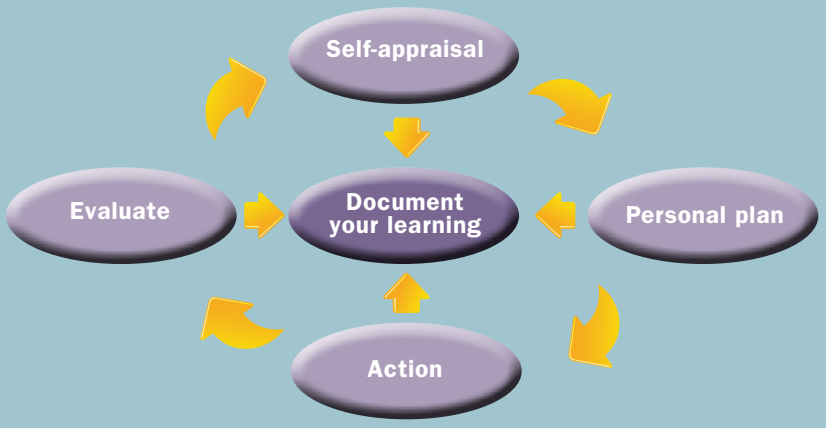

Menopause and the role of HRT

In this month's CPD article, Colette Jackman provides an overview of menopause, including a look at HRT, a number of therapies, and osteoporosis.

Menopause: definition and diagnosis

Menopause can be defined as the biological stage in a woman's life when menstruation ceases permanently. This is due to the depletion of ovarian follicles, resulting in the loss of oestrogen and progesterone. The average age of menopause is 51 years.

Natural menopause is recognised after 12 consecutive months of amenorrhea, assuming no other physiological cause. Induced menopause follows

either surgical removal of both ovaries (with or without hysterectomy), or cessation of ovarian function by chemotherapy or radiation. Perimenopause is defined as the period before menopause, when clinical symptoms first appear.

Premature Ovarian Insufficiency (POI) or premature menopause is usually defined as menopause occurring before the age of 40.

For some women, menstruation stops suddenly, for others it may be intermittent for several years. Therefore, patient needs are individual and should be dealt with on a case-by-case basis. Cigarette smoking has been shown to accelerate the onset of menopause by about two years; and trials have shown that smokers have lower levels of oestrogen than non-smokers.

Menopausal symptoms

During menopause, approximately 85% of women report experiencing symptoms of varying type and severity.

Many women seek help for the management of physical symptoms, for example, flushing, sweating, fatigue, joint pain and dizziness. The recognition of psychological symptoms such as memory loss, depression, anxiety and insomnia has grown in recent years, and they are now considered as equally detrimental to a woman's health.

The severity of menopausal symptoms is linked to several factors, for example: low body weight, low levels of exercise and lower socio-economic class. Surgery-induced menopause is associated with more severe symptoms in almost all patients.

After menopause, the major source of oestrogen in the body is from the conversion of adrenal androgen in fatty tissue. Thus, the amount of body fat plays a crucial role in oestrogen levels in post-menopausal women. Thinner women are more susceptible to some of the long-term outcomes of the menopause, such as osteoporosis.

Assessment of menopausal women should consider factors including the patient's age; time since menopause onset; symptom severity and impact on quality of life; and overall risk for cardiovascular disease and osteoporosis. A major consideration is the personal and family history of breast, endometrial or ovarian cancer, and also colon cancer. A menopausal woman should be encouraged to participate in national screening programmes for breast and cervical cancer.

Hormone replacement therapy (HRT)

In general, the benefits of hormone replacement therapy (HRT) outweigh the risks for most women with menopausal symptoms aged <60 years or within ten years of menopause. HRT is also prescribed to reduce the risk of developing long-term conditions such as osteoporosis, heart disease, and cancer.

The choice of treatment should be individualised to the patient. Factors to consider when determining which therapy to choose include:

- Indication;
- Risk factors;
- Whether the patient has a uterus;
- Symptoms — type, location and severity; and
- Patient preference.

