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# Practical implementation tips: hormone replacement therapy



**Claire Bellone and Dr Nick Panay offer tips on hormone replacement therapy for women experiencing menopausal symptoms**

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- how to help your patients make an informed choice about HRT
- tailoring the dose of HRT to the woman and her symptoms
- the different routes of administration of HRT.

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The recent publication of NICE Guideline (NG) 23 on Menopause: diagnosis and management has opened a new era for diagnosis and management of the menopause.<sup>1</sup> Dogged by 15 years of mixed and often negative press, many GPs have been dissuaded from prescribing hormone replacement therapy (HRT) and many women discouraged from using it. The reassuring message of the NICE guideline is that symptomatic women will gain symptomatic benefit from HRT,

which should even be considered for those women with co-morbidities.

## 1 Use a clinical assessment to inform the diagnosis

Clinical assessment is not always as straightforward as it first appears. Typically we know that most women experience menopause between the ages of 45–55 years, but with increasing frequency we are seeing more women under the age of 40 with symptoms. This in part is due to increasing survival rates from childhood illness and cancers.<sup>2-4</sup> Other more common presentations are women who remain amenorrhoeic at 6 months after discontinuing contraception.<sup>5</sup>

Early diagnosis is a key part of:

- reducing comorbidities associated with the menopause, e.g. osteoporosis and cardiovascular disease (CVD)<sup>1</sup>
- increasing fertility options before personal or funding options are limited, e.g. *in vitro* fertilisation with ovum donation, surrogacy, egg freezing.

NICE NG23 encourages clinical assessment skills to diagnose the menopause in the normal presenting age group;<sup>1</sup> however, women under 45 years should have follicle-stimulating hormone (FSH) levels checked where any doubt exists.<sup>1</sup> Anti-Müllerian hormone testing can also help confirm the diagnosis if it is otherwise unclear.<sup>6</sup>

## 2 Listen to the patient's concerns about initiating treatment

Hormone replacement therapy is ideally started around the time of the menopause transition, which occurs on average at 51 years of age.<sup>1</sup> At this stage of the menopause women will likely be at their fittest and are unlikely to have significant CVD risk. This epoch is described as the 'window of opportunity' when HRT can promote cardiovascular health while also reducing the relative risk of Alzheimer's, osteoporosis, and bowel cancer.

A patient-focused consultation will generally result in a management plan acceptable to the woman. Although HRT is likely to be the best option for symptom relief, it may not be what the patient wants at their first visit. We have all experienced the mixed messages around risks with HRT, so allaying a patient's misconceptions and listening to their concerns is of paramount importance. Several appointments may be needed before a final plan is agreed as the information is digested and non-hormonal options are also explored.

## 3 Explain the risks and benefits

As clinicians and patients we all have an opinion on HRT. NICE NG23 has been developed to enable evidence-based decision making,<sup>1</sup> alleviating the burden of personal opinion and bias. Educating the patient will ensure the right plan is agreed but explaining the potential risks of HRT is more challenging.

Risk can be presented as either relative or absolute; relative risk often gives rise to greater anxiety, with breast cancer and venous thromboembolism (VTE) being the primary concern. The use of pictograms to demonstrate absolute risk will facilitate open discussion and greater clarification in your consultation. These can be downloaded from the British Menopause Society website.<sup>7</sup> NICE NG23 includes tables showing the absolute rates of coronary heart disease, stroke, breast cancer, and fragility fractures for different types of HRT compared to no HRT. The tables for coronary heart disease and breast cancer are shown in Tables 1 and 2, respectively (see below).

Table 1: Absolute rates of coronary heart disease for different types of HRT compared with no HRT (or placebo), different durations of HRT use, and time since stopping HRT for menopausal women<sup>1</sup>

<b>Difference in coronary heart disease incidence per 1000 menopausal women over 7.5 years (95% confidence interval (baseline population risk in the UK over 7.5 years: 26.3 per 1000*))</b>			

		Current HRT users	Treatment duration <5 years	Treatment duration 5–10 years	>5 years since stopping treatment
Women on oestrogen alone	RCT estimate <sup>†</sup>	6 fewer (-10 to 1)	No available data	No available data	6 fewer (-9 to -2)
	Observational estimate <sup>‡</sup>	6 fewer (-9 to -3)	No available data	No available data	No available data
Women on oestrogen + progestogen	RCT estimate <sup>†</sup>	5 more (-3 to 18)	No available data	No available data	4 more (-1 to 11)
	Observational estimate <sup>‡</sup>	No available data	No available data	No available data	No available data

HRT=hormone replacement therapy; RCT=randomised controlled trial

For full source references, see **Appendix M in the full guideline**

**(<http://www.nice.org.uk/guidance/ng23/evidence>).**

\* Results from Weiner 2008 were used for the baseline population risk estimation.

† For women aged 50–59 years at entry to the RCT.

‡ Observational estimates are based on cohort studies with several thousand women.

NICE. *Menopause: diagnosis and management* (<http://www.nice.org.uk/guidance/ng23>, NICE Guideline 23. NICE, 2015.

