The last few years has seen a dramatic rise in the number of women seeking advice for the menopause and hormone replacement therapy (HRT). Navigating the complexities of HRT and being able to discuss the options available in primary care is, therefore, essential. The aim of this article is to provide key considerations for primary care physicians (PCPs) when considering HRT implementation and also the role of testosterone and vaginal oestrogen for symptom management (Figure 1). It is beyond the scope of this article to discuss the role of tibolone, selective oestrogen receptor modulators (SERMs), and dehydroepiandrosterone (DHEA) for managing menopausal symptoms, and PCPs would be encouraged to seek specialist input prior to commencing these treatments.

**KEY CONSIDERATION 1: IS HRT APPROPRIATE?**

Although hot flushes and night sweats are commonly associated with menopause, a wide plethora of symptoms including brain fog, insomnia, and reduced libido have been reported. Although HRT has been shown to be beneficial for symptomatic women who are peri-menopausal (last menstrual period [LMP] within last 12 months) or menopausal (more than 12 months since last LMP), a holistic review of lifestyle factors and exploring natural or herbal therapies is crucial prior to its implementation. Contraindications to its implementation should also be considered.

**Table 1. Progesterone cover for HRT**

<table>
<thead>
<tr>
<th>Progesterone</th>
<th>Comments</th>
<th>Side effects</th>
<th>Sequential combined regimen</th>
<th>Continuous combined regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Utrogestan</td>
<td>Micronised progesterone, bio-identical and helps with sleep and safe for those with previous history of VTE and migraines</td>
<td>Nausea Fluid retention</td>
<td>200 mg for 12 days per month, to take at night</td>
<td>100 mg every night</td>
</tr>
<tr>
<td>Desogestrel</td>
<td>Contraceptive action Off-licence use and not first line</td>
<td>Nausea Fluid retention</td>
<td>150 mg daily</td>
<td>150 mg daily</td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td>Use with caution with previous history of hormone-sensitive breast cancer, VTE, and migraines</td>
<td>Mood changes Fluid retention Breast tenderness</td>
<td>10 mg daily for 12 days per month</td>
<td>Minimum of 2.5 mg daily up to 5 mg daily</td>
</tr>
<tr>
<td>Norethisterone</td>
<td>Use with caution with previous history of hormone-sensitive breast cancer, VTE, and migraines</td>
<td>Mood changes Fluid retention Breast tenderness</td>
<td>5 mg for 12 days per month</td>
<td>5 mg daily or consider Noriday 3 tablets daily</td>
</tr>
<tr>
<td>Intrauterine contraceptive device</td>
<td>Mirena can remain in situ for 5 years (off-licence use) for endometrial protection and contraceptive cover</td>
<td>Irregular or heavy bleeding</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

**HRT = hormone replacement therapy. VTE = venous thromboembolism.**
Is HRT appropriate?

**Contraindications to HRT**
- Previous or current history of hormone-sensitive breast cancer
- Endometrial cancer
- Endometrioid ovarian cancer
- BMI>40

**IF HRT contraindicated, consider alternatives and refer to menopause specialist services**
- Gabapentin (300 mg OD–900 mg TDS)
- Pregabalin (50–300 mg)
- Venlafaxine (37.5 mg OD–TDS)
- Clonidine (50 mg BD–75 mg BD/50 mg TDS)

If HRT is appropriate, consider regimen

<table>
<thead>
<tr>
<th>Regimen 1</th>
<th>Regimen 2</th>
<th>Regimen 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>For women with no uterus</td>
<td>Intact uterus and period within last 12 months</td>
<td>Intact uterus and period more than 12 months ago</td>
</tr>
<tr>
<td>Oestrogen-only HRT</td>
<td>Sequential combined HRT</td>
<td>Continuous combined HRT</td>
</tr>
</tbody>
</table>

HRT preparation — oral or transdermal

**Oral**
- Oestrogen only
- Combined oestrogen/progesterone

**Transdermal**
- Patch (oestrogen only or as combined oestrogen/progesterone)
- EstroGel/Sandrena/Lenzetto — oestrogen only
- Will need progesterone cover separately if on Regimen 2 or 3 (Table 1)

Consider additional therapy

**Testosterone**
- Should be commenced once adequately oestrogenised for low libido and fatigue
- Check total testosterone levels prior to and after 6–12 months of commencing supplementation
- Transdermal preparations
  - Testogel — ¼ 40.5 mg sachet every day
  - Androfene — 0.5 ml every day
  - Testim gel — 0.5 ml every day
  - Tostran — 1 pump alternate days

**Vaginal oestrogen**
For vaginal dryness and/or genitourinary symptoms
- Start on a daily dose for 2 weeks then gradually reduce every 2 weeks to three times a week, then twice weekly, then once weekly. Can remain on once- or twice-weekly dose for maintenance

**Figure 1. Flowchart of key considerations when commencing HRT.**

**BD** = two times a day, **OD** = once a day, **TDS** = three times a day.

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**Provenance**
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Rima Chakrabarti is a member of the British Menopause Society (BMS).

**Discussion this article**

Use include previous or current history of hormone-sensitive breast cancer, endometrial cancer, and endometrioid ovarian cancers. Potential alternatives in these cases include gabapentin, pregabalin, clonidine, and venlafaxine, and can be started in primary care following a risk versus benefit discussion.

**KEY CONSIDERATION 2: WHAT PREPARATION AND REGIMEN ARE REQUIRED?**

Once the decision is made to commence HRT, it is important to consider whether a combined oestrogen/progesterone or oestrogen-only preparation is required. For all women with an intact uterus, the former is vital for reducing the risk of endometrial hyperplasia. While combined HRT is available as either a sequential or continuous regimen, the preparations vary by the type of progesterone used and dose of oestrogen.

With the management of menopausal symptoms determined by the latter, prescription is often guided by availability. While both sequential and continuous combined regimens deliver a daily dose of oestrogen, sequential regimens deliver progesterone for up to 12 days per month (compared with continuous regimens that deliver a daily dose). Sequential regimens are recommended for peri-menopause to reduce the risk of breakthrough bleeding and these women should be counselled that they may experience a withdrawal bleed on their progesterone-free days. Generally, women can be switched from a sequential to a continuous regimen after 2 years if they are below the age of 50 years, or after 1 year after the age of 50 years.

**KEY CONSIDERATION 3: WHAT IS THE MOST APPROPRIATE ROUTE AND DOSE OF HRT TO START ON?**

Once the preparation and regimen have been decided, the next step is to choose the route and dose of HRT. With HRT available either as an oral or transdermal preparation, the latter bypasses first-pass metabolism of the liver and is suitable for women with a history of venous thromboembolism (VTE), liver disease, malabsorptive diseases, and migraines. Available as a patch, gels (EstroGel, Sandrena), or spray (Lenzetto), transdermal preparations are also favoured for women with a BMI>30. For those with a BMI>40, referral to a specialist menopause clinic would be recommended.

The patch is available as either oestrogen only or as a combined oestrogen/progesterone patch, is applied to the thighs, and changed on a twice weekly basis. In contrast, EstroGel, Sandrena, and Lenzetto are oestrogen only and are applied every day. With the exception of Lenzetto, which is applied on the arms, EstroGel and Sandrena are applied to the thighs. Additional progesterone cover must therefore be prescribed separately for those with an intact uterus, and further information on dosage and options for progesterone cover are provided in Table 1.

The starting dose of oestrogen should be guided by age, with women below the age of 50 years generally requiring high doses compared with women between 50–59 years, who may note alleviation of their symptoms at low or medium doses. It is also advised that HRT should be commenced for women over the age of 60 years or more than 10 years from their LMP at low or ultra-low doses and transdermally. To reduce the risk of oestrogenic side effects...
Table 2. Guide for prescribing HRT

<table>
<thead>
<tr>
<th>HRT Regimen</th>
<th>Oestrogen strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (once a day tablets)</td>
<td>Ultra-low</td>
</tr>
<tr>
<td>Oestrogen only</td>
<td>Alternate-days Elleste Solo 1 mg or Zumenon 1 mg</td>
</tr>
<tr>
<td>Sequential combined</td>
<td>Elleste Duet 1 mg Femoston 1/10</td>
</tr>
<tr>
<td>Continuous combined</td>
<td>Femoston Conti Low Femoston Conti Klivance</td>
</tr>
<tr>
<td>Patch (applied on thigh and changed twice weekly)</td>
<td>Oestrogen only</td>
</tr>
<tr>
<td>Sequential combined</td>
<td>Evorel 25 Estradot 25 &amp; Utrogestan 200 mg for 12 days/month</td>
</tr>
<tr>
<td>Continuous combined</td>
<td>Evorel 25 Estradot 25 patch &amp; Utrogestan 100 mg every night</td>
</tr>
<tr>
<td>Estrogel (daily application to thigh)</td>
<td>Oestrogen only</td>
</tr>
<tr>
<td>Sandrena (daily application to thigh)</td>
<td>0.5 mg sachet</td>
</tr>
<tr>
<td>Lenzetto (daily spray to arms)</td>
<td>Oestrogen only</td>
</tr>
</tbody>
</table>
| HRT = hormone replacement therapy. Blacked out cells = no option.

(bloating, breakthrough bleeding, nausea, and headache), it is recommended that all women should start on a lower dose initially and be reviewed at 4 months and thereafter, at a minimum, annually to ensure symptom management. While it is beyond the scope of this article to provide a detailed breakdown of all the different types and doses of HRT available, a prescribing guide outlining the oestrogen dose equivalence between some of the products available is provided in Table 2.6

**KEY CONSIDERATION 4: IS TESTOSTERONE OR VAGINAL OESTROGEN REQUIRED?**

**Testosterone**

Testosterone supplementation on its own is not recommended because of the side effects of bloating, acne, and hair growth.7 While switching women from oral to transdermal HRT can increase the levels of free circulating testosterone, testosterone supplementation is recommended for women who continue to experience low libido and fatigue despite adequate oestrogen replacement.7 Contraindications to its use include active liver disease and hormone-sensitive breast cancer. Prior to its implementation, discussion with a specialist menopause service would be recommended and total testosterone levels should always be checked prior to commencement and again 6–12 months after initiating therapy with the aim of keeping levels within the female’s physiological range. With testosterone implants becoming increasingly difficult to source, transdermal preparations available in the UK can either be administered daily or on alternate days. Application should be on the thighs but not over the same area if transdermal HRT is concurrently being used.

**Vaginal oestrogen**

With vaginal oestrogen now available over the counter, its use is recommended for women experiencing genitourinary symptoms such as vaginal dryness, superficial dyspareunia, vulvovaginal irritation, and increased urinary frequency and urgency. Available either as a pessary or a cream, women should be advised to commence on a daily dose for 2 weeks before being gradually reduced every 2 weeks and can remain on a lifelong twice-weekly or once-weekly regimen. For women with a previous or current history of breast cancer, input from a specialist menopause service would be recommended prior to commencing vaginal oestrogen.

It is recognised that prescribing HRT can be challenging within primary care. By providing a breakdown of the key considerations, the aim is that this can guide PCPs to be more confident in initiating HRT and seeking specialist input when appropriate.

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