NICE guideline: diagnosis and management of the menopause

STEVE CHAPLIN

The new NICE guideline on the menopause published in November provides information on diagnosis and the risks and benefits of HRT to enable shared decision making between women and healthcare professionals. Steve Chaplin provides an overview of the guidance.

It is not often the scientific community gets things wrong in a big way but it has with HRT. Between the 1960s and 1990s, HRT was widely recommended for the treatment of menopausal symptoms and to prevent osteoporosis. In the 2000s, two influential studies – the Women’s Health Initiative in the USA and the Million Women Study in the UK – reported that HRT was associated with an increased risk of breast cancer and heart disease. Cautious but daunting advice from the regulatory authorities about the balance of benefit and risk did little to reassure women or their doctors: prescribing volume halved in a three-year period, continuing to decline until the present day (see Figure 1).

Now, the tide has turned again. Those influential studies (see Table 1) have been criticised, reanalysed and reinterpreted in light of new evidence. NICE’s new guideline on the diagnosis and management of the menopause seeks to rehabilitate HRT as a much-needed option because, NICE believes, “...the effects of menopause are often not fully understood. As a result, women do not always get the help they need from their GP, nurse, practice or hospital specialist to manage their symptoms effectively.”

This lack of help, compounded by misunderstanding of the benefits and risks of HRT, means that women “suffer in silence” when their home and work life is impaired by symptoms.

The guideline is divided into five sections – diagnosis, information and advice, short-term symptom management, long-term use of HRT and premature ovarian insufficiency. Unusually, there are three further sections addressing the challenges in implementing the guideline: stopping use of the follicle-stimulating hormone (FSH) test for diagnosis, communicating the risks and benefits of HRT, and specialist service provision.

Diagnosis

The menopause (see Box 1) is a clinical diagnosis made in women aged over
45 years who, apart from menopausal symptoms and cessation of menstruation, are otherwise healthy. The diagnosis is based on symptoms alone in women without a uterus. Clinicians should take into account the difficulty of reaching the diagnosis in women who are taking hormonal therapy for the treatment of heavy periods.

The guideline states: “If a woman is aged over 45 years and has not had a period for at least 12 months, or has vasomotor symptoms and irregular periods (or just symptoms if she doesn’t have a uterus), this is adequate information to diagnose menopause and perimenopause respectively.”

Hormonal tests should not routinely be used when diagnosing the menopause. In particular, the FSH test is inappropriate for women taking combined hormonal contraception or a high-dose progestogen, nor should it be used for women aged over 45 years.

Blood levels of FSH fluctuate markedly during the years leading up to menopause and they therefore do not help when forming what is actually a clinical diagnosis. NICE’s “do not do” list also includes measuring anti Müllerian hormone (an indicator of ovarian reserve), inhibin A or B (which inhibit FSH production), oestradiol, antral follicle count and ovarian volume.

However, an FSH test should be considered for women aged 40–45 years with menopausal symptoms, including a change in their menstrual cycle, and in women under 40 years when the menopause is suspected, in whom premature ovarian insufficiency is a possibility.

### The challenge: stopping FSH tests

- **US randomised double-blind prevention trial in postmenopausal women aged 50–79 years**
  - Primary endpoint: coronary heart disease; invasive breast cancer was the primary safety outcome
  - **Combined HRT arm:**
    - n=16 608
    - Conjugated oestrogens plus medroxyprogesterone acetate vs placebo
    - Stopped early when excess breast cancer risk apparent
  - **Oestrogen only arm:**
    - n=10 739
    - Conjugated oestrogens vs placebo
    - Stopped early when overall benefit apparent but stroke risk increased

- **Observational study**
  - Participants self-selected and self-reported HRT users
  - Women were already having a mammogram and may have been at higher risk of cancer or more aware of potential cancer risks because they were taking HRT
  - Follow-up from national cancer registries not by subsequent questionnaires; changes in HRT use after initial registration not recorded