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Table 2: Absolute rates of breast cancer for different types of HRT compared with no HRT (or placebo), different durations of HRT use and time since stopping HRT for menopausal women<sup>1</sup>

Difference in breast cancer incidence per 1000 menopausal women over 7.5 years (95% confidence interval) (baseline population risk in the UK over 7.5 years: 22.48 per 1000*)				
	Current	Treatment	Treatment duration	>5 years since

		<b>HRT users</b>	<b>duration &lt;5 years</b>	<b>5–10 years</b>	<b>stopping treatment</b>
<b>Women on oestrogen alone</b>	<b>RCT estimate<sup>†</sup></b>	4 fewer (-11 to 8)	No available data	No available data	5 fewer (-11 to 2)
	<b>Observational estimate<sup>‡</sup></b>	6 more (1 to 12) <sup>§</sup>	4 more (1 to 9)	5 more (-1 to 14)	5 fewer (-9 to -1)
<b>Women on oestrogen + progestogen</b>	<b>RCT estimate<sup>†</sup></b>	5 more (-4 to 36)	No available data	No available data	8 more (1 to 17)
	<b>Observational estimate<sup>‡</sup></b>	17 more (14 to 20)	12 more (6 to 19)	21 more (9 to 37)	9 fewer (-16 to 13) <sup> </sup>

HRT=hormone replacement therapy; RCT=randomised controlled trial

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**(<http://www.nice.org.uk/guidance/ng23/evidence>).**

\* Office for National Statistics (2010) breast cancer incidence statistics.

<sup>†</sup> For women aged 50–59 years at entry to the RCT.

<sup>‡</sup> Observational estimates are based on cohort studies with several thousand women.

<sup>§</sup> Evidence on observational estimate demonstrated very serious heterogeneity without plausible explanation by subgroup analysis.

<sup>|</sup> Evidence on observational estimate demonstrated very serious imprecision in the estimate of effect.

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## 4 Put the risks into perspective

Hormone replacement therapy is often misconstrued as a panacea that improves quality of life at the expense of shortened life expectancy; however, this could be far from the truth when, globally, women on HRT live longer, healthier lives than those not on HRT.<sup>8</sup> What we often side step is that obesity, sedentary lifestyle, uncontrolled hypertension, and alcohol intake have a greater effect on mortality and morbidity in the postmenopausal woman when directly compared with HRT risks.<sup>9</sup> These are all modifiable factors and should

be integrated into a holistic assessment. Useful tools already available to aid this discussion are the World Health Organization's Fracture Risk Assessment tool, FRAX<sup>®</sup>,<sup>10</sup> and the ClinRisk QRISK<sup>®</sup>2 prediction algorithm for CVD.<sup>11</sup>

## 5 Beware of Dr Google's influence

In the search for a safe HRT, more and more women are resorting to 'Dr Google' and being lured into believing that there is a safe, risk-free HRT. We should be duly cautious of this burgeoning market.

Compounded unlicensed bioidentical hormone therapies (also known as natural hormone therapies) are touted as novel and not available on the NHS. Bioidentical hormones are identical at a molecular level to those found in our own bodies. These therapies often claim that they must be safe as they are of natural plant origin; however, an unlicensed hormone is just that: unlicensed, with no safety, efficacy, or quality control data.<sup>12</sup>

Bioidentical HRT has actually been available on the NHS for some years. Unlike many combined oral contraceptive pills (COCPs), which use synthetic ethinyl oestradiol, the 17- $\beta$  oestradiol found in most HRT options is bioidentical to ovarian oestrogen, and can be administered as a patch, gel, tablet, or implant. The only exception is the equine-derived conjugated oestrogens found in some therapies.

## 6 Discuss the different routes of administration

By convention, oral drugs are most commonly prescribed, but the route of administration is integral to your discussion with the patient regarding HRT.

NICE NG23 recommends that women with significant CVD risk should use transdermal oestrogen.<sup>1</sup> As with the COCP, first-pass liver effects cause an increase in clotting factors and therefore an increase in VTE risk. Bypassing the liver reduces this risk to no greater than baseline.<sup>1</sup> The transdermal route also allows for a more natural delivery, using lower doses while maintaining efficacy through greater dosing flexibility.

Oral micronised natural progesterone also has favourable safety data, which showed no significant increase in breast-cancer risk compared with non-users.<sup>13</sup>

## 7 Tailor the dose to the woman and her symptoms

There is a common misconception that the lowest available dose should be prescribed, often at the expense of symptom relief or long-term health benefits. The goal of therapy is to establish a dose that effectively treats symptoms, and also offers bone protection. Standard doses, as recommended in the British National Formulary,<sup>14</sup> are suitable for women around the age of the menopause.

Not surprisingly, women under 40 years of age often need higher doses to achieve symptom relief or to ensure adequate bone protection. This higher dosage needs to be maintained until the average age of the menopause, 51 years, and brings no known associated increase in risks.