The principal hormones used in HRT are oestrogen and progestogen.

An increased incidence of endometrial hyperplasia has occurred in women receiving oral oestrogen alone, but this incidence is significantly reduced by adding a progestogen. For women who have undergone a hysterectomy, unopposed oestrogen therapy is recommended.

Table 1: **Transdermal Oestrogen Therapy**
Courtesy of JJ Keating, University College Cork

Product	Dose and type of oestrogen	Formulation
Evorel®	50 mcg estradiol	Transdermal patch Change patch every 3 – 4 days
Estradot®	25 mcg, 37.5 mcg, 50 mcg, 75 mcg, 100 mcg estradiol hemihydrate	Transdermal patch Change patch every 3 – 4 days
Divigel®	0.1% gel – 1 mg estradiol hemihydrate per sachet	Transdermal gel Apply daily
Oestrogel®	Pump-pack – 750 mcg estradiol per actuation	Transdermal gel Apply daily

Oestrogen therapy

Oestrogen is available in both oral and transdermal forms as well as in topical/vaginal forms which are used for local symptoms such as vaginal dryness.

Oral foms include Premarin®, Fematab® and Estrofem®. Premarin contains conjugated oestrgoens and Fematab® 1mg, 2mg and Estrofem® 2mg contain estradiol which is bioidentical. Formulations are generally taken once daily with dose adjusted as required to manage symptoms.

Transdermal formulations are associated with a lower risk of venous thromboembolism than oral forms. They should be considered first-line if BMI > 30 kg/m2 or in smokers.

Table 1 (above) provides an overview of the different formulation types available (all Tables are courtesy of J.J. Keating DVetPharm, BSc(Pharm), MA(TLHE), C.Sci., C.Chem., PhD, MPSI, MRSC, Pharmacist and Lecturer of Organic and Pharmaceutical Chemistry, Analytical and Biological Chemistry Research Facility (ABCRF), School of Pharmacy, University College Cork).

The main side effects of taking oestrogen include:

- Bloating;
- Breast tenderness or swelling;

"The recognition of psychological symptoms such as memory loss, depression, anxiety and insomnia has grown in recent years, and they are now considered as equally detrimental to a woman's health."

Table 2: **Progestogen Therapy**
Courtesy of JJ Keating, University College Cork

Product	Route	Dose and type of progestogen
Provera®	PO	10 mg medroxyprogesterone acetate
Duphaston®	PO	10 mg dydrogesterone
Utrogestan®*	PO or PV	100 mg, 200 mg micronised progesterone
Mirena®	PV	52 mg levonorgestrel – IUS

* Care should be taken when supplying the preparation to ensure patient is advised on the correct route for the specific preparation.

Table 3: **Sequential Therapies**
Courtesy of JJ Keating, University College Cork

Product	Dose and type of oestrogen/progestogen
Novofem®	1 mg estradiol (16 days) 1 mg estradiol / 1 mg norethisterone (12 days)
Trisequens®	2 mg estradiol (12 days) 2 mg estradiol / 1 mg norethisterone (10 days) 1 mg estradiol (6 days)
Femoston® **1 / 10** **2 / 10**	1 mg estradiol (14 days) 1 mg estradiol / 10 mg dydrogesterone (14 days) 2 mg estradiol (14 days) 2 mg estradiol / 10 mg dydrogesterone (14 days)

- Swelling in other parts of the body;
- Feeling sick;
- Leg cramps;
- Headaches; and
- Vaginal bleeding.

These side effects will often pass after a few weeks. Leg cramps should be investigated to rule out a potential clot. To ease gastric effects, advise a patient to take their oestrogen dose with food, which causes the stomach to empty more quickly. If side effects persist, the GP may recommend changing from a tablet to a patch, changing the medication, or lowering the dose.

Progestogen therapy

All women with an intact uterus should take progestogen to protect the endometrium. A variety of preparations are available as outlined in *Table 2 (above)*.

The main side effects of taking progestogen include:

- Breast tenderness;
- Headaches; and
- Mood swings.

Again, these will usually pass after a few weeks.

Sequential Therapies

Sequential combined preparations mimic the menstrual cycle and so result in monthly bleeds. They are indicated for women with an intact uterus who are perimenopausal or early post menopause. Packs are based on a 28-day cycle. Oestrogen is taken continuously, with a progestogen added for the last 12-14 days.

Continuous Combined Therapies

Continuous combined preparations are licensed for postmenopausal women. They give a bleed-free regimen. Oestrogen and progestogen are taken together with no break. A lower daily dose of progestogen is used.

Vaginal Oestrogen Therapy

Oestrogen deficiency causes atrophic changes in the vaginal wall and decreases vaginal blood flow and secretions, leading to irritation and dryness. Many of these problems respond well to the administration of local oestrogen. Low-dose vaginal oestrogen is solely used for urogenital symptom, for example Vagifem® pessary, Ovestin® Cream, Imvaggis® pessary.

Practical tips for patients

- ***Patches:*** should be applied below the waist, on the thigh, buttock or lower stomach, and application sites should be rotated. Apply away from skin folds, and not under tight clothing. They can be cut in half diagonally if a lower dose is required;
- ***Oestrogel application:*** apply to the outer arm or inner thigh, away from the breasts or genitals. Apply one dose to one area i.e., two pumps means one to each upper arm;
- ***Divigel:*** apply to the outer upper thigh, alternate legs daily;

Table 4: **Continuous Combined Therapies**
Courtesy of JJ Keating, University College Cork

Product	Dose and type of oestrogen/progestogen
Evorel Conti® (Patch)	50 mcg estradiol hemihydrate / 170 mcg norethisterone acetate
Kliogest®	2 mg estradiol / 1 mg norethisterone
Activelle®	1 mg estradiol hemihydrate / 0.5 mg norethisterone
Angeliq®	1 mg estradiol hemihydrate / 2 mg drospirenone
Femoston Conti®	0.5 mg / 2.5 mg; 1 mg / 5 mg estradiol hemihydrate / dydrogesterone

- ***Utrogestan (oral/vaginal) progesterone capsules:*** recommended 200mg daily from day 15-26 of cycle — with continuous oestrogen. Bleeding occurs during the break. It can also be taken 100mg daily from day 1-25 to reduce monthly bleeding. Taken before bed as it can act as a mild sedative; and
- ***Vagifem estradiol 10mg pessary:*** treats local symptoms only.

Unscheduled bleeding is a common side effect of HRT within the first three months of treatment. It is usually due to non-adherence to therapy, drug interactions or gastrointestinal upset:

- On a monthly cyclical regime, heavy and/or prolonged bleeding may need an increased dose or duration of progesterone; and
- On continuous combined HRT, irregular breakthrough bleeding can occur in the first 4-6 months; if present after six months refer the woman to her GP.

Shortages of HRT medications have been a feature of community pharmacy practice in recent years. The HSE Medicines Management Programme provides some guidance for prescribers, which can be accessed via hse.ie > Clinical Design and Innovation > National Clinical Programmes > Medicine Management. The British Menopause Society (thebms.org.uk) also provide guidance on switching between different HRT formulations.

Other therapies

Tibolone (Livial®) is a synthetic preparation which has oestrogenic, progestogenic and weak androgenic activity. It is licensed for use in post-menopausal women for menopausal symptoms and osteoporosis. It has no withdrawal bleed.

Raloxifene (Evista) is a selective oestrogen receptor modulator used to treat postmenopausal osteoporosis and the risk reduction of invasive breast cancer in post-menopausal women.

Clonidine is an alpha receptor blocker that can help reduce hot flushes and night sweats in some menopausal women. Clonidine can also cause some unpleasant side effects, including dry mouth, drowsiness, depression and constipation.

Osteoporosis

HRT is usually only indicated for women suffering severe menopausal symptoms, but may be indicated for those with no symptoms if the risk of osteoporosis is high. The efficacy of HRT in preventing osteoporosis is beyond doubt. More women die because of osteoporotic fracture than from cancer of the cervix, endometrium and ovary combined. Women who smoke heavily, have a family history of osteoporosis, drink excessively or have had long-term steroid use are all at higher risk. Here, HRT is not indicated for longer than three years, as no further increase in bone mass density (BMD) is seen after this period. However, BMD is seen to drop dramatically on cessation of HRT. The availability of bisphosphonates in the management of osteoporosis provides a safer and more long-term solution for those with minor symptoms.

Long-term complications of menopause treatment

Cardiovascular disease (CVD)
Studies have suggested an increased risk of CVD with the use of some combination HRT preparations. CVD rarely affects women before the menopause, suggesting that oestrogen deficiency may play a role in the onset of the disease. However, recent trials have not established a favourable risk-benefit profile for the use of HRT in CVD prevention or for menopausal symptom relief in women with a high CVD risk. Therefore, HRT is not recommended in these instances as the potential harm is thought to outweigh the potential benefit.

Venous thromboembolism (VTE)
There is a reported two-to-three-fold increased risk of VTE with the use of HRT. Thus, HRT is contraindicated in women with a previous history of VTE and should be used with caution in those at increased risk. There is a lower risk with transdermal compared to oral formulations. HRT should be discontinued four to six weeks before major elective surgery, and not resumed until the patient is fully mobile again.

Breast cancer
For every 1,000 menopausal women not taking combined HRT, 22 will develop breast cancer, 978 will not. For every 1,000 menopausal women taking combined HRT, 27 will develop breast cancer, 973 will not. Therefore, this is an increase of 5 per 1,000 or 0.5%.

Analysis has shown that the risk of breast cancer increases with each year of use of HRT, becoming statistically relevant after five years of treatment. The increased risk of breast cancer falls following discontinuation of HRT and reverts to baseline risk after five years. The risk of breast cancer is lower with oestrogen monotherapy than combination treatment, but studies are ongoing. Guidelines from England's National Institute for Care and Excellence (NICE), state that HRT should not be offered to women with menopausal symptoms and a history of breast cancer.

Endometrial cancer
Long-term use of unopposed oestrogen monotherapy is associated with an eight-to-ten-fold increased risk of endometrial cancer. The addition of a sufficient dose of progestogen eliminates this risk.

Non-hormonal treatments for menopause

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) may help with hot flushes caused by the menopause, but they are not licensed for this use.

Role of the pharmacist

One of the most important roles of the pharmacist regarding menopausal patients, is to steer them towards accurate information and help them to make an informed decision regarding types of treatment, risk factors and potential side effects.

"Poor compliance with HRT regimes is primarily responsible for therapeutic failure, and this largely arises from lack of information about the benefits and risks."

Poor compliance with HRT regimes is primarily responsible for therapeutic failure, and this largely arises from lack of information about the benefits and risks. Many patients harbour concerns regarding its use, particularly in relation to the risk of developing breast cancer and more recently regarding the risk of cardiovascular disease. However, there is little doubt that for many women, HRT has dramatically improved their quality of life through the alleviation of menopausal symptoms.

It is important to note that some women notice a difference within a few days, but for the majority it is a slow and steady improvement over weeks and months. They may notice physical symptoms improve first; for example, hot flushes and night sweats are often much better after four to six weeks. However, psychological symptoms, such as low mood or anxiety, can take months to improve. It is important that women take HRT as prescribed for at least three to six months before deciding whether it is beneficial or not.

Lifestyle tips

Hot flushes and night sweats may benefit from regular exercise, weight loss (if appropriate), wearing lighter clothing and sleeping in a well-ventilated room.

Those suffering sleep disturbances should observe good sleep hygiene and avoid exercise or meals close to bedtime.

Mood and anxiety disturbances can be helped by adequate sleep, relaxation exercises, avoiding stress triggers.

Complementary therapies

The efficacy of herbal remedies continues to be lower than with traditional HRT. Multiple preparations are available, but their safety is uncertain. Black cohosh is widely used to alleviate menopausal symptoms. It is thought to have oestrogenic activity which raises concerns about its use in women with hormone-sensitive conditions. Liver toxicity has also been reported. Phyto-oestrogens, for example, isoflavones, bind to oestrogen receptor cells and mimic the hormone's effects. They should be avoided in women with a history of breast cancer.

Contraception during menopause

Women in their late 40s and early 50s can still get pregnant naturally. Therefore, contraception should be continued until post-menopause; two years after the last period in women under 50 and one year after the last period in women over 50. If post-menopause cannot be confirmed, contraception should be continued until age 55. Women may use a Mirena with oestrogen for up to five years for endometrial protection as part of an HRT regimen. Women using Mirena for this purpose must have the device changed every five years. All progestogen-only methods of contraception are safe to use as contraception alongside sequential HRT. Combined hormonal contraception can be used in eligible women under 50 as an alternative to HRT, for relief of menopausal symptoms and prevention of loss of bone mass.

Conclusion

The risk-benefit ratio of HRT is favourable for the treatment of significant menopausal symptoms. The minimum effective dose should be used for the shortest necessary duration. The decision to use HRT should be made on a case-by-case basis and reviewed annually. In healthy women without symptoms, there is no indication for the use of HRT, and it should not be used first-line for the prevention of osteoporosis.

If you are interested in learning more about this topic, please see a webinar on menopause that was delivered as part of the IPU Academy Spring 2022 programme: access to the webinar and associated resources is available via the IPU Academy platform — ipuacademy.ie.

Your 5-minute assessment

Answer the following questions true or false:

1. Body Mass Index can be an important factor in severity of menopausal symptoms?
2. Irregular bleeding is a sign that HRT is unsuitable and should be stopped?
3. Women who have undergone a complete hysterectomy require combined continuous HRT?
4. Oestrogen patches can be placed on any area of clean, dry skin?
5. The risk of breast cancer while using HRT is five times that of someone not on HRT?

Answers
1. True. Women of low body weight tend to have more severe menopausal symptoms. **2.** False. Irregular bleeding is common during the first three months of treatment. **3.** False. For women who have undergone a hysterectomy, unopposed oestrogen therapy is recommended. **4.** False. Oestrogen patches should only be placed below the waist — ideally on the thigh or lower back. **5.** False. Studies have shown that an extra five women per 1000 will get breast cancer compared to those not on HRT.

CPD overview

Self-appraisal

- [ ] Can I provide practical advice to patients about identifying the signs and symptoms of menopause?
- [ ] Can I advise patients regarding the risks and benefits of HRT?
- [ ] Can I describe the different regimens used for HRT?
- [ ] Can I advise patients on the practical usage of HRT and related products?

Personal plan

Including a list of desired learning outcomes in a personal learning plan is a helpful self-analytical tool.

- [ ] Create a list of desired outcomes.
- [ ] How will I accomplish these learning outcomes?
- [ ] Identify professional resources available to achieve learning objectives.

Action

Activities chosen should be outcomes based to meet learning objectives.

- [ ] Read this article and answer the attached MCQs.
- [ ] Review the advice and information provided to patients to whom HRT is dispensed.
- [ ] Review over-the-counter products available for menopause in the pharmacy, and evaluate which are suitable for recommendation.
- [ ] Evaluate professional resource materials and patient support materials available in the pharmacy and source additional material if necessary.
- [ ] Identify patients who have been on HRT for more than two years and who may benefit from a review of their therapy.

Evaluate

Consider outcomes of learning and impact of learning.

- [ ] Do I now feel equipped to explain the symptoms of menopause?
- [ ] Can I provide effective advice on its treatment and give advice that will lead to better symptom control?
- [ ] Can I give information regarding the risks and benefits of HRT?
- [ ] Have I met my desired learning outcomes?
- [ ] Have further learning needs been identified?

Document your learning

- [ ] Create a record in your CPD portfolio.
- [ ] As part of this record, complete the short questions at the end of this article and save associated reference resources.