<table>
<thead>
<tr>
<th>Women’s Health Initiative</th>
<th>Million Women Study</th>
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<tr>
<td><strong>Design and first reported analysis</strong></td>
<td><strong>28</strong></td>
</tr>
<tr>
<td>• US randomised double-blind prevention trial in postmenopausal women aged 50–79 years</td>
<td>• 1 084 110 UK women aged 50–64 years attending NHS Breast Screening Programme surveyed by questionnaire between 1996–2001. Followed up for cancer incidence and death</td>
</tr>
<tr>
<td>• Primary endpoint: coronary heart disease; invasive breast cancer was the primary safety outcome</td>
<td>• Current HRT use associated with increased risk of breast cancer, with greater risk for combined HRT</td>
</tr>
<tr>
<td>• Combined HRT arm: n=16 608 Conjugated oestrogens plus medroxyprogesterone acetate vs placebo</td>
<td></td>
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<table>
<thead>
<tr>
<th>Criticisms</th>
<th>Observational study</th>
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<tbody>
<tr>
<td>• Only one dose and type of HRT</td>
<td>• Participants self-selected and self-reported HRT users</td>
</tr>
<tr>
<td>• Dose too high for older women</td>
<td>• Women were already having a mammogram and may have been at higher risk of cancer or more aware of potential cancer risks because they were taking HRT</td>
</tr>
<tr>
<td>• Compared with UK, US women older (mean age 63 years, two-thirds over 60 years), therefore higher absolute risk of stroke, heart disease and breast cancer</td>
<td>• Follow-up from national cancer registries not by subsequent questionnaires; changes in HRT use after initial registration not recorded</td>
</tr>
<tr>
<td>• Most women were overweight (average BMI of 28.5) – a recognised risk factor for heart disease and breast cancer</td>
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<td>• High number of dropouts</td>
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**Table 1. Summary of the Women’s Health Initiative and the Million Women Study**

The perimenopause is the time in which a woman has irregular cycles of ovulation and menstruation leading up to menopause and continuing until 12 months after her final period. The menopause is a biological stage in a woman’s life that occurs when she stops menstruating and reaches the end of her natural reproductive life. Usually it is defined as having occurred when a woman has not had a period for 12 consecutive months (for women reaching menopause naturally). The changes associated with menopause occur when the ovaries stop maturing eggs and secreting oestrogen and progesterone.

Postmenopause is the time after menopause has occurred, starting when a woman has not had a period for 12 consecutive months.

Facts and figures
- Average age at onset in the UK is 51 years
- Premature menopause affects 1 per cent of women under 40 years
- 80 per cent of those going through the menopause (1.5 million women) experience some symptoms
- Menopause symptoms continue for about four years after the last menstrual period but in 10 per cent of women they may last for 12 years


Box 1. About the menopause

is unlikely to be informative and is not recommended.

Information and advice
Women should know how the menopause progresses, its common symptoms (see Table 2) and the long-term health implications. They should be informed about lifestyle changes and interventions that could improve their general health and wellbeing, and the benefits and risks of treatment.

The treatments of main interest are HRT and clonidine, along with cognitive behaviour therapy (CBT). Women in the perimenopausal and postmenopausal stages should be offered information about contraception in line with advice for the over-40s from the Faculty of Sexual and Reproductive Healthcare.

Women who are likely to experience a surgical or medical menopause, eg due to cancer therapy, should receive support and information beforehand and be offered referral to a healthcare professional with expertise in the menopause.

Managing short-term symptoms
The guideline, while prefacing its recommendations with advice to adapt treatment to a woman’s changing symptoms, is specific about the treatments that are appropriate. For vasomotor symptoms, women should be offered a choice of oestrogen/progestogen preparations (or oestrogen-only for women without a uterus) after discussing the benefits and risks of short (up to five years) and long-term treatment.

Clonidine, SSRIs and SNRI antidepressants should not be prescribed as first-line treatment for vasomotor symptoms alone, and there is no evidence that SSRIs or SNRIs help in the absence of depression. Instead, NICE recommends HRT to improve low mood, or CBT for low mood and anxiety associated with the menopause.

HRT should improve altered sexual desire but if it does not, a testosterone supplement should be considered. This, however, is an unlicensed indication. Similarly, if urogenital atrophy persists despite systemic HRT, a vaginal oestrogen should be prescribed for as long as needed. Topical treatment is also recommended for women in whom HRT is contraindicated, subject to advice from a menopause expert. If symptoms do not improve with a vaginal oestrogen, the dose can – on expert advice – be increased.

Women should be informed that symptoms often return when treatment is stopped. Vaginal oestrogen is normally well tolerated, so women should report any unscheduled vaginal bleeding to the GP. Moisturisers and lubricants can be used as alternatives or adjuncts. NICE advises against offering routine measurement of endometrial thickness during treatment for urogenital atrophy.

Treating HRT is not a prescribe-and-forget affair. Treatment should be reviewed after three months then annually (unless there are indications for an earlier appointment). If the recommended treatment is ineffective or poorly tolerated, women should be offered referral to a menopause specialist. Referral might also be considered when HRT is contraindicated or the best treatment option is uncertain.

Women should be warned that unscheduled vaginal bleeding may occur during the first three months of HRT use. Though expected, this should still be reported at the three-month review. Any bleeding after then should be reported promptly and, if this occurs, referral for suspected endometrial cancer may be appropriate. Women should also be aware that when they stop HRT, a gradual reduction in dose will limit symptom recurrence in the short term but will make no difference in the longer term.