Conversely, symptomatic women over 60 years initiating HRT may need to be started on suboptimal transdermal doses due to the higher VTE risk observed in the first year. The dose may be slowly increased over time until therapeutic symptom relief is achieved.<sup>15</sup>

## 8 Listen to the woman's concerns about libido and desire

The impact of low libido during the menopause, either on a personal level or within a relationship, is often underreported. Taking time to listen to a woman's concerns will have a profound impact, as being believed and understood is healing in itself. Good advice about the use of vaginal lubricants and moisturisers can change a situation from the unthinkable to a positive pleasure. Vaginal moisturisers should be used as a treatment to rehydrate the vaginal tissues and increase moisture whereas lubricants are designed for intimacy.<sup>16</sup> The message is to choose a good product, designed for that specific use.

Moisturisers and lubricants alone may be insufficient in some cases. Vaginal oestrogen, used either concurrently or on its own, may be introduced to effectively alleviate many vaginal atrophy symptoms.<sup>1</sup> Vaginal oestradiol tablets may be considered for long-term use due to low systemic absorption; there is little concern regarding endometrial stimulation.<sup>17</sup>

Testosterone, the third hormone in HRT, may also be replaced.<sup>1</sup> Testosterone levels generally fall from around 35 years of age and are not altered by the menopause transition; however, combined with menopausal changes, this can have a distressing impact. Measurement of the Free Androgen Index ( $[\text{total testosterone}/\text{sex hormone binding globulin \{SHBG\}}] \times 100$ ) is not essential for a diagnosis of low sexual desire or related symptoms, but can confirm the need to replace testosterone and that supraphysiological levels are not likely to occur.

Unfortunately, there is no licensed product for women but male transdermal testosterone gel can be titrated to the female dose. [NB At time of publication, the treatment detailed above is not licensed for the aforementioned indication; the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good practice in prescribing and managing medicines and devices*<sup>18</sup> for further information.] One 5 g tube/sachet of gel containing 50 mg testosterone should be used over 7–14 days depending on the individual's response. The gel should be applied daily, and sparingly to the lower abdomen in the top of the pubic hair line, or to the upper inner thigh, rotating areas to avoid patch hair growth.<sup>19</sup>

A final caveat is that, unlike transdermal oestrogen, oral oestrogen will increase SHBG levels and therefore reduce libido. This effect can be observed with the COCP and is a frequent complaint of pill users. Women with low libido should therefore be treated with transdermal oestrogen with or without testosterone.<sup>12,19</sup>

## 9 Consider the menopause when diagnosing depression or anxiety

Depression and anxiety are common presentations of the perimenopause and also later on in the menopause. It is not uncommon for practitioners to prescribe women antidepressants as a first-line treatment, rather than considering this as part of the spectrum of hormone depletion symptoms. Severe menopausal depression may also follow a history of premenstrual syndrome (PMS) and postnatal depression; this triad may be referred to as hormone dependant depression. In these instances the patient's clinical history adds strength to and confidence in the prescribing decision.

Misunderstanding of the distress experienced by women at this time could be a result of fears around HRT risks. Given the new evidence supporting the use of HRT, especially in the perimenopause, a shift change in practice is required. The risks associated with HRT do not generally apply to women under the age of 50 years.<sup>20</sup> Benefits in psychological morbidity may be achieved in premature, early, and natural menopause.

## 10 Prescribe progestogen for endometrial protection

Progestogens are prescribed for protection against endometrial hyperplasia and risk of malignancy. In women with an intact uterus these must always be combined with oestrogen, either sequentially for the perimenopause or cyclically after 12 months of amenorrhoea.<sup>1</sup> Selection may be determined by a history of progestogenic side-effects reported with prior use of the COCP or perhaps a history of PMS. Androgenic progestogens (e.g. norethisterone) are more likely to cause intolerable PMS-type side-effects,<sup>21</sup> whereas natural progesterone can be better tolerated. Where PMS-type side-effects predominate, a low-dose regimen may be advocated.

## 11 Prescribe contraception when necessary

Many perimenopausal women also experience menorrhagia, or require contraception. Some levonogestrel-releasing intrauterine systems (IUSs) are licensed for both these instances,<sup>14</sup> and being low-dose local progestogens they may also benefit women with PMS.

Although not licensed within HRT use, it is possible to use the progesteroneonly pill (POP) in conjunction with a combined HRT.<sup>5</sup> The POP cannot be used without HRT progestogen as it does not provide adequate endometrial protection. Contraceptives containing endogenous oestradiol, rather than ethinyl oestradiol, may

be suitable for symptomatic perimenopausal women requiring contraception.

# 12 Get the first prescription right

Given all the choices, it is understandable that the first prescription may be difficult to optimise; however, listening to your patient, and working through the risks and benefits will help to make it self-evident what to prescribe. Most women will self-select the prescription that offers the lowest risks, whatever their current health status. This is often transdermal oestrogen with natural progesterone. Where simplicity is the main driver, then an oral combined option may be indicated such as oestradiol and dydrogesterone.

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