Hormone replacement therapy: patterns of use studied through British general practice computerized records

Martin Lawrence, Lesley Jones, Tim Lancaster, Edel Daly and Emily Banks


Objective. We aimed to describe the longitudinal pattern of hormone replacement therapy (HRT) consumption in a cohort of long-term users (defined as use for >1 year).

Method. We carried out longitudinal analysis of prescription data derived from GPs’ computer records. Subjects were recruited through 15 general practices in the former Oxford, South West and North West Thames Regions that contributed to the VAMP/OPCS general practice research database. All women in the practices aged 45–64 years in September 1991 were identified. Of these, the analysis concerned the 1224 long-term users and 1154 non-user controls who remained in the practices from September 1991 to March 1995; 868 (71%) of the users and 698 (61%) of the controls also provided questionnaire data.

Results. The prevalence of HRT use was 15% in 1992, a rise of 16% from 1991. The prevalence of long-term use was 10%; 22% of the cohort identified as taking HRT between April and September 1991 had left the practices or were not taking HRT 1 year later. But for the group defined as long-term users in 1992, the rate of discontinuation was less than 5% per year over the following 2½ years. Users of opposed therapy were 50% more likely to discontinue than users of unopposed therapy. Almost all women who had or had not undergone hysterectomy were taking unopposed or opposed therapy, respectively. Over 80% of prescriptions were for oral therapy. A third of users of either opposed or unopposed therapy changed the formulation during the 4 years of observation, and two-thirds of those who used both forms changed at least once in addition. Two changes were required to accommodate 94% of users.

Conclusions. Once women have taken HRT for a year, their continuation rate is over 95% per annum. Although the majority of women stayed with one formulation, a substantial minority changed formulation quite frequently, three formulations being required to accommodate 94% of long-term users over 4 years. Any trial of HRT use will need to recruit long-term users and allow for change in formulation of HRT in its protocol.

Keywords. General practice, hormone replacement therapy (HRT), prescribing.
by the equivalent length or time throughout life. A survey of GPs in the MRC research framework in 1991 reported that 878/929 (89.7%) of responders believed therapy with HRT for less than 10 years to be effective in preventing osteoporosis. Recent evidence, however, suggests that protection from heart disease1 and osteoporosis2–8 is largely confined to current users, so that a few years after discontinuation any benefit is lost—for example the risk of hip fracture in women over 75 years, when most hip fractures occur,9 is the same in those women who have and those who have not taken HRT before the age of 60.8 Risk of breast cancer also appears to be related not only to duration of use, but also to current usage, with risk diminishing following cessation of HRT.5

It is therefore becoming necessary to consider patterns of recommended HRT use. For instance, should women be advised to consider taking HRT on a very long-term basis from the outset, or perhaps to take it for a period around the menopause and then stop, restarting at an older age when the risk of heart and bone disease substantially exceeds that of breast cancer2–8

In order to appreciate the extent of the problem, it would be helpful to know women’s usual behaviour in the use of HRT, but there have been relatively few population-based studies of HRT in the UK.10–17 The majority of studies are based in general practices and use questionnaires and/or medical records. Some11–17 report on rates of current HRT use (up to 1992, 2–9%; 1993–1996, 15–29% in women aged 45–69 years): some10,13,16,17 report rates of ever-use (up to 1992, 10–30%; 1993–1996, 35–48%): but only one16 reports on the prevalence of use over time in the same population, and none consider changes in the pattern of use in a particular group. Population-based figures on national rates are also lacking, although a recent study reports national trends estimated from Government prescription data.18 It is therefore timely to report a study in which a cross-sectional sample of women has been identified and the long-term users (defined as women who have received at least two prescriptions at an interval of 6 and 18 months apart) followed over a 4-year period in order to review their behaviour with regard to continuing, stopping or changing their HRT usage.