HRT (including tibolone and progestogens) is contraindicated in women with breast cancer and should not be offered routinely to those with a history of breast cancer. In these cases, women should be offered information about their treatment options – these include the SSRI antidepressants paroxetine and fluoxetine (but not for women taking tamoxifen)

<table>
<thead>
<tr>
<th>Category</th>
<th>Symptoms</th>
</tr>
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<tbody>
<tr>
<td>Vasomotor</td>
<td>Hot flushes, sweats</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Joint and muscle pain</td>
</tr>
<tr>
<td>Mood</td>
<td>Low mood</td>
</tr>
<tr>
<td>Urogenital</td>
<td>Vaginal dryness</td>
</tr>
<tr>
<td>Sexual</td>
<td>Low sexual desire</td>
</tr>
</tbody>
</table>

Table 2. Common symptoms of the menopause*
and offered referral to an expert in menopause. Alternatives for hot flushes are clonidine, venlafaxine and gabapentin but their adverse effects are significant and women should be fully informed of the risks.

Complementary therapies
Women may prefer natural or non-pharmacological “complementary” products to a conventional licensed medicine. NICE acknowledges there is some evidence to support the effectiveness of black cohosh and isoflavones (both of which are available from high street outlets) but warns that the pharmaceutical consistency and safety of preparations containing these agents is unknown. Further, they may affect the metabolism of other medicines. This uncertainty also applies to bioidentical hormones – unregulated preparations of plant-derived hormones similar to human hormones – and to St John’s wort, an enzyme inducer with potentially serious drug interactions with tamoxifen, anticoagulants and anti-epileptic drugs.

Risks and benefits of long-term HRT
The guideline states:
“A knowledge gap among some GPs and other healthcare professionals could mean that they are reluctant to prescribe HRT because they overestimate the risks and contraindications, and underestimate the impact of menopausal symptoms on a woman’s quality of life.”

NICE wants women considering HRT to have the facts about what they stand to gain and the risks they run. Surprisingly, there is nothing in the guideline to quantify symptom relief – something that is probably uppermost in a woman’s mind and certainly a major factor in their decision whether or not to proceed with treatment. Instead, NICE presents definitive evidence on how HRT affects the risk of venous thromboembolism (VTE), type 2 diabetes, dementia, muscle strength, and (in detail) coronary heart disease, stroke, breast cancer and osteoporosis.

Oral HRT increases the risk of VTE but transdermal HRT does not. A patch or gel formulation should therefore be considered for women at risk of VTE (including those with a BMI >30kg per m²). Women at high risk should be referred to a haematologist.

The challenge: communicating risks of HRT
NICE accepts that communicating the benefits and risks of HRT will be a challenge. There is a need to improve knowledge among health professionals about the long-term benefits and risks of HRT.

To improve knowledge, the guideline states that clinical commissioning group prescribing leads could:
• Help develop formularies of good HRT prescribing for GPs with the support of GPs with a specialist interest in menopause and consultant gynaecologists
• Use briefings and newsletters to help disseminate prescribing knowledge on HRT.

GPs could:
• Set up local meetings or teaching sessions for interested GPs in each practice who can then disseminate information among their partners
• Use the guideline and NICE’s clinical knowledge summary on HRT (cks.nice.org.uk/menopause#scenariorecommendation: 3) to ensure that they are informed of the actual long-term benefits and risks of HRT for each individual and are not basing decisions on perceived knowledge

HRT has no effect on the risk of type 2 diabetes, nor does it affect glycaemic control. There are suggestions that it may reduce the risk of dementia and other neurodegenerative disorders but NICE states this benefit is unknown. Women should be informed of the limited evidence suggesting HRT may improve muscle mass and strength, though the importance of daily activities for maintaining strength is emphasised.

Prescribers will certainly not be short of statistics when they discuss HRT with...
their patients. NICE provides four tables quantifying the absolute rates of coronary heart disease, stroke, breast cancer and fragility fracture associated with HRT use for different types of HRT (oestrogen/progestogen and oestrogen alone) compared with no HRT (or placebo), for different durations of HRT use and time since stopping HRT (see Tables 3–5).

The tables in the guideline are clearly not intended for lay people and are not included in the version of the NICE guideline for the public. There is a similar table in the BNF; this is based on a 2007 analysis whereas NICE’s sources range from 1992 to 2013 but it is shorter and easier to use. An update to synchronise the BNF with the NICE tables would therefore be helpful.

