HRT: a guide to starting, stopping and troubleshooting

Types of HRT

A therapeutics article in the BMJ provides a useful summary on the types of HRT (BMJ 2012;344:e763). Dropping oestrogen levels cause menopausal symptoms, and HRT is designed to top up these levels. Unopposed oestrogens cause endometrial proliferation, so for women with an intact uterus, progestogen is also administered to counteract this.

There are three main types of HRT.

Oestrogen-only

- For women who have had a hysterectomy or have an IUS.
- Available as tablet, patch or topical gel.
- Can be prescribed with a progestogen (oral, IUS, gel or pessaries) to provide combined hormonal therapy.

Sequential combined HRT

- Oestrogen with progestogen added sequentially (usually 12–14d) to trigger a bleed.
- This formulation minimises irregular bleeding in perimenopausal women.
- After a minimum of 1y of sequential combined, switch to continuous combined to protect endometrium.

Continuous combined HRT

- Daily dose of oestrogen and progestogen: use only once women are a year or more from their last period, otherwise spotting and erratic bleeding is likely.

In low-risk perimenopausal women who also need contraception, CHC will treat hot flushes.

Starting HRT

Indications for prescribing HRT

- For control of vasomotor symptoms impacting on quality of life in perimenopausal and menopausal women.
- HRT is recommended for women with premature (<40y) and early (<45y) menopause until the age of 50y for symptom control and bone protection.
- Low libido and low mood are not indications for oral HRT, though they may be helped by taking it!

How effective is HRT?

- It is the most effective available treatment for vasomotor symptoms: it reduces frequency of flushes on average by 18 per week, and severity by 87%.
- Evidence shows it reduces fracture risk and vaginal dryness, and improves sexual function, sleep and muscular pains.

Contraindications to HRT (BNF online accessed 10 January 2016)

- History of breast cancer or other oestrogen-dependent cancers.
- Active/recent arterial thromboembolic disease (e.g. angina). Avoid HRT in uncontrolled hypertension.
- Current venous thromboembolism or thrombophlebitis, or history of recurrent VTE (unless already on anticoagulation – the view from a haematologist in Oxford was that the risk of HRT precipitating VTE in anticoagulated women was low, so it is reasonable to prescribe along with an explanation to the patient; transdermal preparations would be preferred).
- Thrombophilic disorder.
- Undiagnosed vaginal bleeding.
- Untreated endometrial hyperplasia.
- Liver disease (with abnormal LFTs).
- Dubin–Johnson and Rotor syndromes, unless monitored closely (rare genetic disorders leading to increased bilirubin).

Migraines do not seem to be exacerbated by low dose HRT, but transdermal preparations may be preferable.

Formulations

The tables below show the different types and formulations of HRT which are available in this country. For more information on the different constituents and their relative merits, please see the article on HRT formulations: bio-identical, conjugated and synthetic.

There is no ‘Microgynon’ of HRT, so prescribing is often based on a personal preference. Transdermal preparations are associated with lower cardiovascular risk.

Sequential combined preparations
### Continuous combined HRT

<table>
<thead>
<tr>
<th>Route</th>
<th>Oestrogen</th>
<th>Progestogen</th>
<th>Name</th>
<th>Cost (3m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO</td>
<td>Oestradiol valerate 2mg</td>
<td>Norethisterone 1mg (12 tabs)</td>
<td>Cilcoret</td>
<td>£9.23</td>
</tr>
<tr>
<td></td>
<td>Oestradiol 1mg</td>
<td></td>
<td>Novofem</td>
<td>£11.43</td>
</tr>
<tr>
<td></td>
<td>Oestradiol 1–2mg</td>
<td>Norethisterone 1mg (10 tabs)</td>
<td>Elleste Due</td>
<td>£9.20</td>
</tr>
<tr>
<td></td>
<td>Oestradiol 1mg (10 tabs) 2mg (12 tabs)</td>
<td></td>
<td>Trisequens (phasic preparation)</td>
<td>£11.10</td>
</tr>
<tr>
<td>PO</td>
<td>Oestradiol 1–2mg</td>
<td>Hydrogestosterone 10mg (14 tabs)</td>
<td>Femoston</td>
<td>£16.16</td>
</tr>
<tr>
<td>PO</td>
<td>Oestradiol valerate 2mg</td>
<td>Norgestrel 500mcg (16 tabs) + 7d pill-free interval</td>
<td>Cyclo-Progynova</td>
<td>£3.11</td>
</tr>
<tr>
<td>PO</td>
<td>Oestradiol valerate 2mg (70 tabs)</td>
<td>Medroxyprogesterone acetate 20mg (14 tabs) + 7d pill-free interval</td>
<td>Tridesta (long cycle preparation)</td>
<td>£20.49</td>
</tr>
<tr>
<td>Patch</td>
<td>Oestradiol 50mcg/24h</td>
<td>Norethisterone 170mcg/24h (2 patch/w for 14d)</td>
<td>Everol Sequil</td>
<td>£11.09</td>
</tr>
<tr>
<td>Patch</td>
<td>Oestradiol 50mcg/24h</td>
<td>Levonorgestrel 10mcg/24h (1 patch/w for 14d)</td>
<td>Femseven sequil</td>
<td>£37.54</td>
</tr>
</tbody>
</table>