Such information is especially pertinent since there is a recognized need for a randomized controlled trial of HRT in order to establish more precisely the costs and benefits.19 In view of the paucity of data on women’s normal usage of HRT, it is difficult to estimate the problems of retaining the participants on consistent therapy, whether they are taking active medication or placebo. These observational data give a good indication of women’s normal choices in changing or stopping therapy, and so provide information on the pressures that will result from the need to hold the groups in an intervention trial.

The VAMP/OPCS database of general practice records offers a method for recruiting and monitoring the HRT usage of large numbers of women. This is a database of computerized patient records regularly supplied by certain general practices, stripped of identifying features. The quality of the recording has been extensively validated.20 We report here a study of the HRT consumption patterns, between April 1991 and March 1995, in the women in 17 of the practices contributing to the database.

Method

We have already reported in detail the methods of identification and recruitment of study subjects, so the method will only be briefly summarized here.20 In 1993, 17 practices, whose records had been validated as of adequate quality by the VAMP/OPCS database prior to April 1991, agreed to allow us to have access to their anonymized computerized records, and to approach their patients directly. All the women in the practices aged 45–64 years on September 30 1992 were selected. Those who had received a prescription for HRT between April and September 1991 and between April and September 1992 were identified, and those common to both groups were classified as long-term users, having received a minimum of two prescriptions at an interval greater than 6 months. For each long-term user, the next oldest woman on the register who had not received HRT in the preceding 5 years was selected as a control. Each of the long-term users and controls was sent a questionnaire concerning their social and medical history, and an invitation to take part in the study. The invitations were mailed by the GPs who identified the patients’ addresses from their computer code: thus the identities of the women were not available to the researchers until they replied giving their consent. Data from the questionnaire and from their computerized medical record were therefore available for the women agreeing to take part in the study, and anonymized computer records data only were available for the women identified as users or controls who did not reply or declined to take part in the questionnaire-based study.

In January 1996, the anonymized computer records of all the women identified as long-term users or controls was supplied by the VAMP/OPCS database. Two practices had ceased to use the system in 1993, and their patients were excluded from the follow-up analysis. Data for all the remaining 15 practices were available up until March 1995. For these practices the registration data were searched, and all women who had left the practices before March 1995 were excluded from the analysis.

In reporting the characteristics of users and non-users of HRT, we previously restricted the analysis to patients responding to the questionnaire invitations, since the socio-demographic and past medical information were inadequate on the computerized database. The current analysis is mainly concerned with drug usage and so
(except where stated otherwise) has been carried out using the computerized records of all the women selected as long-term users or controls, including both those who did and those who did not respond to the questionnaire invitation.

Pattern of HRT Consumption
The 4 years April 1991–March 1995 were divided into eight 6-month periods. All patients had to have received an HRT prescription in the first and third periods to be entered into the study. Most women on HRT receive prescriptions at least once every 6 months and so, to allow for women who might have received a prescription just before and just after a 6-month period, they were regarded as continuous users if they did not have more than one consecutive period without receiving an HRT prescription. Comparison was then made of the rate of stopping HRT of all users identified in April–September 1991, and of the ‘long-term’ users who were using HRT in April–September 1992 and had previously been using it in April–September 1991.

Further analyses were carried out to determine the number of different formulations of HRT used by women during the 4 years of observation; and (for patients responding to the questionnaire invitation only, since only in these patients did we have adequate hysterectomy information) to compare HRT usage between patients who had or had not undergone hysterectomy.