Despite this abundance of data, the only clear message to emerge is that if HRT has any effect on the risk of coronary heart disease, stroke or breast cancer, it is small compared with the background variation in the general population. How small, and the importance of even that change in risk, is a more difficult question to answer and a decision aid would be a useful tool to help women understand these data.

**Cardiovascular disease**
Cardiovascular risk factors do not contraindicate HRT use provided they are optimally managed. The key messages about HRT and cardiovascular disease are: the background population rate is low and varies from person to person; the risk is not increased when treatment starts before the age 60 years; and HRT is not associated with increased cardiovascular mortality.

NICE recommends using the data in Table 3 to show that, where figures are available, oestrogen alone is associated with no or a reduced risk and oestrogen/progestogen is associated with little or no increase in risk. The 95 per cent confidence intervals include unity in all instances, meaning that none of these figures is statistically significant.

Similarly, the baseline risk of stroke in women under 60 years is very low. Oral HRT may be associated with a small increase in risk but transdermal administration is not. Observational studies show that current use of combined HRT is associated with a significantly increased risk; evidence from randomised trials is consistent with this but not statistically conclusive.

**Breast cancer**
The overriding message on breast cancer is again reassuring (see Table 4). With a variable baseline risk dependent on an individual’s risk factors, HRT with oestrogen alone has little or no effect on the risk of breast cancer. Combined HRT can be associated with an increased risk, apparently related to duration of use, but the figures for ongoing risk after stopping treatment are not consistent.

**Osteoporosis**
Caveats about a low baseline incidence and individual variability aside, there is at least consistency in the data showing that HRT reduces the risk of fragility fracture (see Table 5). The figures are statistically significant except for a post-treatment effect, and even this supports the contention that protection declines after HRT is stopped. However, NICE further suggests that protection may continue for longer with greater duration of use.

**The challenge: providing enough specialist services**
Another challenge highlighted by the guidance is providing enough specialist services. The number of women aged over 45 years is rising and this will increase demand on services. To tackle variation and potential gaps in service provision, commissioners and clinical commissioning groups could:

- Use Menopause UK’s national menopause map (menopauseuk.org/resources/map-of-menopause-services/) to identify variations in practice and the lack of overall provision
- Clarify current referral routes and promote them if they are effective
- Identify lead clinicians to drive a change in service provision if a gap is identified. Ideally, all CCGs should have a GP with a specialist interest or a community gynaecologist who could do this
- Establish whether current referrals are appropriate. Ideally, services should be provided by a dedicated menopause clinic

<table>
<thead>
<tr>
<th>Estimate based on</th>
<th>Duration of HRT use</th>
<th>Difference in breast cancer incidence per 1000 menopausal women over 7.5 years (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oestrogen alone</td>
<td>RCT*</td>
<td>4 fewer (-11 to 8)  No data  No data  5 fewer (-11 to 12)</td>
</tr>
<tr>
<td>observational</td>
<td></td>
<td>6 more (1 to 12)**  4 more (1 to 9)  5 more (-1 to 14)  5 fewer (-9 to -1)</td>
</tr>
<tr>
<td>Oestrogen plus progestogen</td>
<td>RCT*</td>
<td>5 more (-4 to 36)  No data  No data  8 more (1 to 17)</td>
</tr>
<tr>
<td>observational</td>
<td></td>
<td>17 more (14 to 20)  12 more (6 to 9)  21 more (9 to 37)  9 fewer (-16 to 13)***</td>
</tr>
</tbody>
</table>

RCT – randomised controlled trial; *women aged 50–59 years at entry; **very serious heterogeneity without plausible explanation; ***very serious imprecision in the estimate of effect

Table 4. Absolute rates of breast cancer with duration of HRT use (baseline population risk in the UK over 7.5 years: 22.48 per 1000)
### Table 5. Absolute rates of fragility fracture with duration of HRT use

<table>
<thead>
<tr>
<th>Estimate based on</th>
<th>Duration of HRT use</th>
<th>Difference in any fragility fracture incidence per 1000 menopausal women (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Current</td>
<td>&lt;5 years</td>
</tr>
<tr>
<td>Any HRT</td>
<td>RCT</td>
<td>23 fewer (-10 to -33)</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>69/1000</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>3.43 yrs</td>
</tr>
<tr>
<td>Observational</td>
<td>Baseline</td>
<td>16 fewer (-15 to -18)</td>
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<tr>
<td></td>
<td>Follow-up</td>
<td>15.4/1000</td>
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<tr>
<td></td>
<td></td>
<td>2.8 years</td>
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</table>

RCT – randomised controlled trial; *women aged 50–59 years at entry

### References

### Declaration of interests
None to declare.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics.