psychological, somato-vegetative and urogenital symptoms with each rated between 0 and 4 depending on severity, giving a total score ranging from 0 to 44 where a higher score indicates more severe symptoms.

Data Analysis

The analysis was exploratory and comprised of descriptive statistics; categorical data were summarised by number and percentage of women in each category, and continuous data were summarised by number of women, mean, standard deviation (SD), median and lower and upper quartiles. Baseline characteristics were compared using t-tests (continuous variables) and chi-square tests (categorical variables). MRS scores were compared between survey subjects currently taking HRT and those discontinuing HRT. Database analyses were conducted using SAS version 9.3 and SAS Enterprise Guide version 5.1 and the surveys using SAS version 9.4.

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor. Ethical approval was granted by NRES Committee North East – Country Durham and Tees Valley on 12th May 2012 (reference 12/NE/0212).

Results

Database Study

We identified 8,968 women ≥45 years with a prescription for a study-HRT between 1st January 2006 and 13th January 2010 who met all inclusion and exclusion criteria. These were matched 1:1 on age and GP practice with women not prescribed HRT generating a study population of 17,936 women. Baseline characteristics can be found in **Error! Reference source not found.**. More women in the treated group were a past or current smoker than in the untreated group. Over four times the number of women in the treated group had a menopause diagnosis than the untreated group. The majority of women in the treated group had a menopause diagnosis recorded; however menopause

stage (peri or post) was relatively poorly recorded in both groups. There were significant differences ($p<0.05$) in the pre-specified co-morbid conditions associated with menopause recorded in the 12 months prior to index date, with women in the treated group more likely to have these conditions.

Among women with a menopause diagnosis, mean time between diagnosis and first study-HRT was 513 days (SD=947), but median time was around four weeks (**Error! Reference source not found.**). Mean and median time on treatment were more consistent, at approximately 14 months.

Error! Reference source not found. shows the first study-HRT product prescribed at index date. Almost two thirds of women were prescribed an estradiol and norethisterone therapy at index date followed by conjugated oestrogen and norgestrel (14.8%). Almost all women (95%) changed therapy during the study (**Error! Reference source not found.**). Some women made more than one change to their therapy, with the most popular change being to switch therapy. Among those switching, over 60% remained on some form of HRT (**Error! Reference source not found.**). Just under 7% of women switched administration route, and of these a switch to a patch was most common (51.4%), followed by a switch to oral (42.9%) and then a switch to both oral plus patch (5.7%).

Survey Study

400 questionnaires were sent to GPs with 230 of these forwarded to the women. 116 women returned the questionnaire, consented to participate in the study and provided information about their current HRT status and were included in the analysis. Of the 116 women, three quarters were on HRT and a quarter had discontinued treatment. Demographic characteristics and menopause status can be found in **Error! Reference source not found.**. Women on HRT appear to be slightly more affluent and are more likely to be current smokers than those who discontinued treatment, although these differences were not formally tested.

There were noticeable differences in the severity of menopausal symptoms between women currently taking HRT and those discontinuing HRT (**Error! Reference source not found.**). Women on

HRT had significantly lower scores for somato-vegetative and urogenital symptoms and total MRS score than those discontinuing HRT (all $p<0.05$). Women on HRT were also associated with a lower score for psychological symptoms vs. those discontinuing HRT, although the difference was not statistically significant ($p=0.18$). Among those discontinuing HRT, the main reasons for discontinuation include being advised by a doctor or nurse to stop taking treatment, suffering side-effects or concern about potential side-effects (Table 4). Concern about potential breast cancer was a reason for discontinuing HRT in about one fifth of discontinuing women (**Error! Reference source not found.**).

Discussion

To our knowledge, this study is the first to use observational data linked to a survey to investigate characteristics of women treated in general practice with combined (cyclical or continuous) HRT, patterns of HRT therapy, and reasons and outcomes associated with discontinuation of HRT. The survey findings provide valuable insights into the experiences of women, continuing or discontinuing HRT during our study period. The findings reflect a period when primary care management of the menopause was very likely influenced by results from the Women's Health Initiative (2002) (15) and the Million Women study (2002)(16). Despite limitations of using observational data, such as absence of detailed coding and potential bias, this study has important strengths as it describes patterns of HRT usual usage in general practice from 2006 up to 2010, provides information on women's experiences with HRT and sheds light on how HRT was prescribed and taken in usual practice compared with the recommendations of the new NICE guidelines on the management of the menopause issued in late 2015 (9).

Our results show the time between menopause diagnosis in the GP record and treatment initiation varied greatly with a median of 4 weeks and a mean of almost 17 months. Mean and median times on HRT were, in general, consistent at just over a year. This duration is relatively short in contrast

with the new NICE guidance (1,9) which does not state a limit for the duration of HRT but suggests women going through the menopause should have an annual review and only undertake a trial withdrawal if they are symptom free after 1-2 years on treatment. This recommendation is based on the understanding that if symptoms return, HRT will be reinitiated, as vasomotor symptoms can continue for many years (5). Our study also indicates almost all women treated with HRT in the database study changed treatment during the follow up period. This is consistent with the new NICE guideline advice (1,9) which suggests side-effects may be managed by change of dose, type or administration route of HRT.

Women remaining on HRT had lower MRS scores indicating less severe menopause symptoms and therefore better HRQoL than those who had stopped treatment. The main reason given for stopping treatment was stated to be on the advice of a doctor or nurse which could imply this was not a shared decision. However, side-effects and potential side-effects were also common reasons for stopping as was the perceived increased risk of breast cancer.

A factor that was, and perhaps still is, linked to women stopping (or not starting) HRT to manage menopause symptoms was the publication of two large studies – the Women's Health Initiative (2002) (15) and the Million Women study (2002) (16). Reid and Magee (17) summarise the limitations of these two studies, relative to the 'younger newly menopausal women initiating HRT', who did not form the majority of women in these studies. After the studies were published, the number of prescriptions for HRT almost halved in Canada (17) and decreased by 80% in the UK (18). They comment that in the years since these studies were published to the present day, many health professionals were trained in an environment where '*use of HRT is frowned upon'* (17). The current climate, reflected by the 2015 NICE guidance (1,9) emphasises the importance of HRT to manage the symptoms of the menopause that cause an impact for an individual and promotes discussion about the balance between the benefits and risks of HRT. The potential for management of side-effects of HRT, persisting with treatment or switching to different doses and methods of administration to

obtain symptom relief, with full discussion of risks and benefits relating to the individual woman, the frequency and impact of symptoms and promoting annual review of menopause management is reflected in current NICE guidance (1,9).

There were some limitations of this study: our survey sample was relatively small, including 116 respondents out of the 230 who were sent surveys. The survey sample was dominated by people who were continuing HRT. These respondents could be a biased sample; they were perhaps motivated to respond because HRT was perceived to be a 'successful treatment' for them. We originally sent 400 surveys to GPs who were asked to give the surveys to eligible survey subjects. But 170 surveys were not forwarded by some GPs for unknown reasons and we could not identify the GPs who did not forward the surveys due to the anonymous nature of the survey – another factor that may contribute to bias. The stage of the menopause (e.g. peri-menopause or post-menopause) was poorly recorded in women treated or not treated with study-HRT. This may be due to poor recording in the database or may reflect a lack of distinction by the GP. Since the menopause stage may impact prescribing decisions (cyclical or combined HRT) it is important to have made the distinction and prescribe appropriately. This could be a focus for further research. Another limitation is that we only know when a woman was diagnosed, not when menopause symptoms started. Consequently, the time between diagnosis and treatment may be different from the amount of time a woman experienced menopausal symptoms. Future research to measure time from onset of symptoms to treatment initiation would be informative. Finally, prescribing decision may be influenced by aspects other than a diagnosis, and these factors may not be captured in routine data. We do not know all the factors that may have influenced a decision to initiate HRT and decisions to discontinue or continue HRT.

In summary, in our general practice study population and over the study period, duration of HRT was just over one year, relatively short compared to current NICE recommendations (1,9). About 95% of women switched HRT during the their course of treatment which is more consistent with NICE

advice on how to manage side-effects of HRT(1,9). Women continuing on HRT experienced less severe menopause symptoms compared with those discontinuing treatment. Advice from health professionals and concerns about side-effects were among major reasons for discontinuation of HRT.

Looking to the future, in the context of new NICE guidance and reflecting on our study findings, it is important to encourage dialogue between women and health professionals to enable informed choices to be made concerning using HRT, to aid the menopause transition. Future research using routine, medical records data to explore the impact of the 2015

NICE menopause guidance (9) on HRT use in general practice is warranted in order to establish whether guidelines are being implemented.

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Tables

Table 1. Women characteristics at index date by HRT status.

	Treated with study-HRT	Not treated with HRT	p-value
N	8,968	8,968	
Age at index date (years)			
Mean (SD)	50.5 (4.2)	50.5 (4.3)	0.806
Median (IQR)	50.0 (48.0 – 52.0)	50.0 (47.0 – 53.0)	
Age at menopause diagnosis (years)*			
Mean (SD)	49.2 (4.0)	48.5 (4.4)	<0.001
Median (IQR)	49.0 (47.0 – 51.0)	49.0 (46.0 – 51.0)	
Smoking status, n (%)**			
Current smoker	2,087 (23.6)	1,641 (19.1)	
Past smoker	2,245 (25.4)	1,666 (19.4)	<0.001
Never smoker	4,524 (51.1)	5,286 (61.5)	
Unknown	112	375	
Townsend score, n (%)**			
1 (most affluent)	2,618 (30.3)	2,670 (30.7)	0.274
2	2,096 (24.2)	2,170 (24.9)	

3	1,720 (19.9)	1,722 (19.8)	
4	1,385 (16.0)	1,291 (14.8)	
5 (least affluent)	835 (9.7)	853 (9.8)	
Unknown	314	262	
Menopause diagnosis, n (%)			
Any type recorded	7,664 (85.5)	1,636 (18.2)	<0.001
Peri-menopause specified	948 (10.6)	241 (2.7)	<0.001
Post-menopause specified	584 (6.5)	249 (2.8)	<0.001
Co-morbid conditions recorded in the 12 months prior to index date			
Sleep problems	211 (2.4)	77 (0.9)	<0.001
Osteoporosis	37 (0.4)	17 (0.2)	0.006
Low bone density	10 (0.1)	1 (0.0)	0.007
Vulvar vaginal atrophy	77 (0.9)	17 (0.2)	<0.001
Vaginal dryness	37 (0.4)	12 (0.1)	<0.001
Depression	789 (8.8)	345 (3.9)	<0.001

* Age at the time of menopause diagnosis is not necessarily the age menopause began

** Percentages displayed are of non-missing values

Table 2. Days between menopause diagnosis and HRT initiation and duration of HRT

	Mean	Standard Deviation	Median	Quartiles	
				Lower	Upper
Days between diagnosis and HRT treatment (N=7,022)*	513.1	947.4	28.0	0.0	662.0
Duration of HRT (days) (N=8,968)	432.4	317.7	420.0	84.0	756.0

*1,946 women excluded as 1,304 did not have a menopause diagnosis and 642 had a diagnosis after their first study-HRT prescription.

Table 3. Characteristics of women completing survey questionnaire by discontinuation status (N=116)*

	Currently taking study-HRT	Discontinued HRT
N	89	27
Age at index date (years)		
Mean (SD)	49.5 (3.4)	49.4 (3.8)
Median (IQR)	49.0 (47.0 – 52.0)	49.0 (46.0 – 51.0)
Age at menopause diagnosis (years)**		
Mean (SD)	48.6 (3.6)	48.3 (3.7)
Median (IQR)	48.0 (46.0 – 51.0)	48.5 (46.0 – 51.0)
Smoking status, n (%)***		
Current smoker	18 (20)	2 (7)
Past smoker	22 (25)	13 (48)
Never smoker	49 (55)	12 (44)
Unknown	0	0
Region, n (%)		
England	67 (75)	21 (78)
Wales	3 (3)	3 (11)

Scotland	16 (18)	3 (11)
Northern Ireland	3 (3)	0 (0)
Townsend score, n (%)***		
1 (most affluent)	27 (31)	8 (30)
2	26 (30)	7 (26)
3	15 (17)	4 (15)
4	14 (16)	4 (15)
5 (least affluent)	4 (5)	4 (15)
Unknown	3	0
Menopause diagnosis, n (%)		
Any type recorded	77 (87)	24 (89)
Peri-menopause specified	11 (12)	3 (11)
Post-menopause specified	6 (7)	1 (4)

* Demographics found by linking women surveys to database data using pseudonymised women ID.

** Age at the time of menopause diagnosis is not necessarily the age menopause began

*** Percentages displayed are of non-missing values

Table 4. Reasons for discontinuation of HRT (N=27)

Reason for discontinuation of HRT	n (%)
N	
The medication did not adequately relieve my menopausal symptoms	1 (4)
The prescription charge was too high	1 (4)
My menopausal symptoms improved	7 (26)
I gained weight	4 (15)
The side-effects bothered me	9 (33)
Breast tenderness/pain	3 (11)
Vaginal bleeding/spotting	3 (11)
Swelling of the hands, arms, feet, ankles, or legs	0 (0)
Feeling sick/nausea	1 (4)
Headache/migraine	3 (11)
Other	5 (19)
I was concerned it *might* cause health problems	8 (30)
Breast cancer	6 (22)
Cancer of the uterus/womb	3 (11)
Weight gain	2 (7)
Blood clots	2 (7)

Stroke/heart disease	2 (7)
Other	2 (7)
My doctor/nurse advised me to stop taking HRT because they felt I no longer needed it	11 (41)
Other reasons	14 (52)

Figures

Figure 1. Treatment phases including first line therapy, switch, add-on, re-start and discontinuation

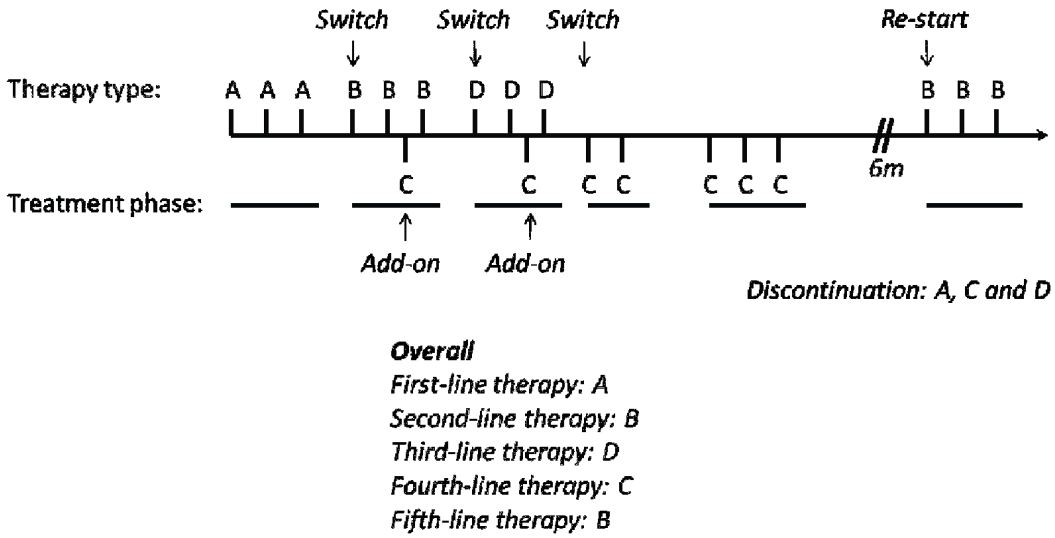


Figure 2. First study-HRT prescribed at index date (N=8,968)

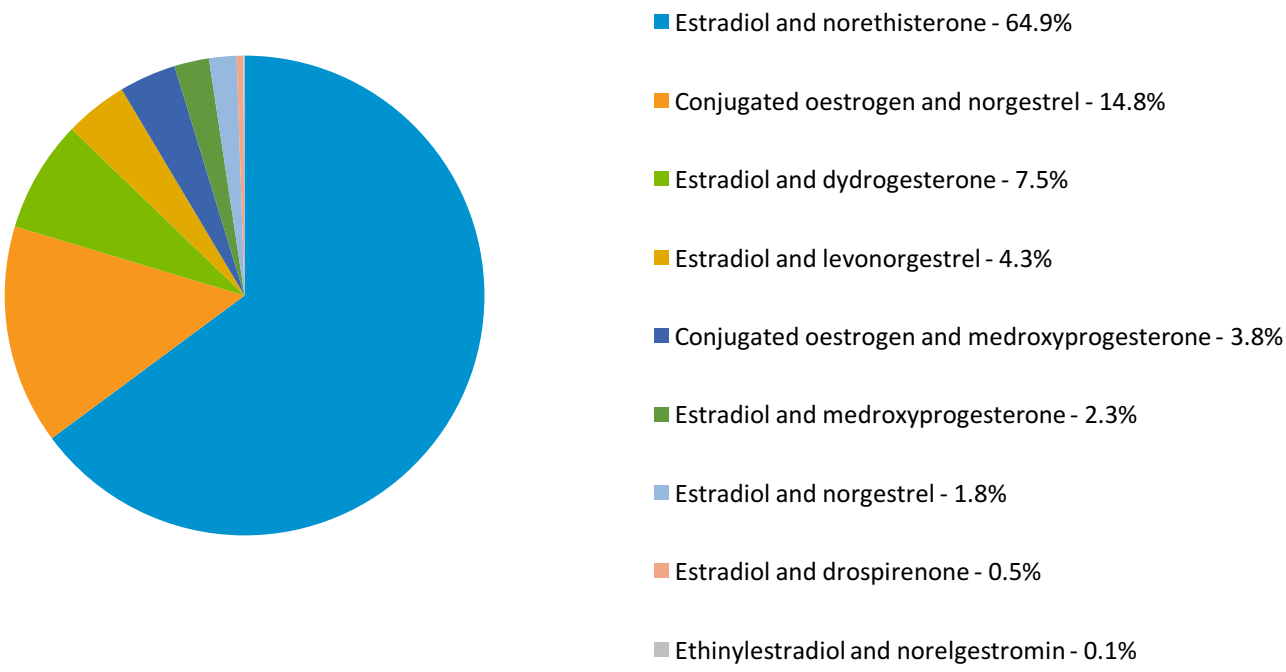


Figure 3. Overall pattern for women treated with study-HRT and changed therapy (N=8,968)

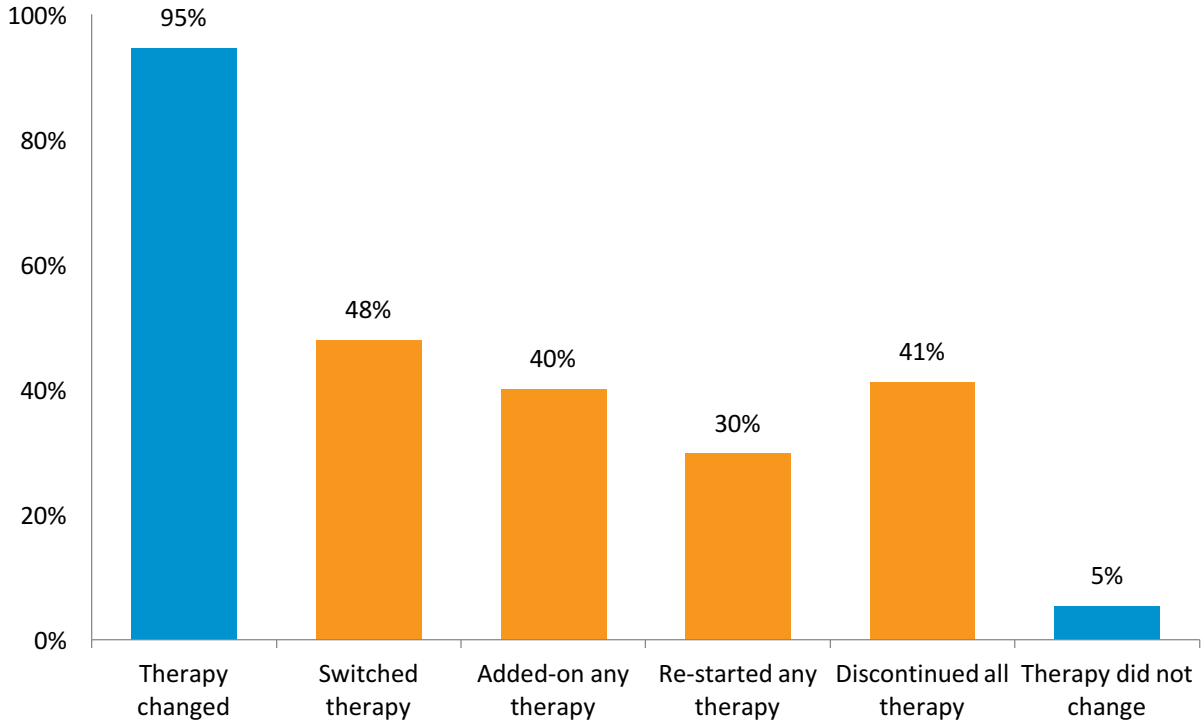


Figure 4. Overall patterns of first switch for women treated with study-HRT and switched therapy (N=4,300)

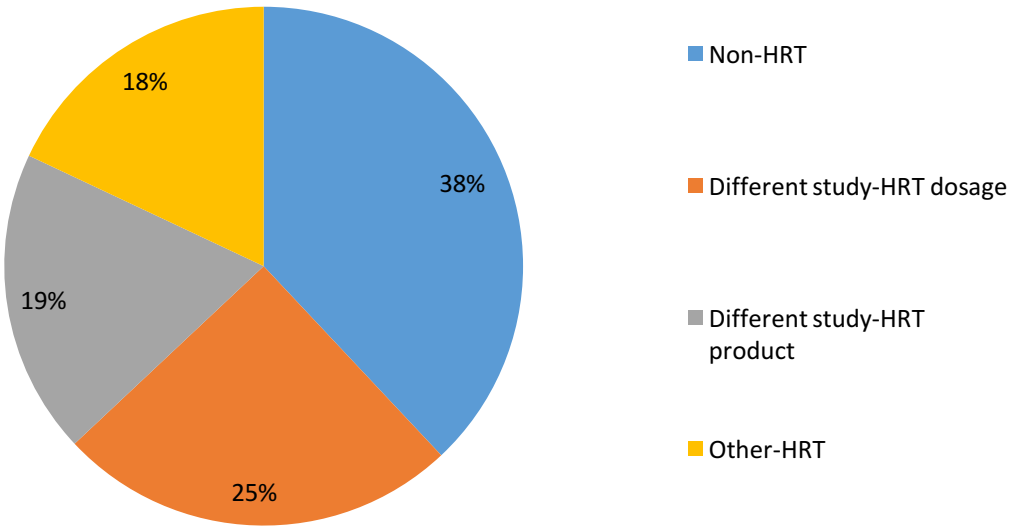
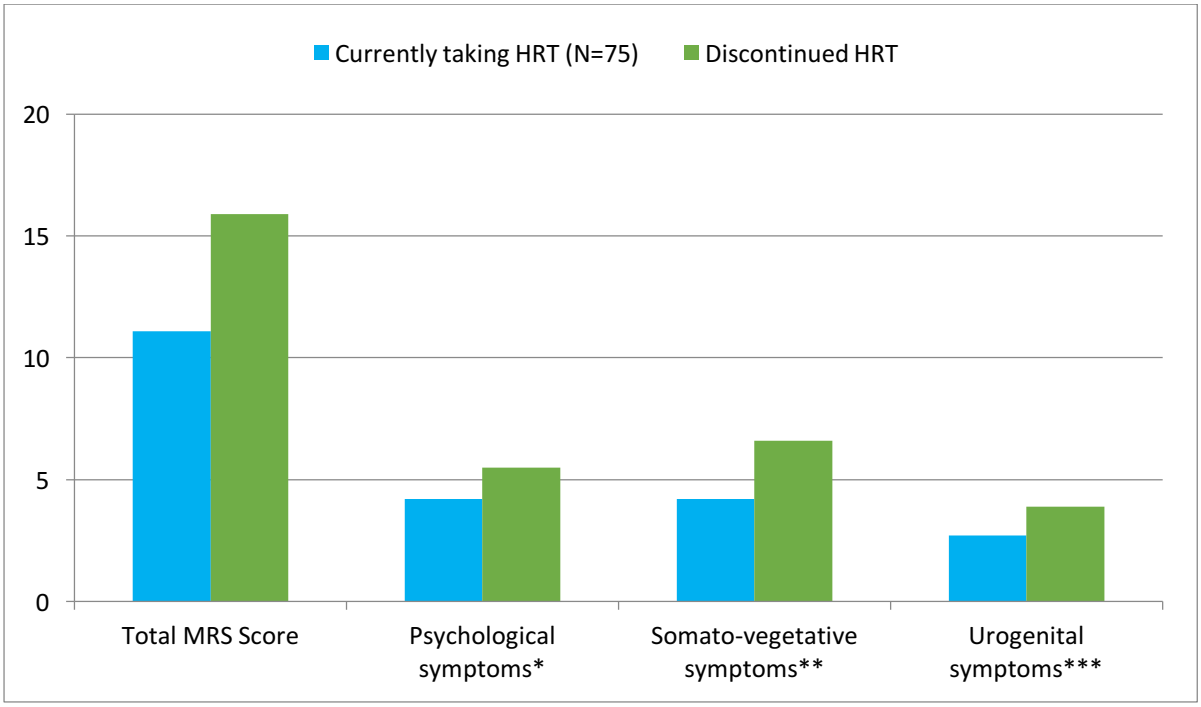

18%
38%
19%
25%
Non-HRT
Different study-HRT dosage
Different study-HRT product
Other-HRT

Figure 5. Mean Menopause Rating Scale (MRS) score by discontinuation status (N=102 women completing all parts of MRS question)



* Psychological symptoms include depressed, irritable, anxious, exhausted (0 – 16 points)

** Somato-vegetative symptoms include sweating/flush, cardiac complaints, sleeping disorders, joint & muscle complaints (0 – 16 points)

*** Urogenital symptoms include sexual problems, urinary complaints, vaginal dryness (0 – 12 points)