Results
In total, 1482 women aged 45–64 years were identified in the 17 practices as long-term users of HRT during April–September 1992, and 1482 women who had not taken HRT in the previous 5 years were selected as controls. Analysis of prevalence data (Table 1) was carried out on the records of these women. One hundred and twenty users and 120 controls were patients of the two practices who changed computer system; 138 of the 1362 users and 140 of the 1362 controls identified in the remaining 15 practices were recorded as having changed their general practice between September 30 1992 and March 31 1995. Sixty-eight of the control women had no computer record. These women were excluded from the follow-up data leaving 1224 long-term users and 1154 non-user

Table 1

<table>
<thead>
<tr>
<th>Practice</th>
<th>Women Aged 45–64 years in Sept 1991</th>
<th>Users of HRT April–Sept 1991 (period 1)</th>
<th>Users of HRT April–Sept 1992 (period 2)</th>
<th>Increase in users between periods 1 and 2</th>
<th>Users in periods 1 and 2 (long-term users)</th>
<th>% users in period 1 continuing long term</th>
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<td>(82)</td>
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<td>195 (16.4)</td>
<td>20 (11)</td>
<td>131 (11.0)</td>
<td>(75)</td>
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<td>853</td>
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<td>132 (15.5)</td>
<td>18 (16)</td>
<td>88 (10.3)</td>
<td>(71)</td>
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<tr>
<td>d</td>
<td>956</td>
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<td>113 (11.8)</td>
<td>2 (2)</td>
<td>80 (8.4)</td>
<td>(72)</td>
</tr>
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<td>e</td>
<td>1366</td>
<td>176 (12.9)</td>
<td>211 (15.4)</td>
<td>35 (20)</td>
<td>141 (8.0)</td>
<td>(80)</td>
</tr>
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<td>126 (14.3)</td>
<td>23 (22)</td>
<td>83 (9.4)</td>
<td>(81)</td>
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<td>171 (15.9)</td>
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<td>138 (16.6)</td>
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<td>90 (10.8)</td>
<td>(78)</td>
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<td>153 (14.4)</td>
<td>1 (1)</td>
<td>112 (10.5)</td>
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<td>100 (11.1)</td>
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<td>93 (9.0)</td>
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<td>132 (11.9)</td>
<td>50 (61)</td>
<td>72 (6.5)</td>
<td>(88)</td>
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<td>196 (15.8)</td>
<td>19 (11)</td>
<td>149 (12.0)</td>
<td>(84)</td>
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<td>(100)</td>
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<td>71 (10.5)</td>
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<td>76 (17.4)</td>
<td>13 (21)</td>
<td>49 (11.2)</td>
<td>(78)</td>
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<td>TOTAL</td>
<td>14 754</td>
<td>1891 (12.8)</td>
<td>2195 (14.9)</td>
<td>304 (16)</td>
<td>1482 (10.0)</td>
<td>(78)</td>
</tr>
</tbody>
</table>

*Two practices included in baseline data, but which withdrew from data collection during the study.
controls for follow-up analysis. Of these, 868 (71%) users and 698 (61%) controls had responded to the questionnaire invitation.

Prevalence of HRT usage and continuation over a year in a cross-section of HRT users

See Table 1. The prevalence of HRT use was 13% (range 7–15 in the 17 practices) in 1991, and 15% (range 11–20) in 1992. This was an increase of 16% (range 1–61) over the year. Ten per cent (range 6.5–12) of women were long-term users, defined as receiving an HRT prescription in April–September of both 1991 and 1992. Of women taking HRT during April–September 1991, 22% (range 0–31%) had stopped or left the practice within a year.

Rates of continuation of long-term users

See Table 2. Of the 1224 women identified as long-term users at the start of the study, 952 received a prescription for HRT in each 6-month period throughout the observation period or until they stopped, and 235 missed only a single 6-month period. Thirty-seven (3%) women had two or more consecutive 6-month periods without a prescription and then restarted during the observation period.

Of the long-term users, 1089 (89%) received a prescription between April 1994 and March 1995, and of these, 1012 (82.7%) received prescriptions for unopposed treatment. Of the 135 (11%) who did not receive an HRT prescription in the year April 1994 to March 1995, 100 (8%) received a prescription for an item other than HRT more than a year after the last HRT prescription. So 83% were certainly continuing, 89% possibly or probably continuing, and 8% had definitely stopped taking HRT 2½ years after recruitment.

These data were further analysed according to the type of HRT taken; 645 (53%) of women took only opposed treatment over the 4 years of review, 449 (37%) took only unopposed and 130 (11%) took both. The rate of continuation of women taking opposed treatment was slightly lower than that for unopposed treatment, 86% versus 92%, but the difference was not significant for this sample size. Ninety-two per cent of women who received both opposed and unopposed treatment were continuing at 2½ years.

The data were further examined between women who did and who did not respond to the invitation to take part in the questionnaire study. The continuation rates were similar for those women responding and not responding, except for a rather lower rate of continuation in women taking opposed therapy and who did not respond (82%) compared with those who did respond (88%).

HRT type and hysterectomy status

See Table 3. This information was analysed only for the 868 long-term users of HRT who responded to the questionnaire, since hysterectomy information derived from the computer records alone was not adequate. Hysterectomy had been carried out in 366 (42%) of these women. Sixty-four of the 366 hysterectomies were only reported by the patient questionnaire and were not on the computer records; these were mainly operations carried out before routine computer recording was begun by the practices.

Of the 366 women who had undergone hysterectomy, 319 (87%) were taking unopposed treatment, and of the
of use of different preparations of HRT

See Table 4. Women’s choice of HRT preparation was examined in two ways—first by reviewing the total number of prescriptions for each formulation during the 4 years of observation, and second by reviewing the number of women who received at least one prescription for any given formulation during that time.

The most frequently prescribed forms of HRT were Prempak (comprising 39% of all HRT prescriptions), Premarin (23%), Estraderm (14%), Estrapak (4%) and Cycloprogynova (4%). No other HRT preparation contributed more than 3% of the total number of prescriptions, and all the other HRT preparations contributed less than 16% of the total.

The distribution based on the number of women who received at least one prescription was similar, although tibolone (Livial) and Trisequens occurred more frequently, since the women who received these preparations had received on average fewer prescriptions for them. In those women using HRT who responded to the questionnaire, the hysterectomy rate was 42% (see Table 3) and if this rate is assumed to apply to the whole 1224 sample, then 89% of patients without hysterectomy had taken Prempak and 14% Estrapak, while 66% of those who had hysterectomy had taken Premarin, and 38% Estraderm.

In addition, the records of the 1154 age-matched controls who were non-users at the start of the study were examined for evidence of them starting HRT. One hundred and eighty-two (16%) started during the 4 years of the study. Their most recent formulation was Prempak (35%), then tibolone/Livial (17%), Premarin (16%) and Nuvelle (8%). Transdermal preparations constituted 10%, and no other preparation was used by more than four (2%) of the women.

Frequency of change of prescription formulation of HRT

This was examined in two ways. First, by reviewing changes between formulations of HRT without taking account of changes of strength (Table 5), and then by reviewing the number of changes of formulation or strength (Table 6).

If no account is taken of a change of strength within a formulation, 836 (68%) of the 1224 women received...
the same HRT formulation throughout. Of those using opposed treatment, 76% stayed with the same formulation, of those on unopposed treatment, 77% did. Less than 1% of these women used more than three different formulations. Of those using both opposed and unopposed treatment, 47% required only one formulation of each type, and 95% were accommodated by one or two further changes.

If change of strength is also considered as a change, then 64% and 62% of users of only opposed or only unopposed therapy, respectively, required no change during the 4 years. Of those using both opposed and unopposed, 35% took only one opposed and one unopposed treatment, and 85% were accommodated by up to two further changes.

Discussion

A particular advantage of using the anonymized database of GPs’ records is that we have access to the records of patients who did and did not agree to take part in the questionnaire-based survey. Although some clinical data are inadequate unless corroborated by patient-provided data, GP records are known to be accurate for prescribing, especially repeat prescribing.20 We are therefore able to report HRT usage patterns both for patients who did and did not agree to take part in the questionnaire study.

The practice population

Almost all the users of HRT were accounted for throughout the study period; there were probably several ‘ghost’ patients (that is patients on the GP’s register who had died or moved away) among those selected as non-user controls. The only selection criterion was negative—that they had not received a prescription for HRT in the previous 5 years. The fact that no computer record existed for 68 (5.6%) of the women strongly suggests that these were indeed ‘ghosts’, leaving only 1294 non-users as controls. All these women had received at least one prescription between 1989 and 1995. The problem of ‘ghost’ patients has been reported in previous studies,21 and in selecting controls for a prescribing study such as this it would have been advisable to insist on an additional positive characteristic—such as the receipt of some item of service—to ensure that the patient was indeed present.

A major problem in undertaking a study using GP-computerized records is the loss to follow-up of patients who leave the practice. In this study population, of the 1362 women users and 1294 non-users of HRT, only 138 (10%) users and 140 (12%) non-users were recorded as having left the practice or dying during the 2½ years follow-up. Moreover it appears that the practices were good at recording transfers, since 1205 (98%) of the 1224 remaining users received a prescription of some kind during the last year of the study, demonstrating that they were indeed still in the practice.

Pattern of consumption of HRT

The method of determining continuing HRT use appeared valid. While 1187 users of HRT had one or less consecutive 6-month periods without receiving a prescription before they stopped or the observation period came to an end, only 37 (3%) women missed two or more 6-month periods and then restarted. These latter women appear to have had a treatment break, although the reason for the breaks cannot be established from this study.

The percentage of women aged 45–64 years in the practices taking HRT in 1991 and 1992 was 12.8% and 14.9%, respectively, rather higher than that reported in other studies at that time.11,12 The percentage of current users increased by 16% between 1991 and 1992. The wide range of prescribing, with a two-fold variation between

<table>
<thead>
<tr>
<th>Women taking</th>
<th>All women</th>
<th>Opposed therapy</th>
<th>Unopposed therapy</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of different formulations</td>
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<td>490 (76.0)</td>
<td>346 (77.1)</td>
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<td>1 (0.2)</td>
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<td>1 (0.2)</td>
<td>3 (2.3)</td>
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<td>5</td>
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<td>3 (2.3)</td>
<td>2 (1.5)</td>
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<tr>
<td>Total</td>
<td>1224</td>
<td>645</td>
<td>449</td>
<td>130</td>
</tr>
</tbody>
</table>
practices, suggests that the main cause of variation is in
doctor rather than patient behaviour. On the other hand,
this was partly due to ‘outlier’ practices, with 13 of the
17 practices lying within 15% of the median rate.

Of women identified in the practices as taking HRT in
April–September 1991, 22% were not in the practice
population taking HRT in April–September 1992. Even
accounting for patients who may have left the practices,
this represents a discontinuation rate in the cross-
sectional defined cohort of 10–15% over the following
year. However, once a group was defined longitudinally,
having taken HRT between April and September 1991
and again a year later, the rate of giving up was much
slower. After 2 1⁄2 years follow-up, 83% were definitely
continuing, 89% were possibly/probably continuing
and only 8% had definitely stopped. This gives a likely
stopping rate of 4.4% a year. Imprecision arises from
the recording uncertainties inherent to a short-term
study with 2 1⁄2 years follow-up of prescriptions, over
half of which were for 3–6 months. But it is clear that
once women have taken HRT for at least a year, their
rate of stopping is between a third and a sixth of that of
a cross-sectional sample of HRT users.

It is often believed that women taking opposed
therapy are less likely to be long-term users than those
on unopposed therapy because of the side-effects of
opposed therapy, especially cyclical bleeding. In this
study, 86–92% of women taking unopposed, but only
80–86% of women taking opposed therapy, were con-
tinuing at 2 1⁄2 years. Although this is quite a high con-
tinuation rate in both groups, the rate of discontinuation
of those women taking opposed therapy was 50%
greater than that of those taking unopposed. Those who
took both opposed and unopposed therapy during the
study had a continuation rate of 84–92%, similar to that
of women taking unopposed therapy. Indeed most of
these women either took mainly unopposed therapy, or
moved from opposed to unopposed during the period of
observation.