### Oestrogen-only preparations

<table>
<thead>
<tr>
<th>Route</th>
<th>Oestrogen</th>
<th>Progestogen</th>
<th>Name</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO</td>
<td>Conjugated oestrogen 300mcg</td>
<td>Medroxyprogesterone acetate 1.5mg</td>
<td>Premique low dose</td>
<td>£55.2</td>
</tr>
<tr>
<td></td>
<td>Oestradiol 1mg</td>
<td>Drosperone 2mg</td>
<td>Angelique</td>
<td>£28.00</td>
</tr>
<tr>
<td>PO</td>
<td>Oestradiol 1mg</td>
<td>Norethisterone 500mcg</td>
<td>Klironov</td>
<td>£13.20</td>
</tr>
<tr>
<td></td>
<td>Oestradiol 1mg</td>
<td>Norethisterone 1mg</td>
<td>Elleste Due conti</td>
<td>£7.02</td>
</tr>
<tr>
<td></td>
<td>Oestradiol 2mg</td>
<td></td>
<td>Nuvelle continuous</td>
<td>£19.00</td>
</tr>
<tr>
<td></td>
<td>Oestradiol 1–2mg</td>
<td>Medroxyprogesterone acetate 2.5–5.0mg</td>
<td>Indimina</td>
<td>£20.58</td>
</tr>
<tr>
<td>PO</td>
<td>Oestradiol 0.5–1.0mg</td>
<td>Hydrogestosterone 2.5–5.0mg</td>
<td>Femoston-conti</td>
<td>£24.43</td>
</tr>
<tr>
<td>Patch</td>
<td>Oestradiol 50mcg/24h</td>
<td>Norethisterone 170mcg/24h</td>
<td>Everol Conti</td>
<td>£37.22</td>
</tr>
<tr>
<td>Patch</td>
<td>Oestradiol 50mcg/24h</td>
<td>Levonorgestrel patch 7mg/24h</td>
<td>Femseven Conti</td>
<td>£44.12</td>
</tr>
</tbody>
</table>

### Progesterone-only preparations

To be used with oestrogen-only HRT. Not commonly prescribed in general practice.

Vaginal preparations (capsules and gels) are NOT licensed for HRT. The doses stated in the table are recommendations from Dr
Nick Panay (consultant gynaecologist at the Chelsea and Westminster Hospital with special interest in menopause).

Due to a lack of evidence, NICE (2015, NG23) uses expert opinion and existing guidance to recommend:

- Initial review at 3m to assess efficacy and tolerability of treatment.
- Annual review unless clinical indications for earlier review (e.g. side-effects, persistent menopausal symptoms). Discuss symptom control, ongoing indication, side-effects.
- Monitor BMI and blood pressure.
- Do a cardiovascular risk assessment and offer appropriate lifestyle advice.
- Check if cervical and breast screening are up to date.
- Ask about bleeding pattern – with combined preparations, unscheduled bleeding may occur in the first 3m of use, but if it persists or starts after 3m of use, further investigation may be needed.
- Consider whether anxiety or depression may be contributing to the somatic symptoms of menopause.

**Troubleshooting**

The British Menopause Society (Post Reproductive Health 2016; 22(4) 165), offers the following advice regarding side-effects of HRT.

**Breakthrough bleeding**

- If this occurs after a switch to continuous combined HRT and does not settle after 3–6m, switch back to a sequential regimen for another year.
- If bleeding is heavy/erratic on a sequential regimen, double the dose of progestogen or increase the duration to 21d.
- Arrange further investigation (USS endometrial biopsy) if persistent bleeding beyond 6m.

**Progestogenic side-effects**

- Fluid retention can occur via stimulation of aldosterone receptors. Consider drospirenone formulation.
- If androgenic side-effects (acne, hirsutism) develop, switch to a non-testosterone derived progestogen (medroxyprogesterone acetate or dydrogesterone).
- Mood swings and PMS-like symptoms can be progestogenic in origin. Halve dose and duration of progestogen (7–10d).
- Progesterone and dydrogesterone tend to have fewer side-effects due to progestosterone receptor specificity, as does localised administration such as via IUS, transvaginal pessaries or gels.
Duration of use and stopping HRT

NICE does not give advice about when to stop HRT, except that it should be stopped at annual review if the risks are thought to outweigh the benefits. The evidence presented suggests the risk of breast cancer increases with duration of use, and that there is no increased risk of CVD if HRT is stopped at 65y.

In its recent recommendations (Post Reproductive Health 2016; 22(4) 165), the BMS advises that:

- HRT dosage, regimen and duration should be individualised.
- Arbitrary limits should not be placed on the duration of usage of HRT; if symptoms persist, the benefits of HRT usually outweigh the risks.
- HRT prescribed <60y has a favourable benefit/risk profile.
- If HRT is prescribed to a woman >60y, use lower doses and preferably a transdermal route.

Tapering HRT versus abrupt withdrawal

Tapering HRT dose (over 2w to 6m in different RCTs), compared with sudden cessation of HRT, reduced short-term recurrence of symptoms but made no difference in the long term.

A guide to starting HRT

- Oestrogen-only HRT is for hysterectomised women or those with an IUS, or may be used with a separate progesterone/progestogen to provide combined HRT.
- Sequential combined HRT is a combination of oestrogen and progestogen given sequentially to allow a withdrawal bleed to prevent irregular spotting.
- Continuous combined HRT gives a daily dose of oestrogen and progestogen, and is more effective at protecting the endometrium. Move from sequential to combined by aged 54y.
- Progestogenic side-effects are common, and transdermal preparations are safer for older women or those at risk of VTE.
- Review your patients annually.

Do you have an ‘HRT formulary’ in your practice?

We make every effort to ensure the information in these articles is accurate and correct at the date of publication, but it is of necessity of a brief and general nature, and this should not replace your own good clinical judgement, or be regarded as a substitute for taking professional advice in appropriate circumstances. In particular check drug doses, side-effects and interactions with the British National Formulary. Save insofar as any such liability cannot be excluded at law, we do not accept any liability for loss of any type caused by reliance on the information in these articles.
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