People who agree to take part in studies are believed
to be more compliant than those who do not. In this case
the pattern of unopposed HRT consumption was similar
in responders and non-responders. However, non-
responders taking opposed therapy chose to continue
therapy less frequently than responders, with 81–88% of
responders but only 76–82% of non-responders
continuing to take opposed therapy after 2 1⁄2 years’
observation.

Types and formulations of HRT
It is clear that GPs have fully appreciated that women
who have had hysterectomies should take unopposed
HRT, while those with an intact uterus should take opposed
therapy. This is quite different from the previously
reported longitudinal study covering the years 1981–1990,
in which it was found that nearly a half of women with
a hysterectomy had been prescribed opposed therapy,
and that nearly one-third of women who had not had a
hysterectomy had been prescribed unopposed therapy.17
In our study there remain a few exceptions. Three per
cent of women taking opposed therapy had a hysterec-
tomy recorded; 2% of those taking unopposed therapy
had no hysterectomy recorded or mentioned on their
questionnaire. Of all long-term users of HRT, only 2%
appeared to be taking opposed and unopposed therapy
without any firm pattern. These rates are much lower
than those reported from the MRC research network in
1991, when 15% of GPs said that they occasionally
prescribed unopposed oestrogen to women with an
intact uterus, and 18% said that they sometimes
prescribed opposed oestrogen to women who had had
a hysterectomy.8

Despite high levels of continuation of taking HRT, a
substantial minority of women changed formulation

<table>
<thead>
<tr>
<th>Number of different formulations</th>
<th>All women</th>
<th>Opposed therapy</th>
<th>Unopposed therapy</th>
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<tr>
<td>8</td>
<td>1 (0.1)</td>
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<td>1 (0.8)</td>
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<tr>
<td>Total</td>
<td>1224</td>
<td>645</td>
<td>449</td>
<td>130</td>
</tr>
</tbody>
</table>
within the 4-year period of observation. Over a third of women using opposed or unopposed therapy throughout, and two-thirds of women who used both, changed the formulation or strength of their HRT during the 4 years. Two changes of opposed or unopposed therapy, and two additional changes of therapy in women who took both opposed and unopposed, were required to accommodate 96% of users.

HRT continued to be prescribed mainly in oral form, with only 17% of prescriptions during the study period being for transdermal preparations, while 24% of women had at some stage during the study received a transdermal preparation. Of those controls who started therapy during the study period, 10% were using a transdermal preparation, so the ratio of transdermal to oral preparations in this study did not appear to be rising, while the use of tibolone and continuous combined preparations did.

Implications for trials of the effects of HRT use
It is well-recognized that the ideal method for testing the effect and cost-benefit of long-term use of HRT will be a randomized controlled trial. It is recognized that there will be major problems in recruiting a large representative group of women, and then holding the intervention and placebo groups. This study emphasizes these problems by demonstrating both the substantial proportion of any cross-section of a group of women who will give up HRT shortly after recruitment, and also the sizeable proportion who will choose to change their HRT type over a few years. On the other hand, the study also suggests methods of recruiting women who may be more likely to continue in a randomized controlled trial.

Many women selected as a cross-sectional cohort of HRT users will withdraw from the study, with up to 20% withdrawing at 1 year, while long-term users withdrew at about a quarter of that rate. In addition, it is unlikely that women with menopausal symptoms wishing to start HRT would be willing to be randomized to placebo, but this might not apply to women who have already been taking HRT for several years and are unsure about the benefits and risks of long-term treatment—randomization would take the decision out of their hands. Such women can be rapidly identified and recruited through GP-computerized records.

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